



Rapid HTA report

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Ultrasonic energy devices for surgery

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Contributions

Authors

Antonio Migliore, Mirella Corio, Maria Rosaria Perrini, Chiara Rivoiro, and Tom Jefferson
Agenas, Agenzia nazionale per i servizi sanitari regionali, Area Funzionale Innovazione, Sperimentazione e Sviluppo, via Puglie 23, 00187 Rome (Italy)

Corresponding author

Antonio Migliore, MSc (migliore@agenas.it)

Clinical experts

Mario Alessiani, MD FACS

Division of General Surgery, Varzi Hospital, University of Pavia (Italy)

Marco Filauro, MD

Division of General and Hepatobiliopancreatic Surgery, Galliera Hospital, Genova (Italy)

Invited reviewers

Chuong Ho, MD MSc

Canadian Agency for Drugs and Technologies in Health (CADTH), Ottawa (Canada)

Björn Fahlgren, MSc

Comité d'évaluation des technologies de santé (CEDIT), Paris (France)

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Authors, Clinical expert and External Reviewers declare that they do not receive benefits or harms from the publication of this report. None of the authors have or have held shares, consultancies or personal relationships with any of the producers of the devices assessed in this document.

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Sommario

Le forbici chirurgiche ad ultrasuoni sono state sviluppate nei primi anni Novanta e sono oggi disponibili per procedure chirurgiche a cielo aperto o endoscopiche. I principi di funzionamento di questi dispositivi riguardano principalmente la vibrazione ad alta frequenza della lama che, una volta a contatto con il tessuto, provoca la dissezione per cavitazione e l'emostasi per mezzo della denaturazione delle proteine. Se confrontata con tecniche convenzionali quali sutura, applicazione clip vascolari, ed elettrocauterizzazione, questa tecnologia si propone di offrire vantaggi in termini di riduzione dei tempi chirurgici, riduzione del rischio di lesioni da calore sui tessuti adiacenti e riduzione dei fumi (che potrebbero limitare la visibilità durante le procedure endoscopiche).

Le forbici chirurgiche ad ultrasuoni rappresentano la tecnologia valutata all'interno di questo rapid HTA report. Il rationale della valutazione deriva dal considerevole volume di spesa di questi dispositivi registrato presso le strutture ospedaliere a livello nazionale. Fornire una guida per un utilizzo evidence-based di questa tecnologia potrebbe contribuire a migliorare l'allocazione dei fondi pubblici.

Abbiamo identificato e descritto tutte le forbici chirurgiche ad ultrasuoni disponibili sul mercato italiano ed eseguito una analisi di contesto per mostrare il loro impatto in termini di spesa e consumo. Abbiamo effettuato una revisione sistematica di studi primari e secondari allo scopo di sintetizzare le evidenze comparative su efficacia e sicurezza relative all'utilizzo della tecnologia in oggetto. Abbiamo considerato i tempi operatori, i tempi di degenza, le perdite di sangue, le complicanze post-operatorie e i decessi come outcome principali. Abbiamo effettuato una revisione sistematica di studi economici che mettevano a confronto le forbici chirurgiche ad ultrasuoni con le tecniche emostatiche convenzionali e gli altri dispositivi chirurgici ad energia.

Abbiamo concluso che, sulla base delle evidenze disponibili, l'utilizzo delle forbici chirurgiche ad ultrasuoni può essere collegato al miglioramento di alcuni outcome rilevanti. Tuttavia, questa affermazione non può essere estesa a tutte le procedure chirurgiche in cui oggi questa tecnologia viene utilizzata. L'evidenza è chiaramente a supporto dell'utilizzo delle forbici chirurgiche ad ultrasuoni in chirurgia tiroidea e colecistectomia laparoscopica (in termini di miglioramento di uno o più outcome). Diversi vantaggi sono dimostrabili anche in chirurgia della mammella e emorroidectomia, data la presenza di diversi studi primari a supporto. Per tutte le altre procedure, la tecnologia è supportata solo da un numero limitato di studi primari, spesso su piccoli gruppi di pazienti e quindi, qualsiasi dichiarazione conclusiva richiede prudenza.

In chirurgia tiroidea l'analisi degli studi economici ha mostrato diversi vantaggi connessi all'utilizzo delle forbici chirurgiche ad ultrasuoni. Nessuna conclusione in merito a tali aspetti può essere tratta per la colecistectomia laparoscopica o qualsiasi altra procedura presa in considerazione.

Si raccomanda pertanto l'utilizzo delle forbici chirurgiche ad ultrasuoni in quelle procedure per le quali l'evidenza a supporto sia stata documentata attraverso studi secondari e studi economici abbiano dimostrato vantaggi reali. Si incoraggiano attività di approfondimento per quelle procedure in cui l'utilizzo della tecnologia in oggetto è supportato da studi primari. Si raccomandano attività di ricerca mirate a supportare l'utilizzo di questa tecnologia laddove le evidenze, di natura clinica ed economica, siano ancora limitate. Tra i dispositivi disponibili sul mercato, si consiglia di preferire quelli per i quali siano stati pubblicati studi clinici, e prendere in considerazione l'uso degli altri solo nell'ambito di iniziative, percorsi e programmi atti a generare evidenza.

Sintesi in italiano

Le forbici chirurgiche ad ultrasuoni sono state sviluppate nei primi anni Novanta e sono oggi disponibili per procedure chirurgiche a cielo aperto o endoscopiche. I principi di funzionamento di questi dispositivi riguardano principalmente la vibrazione ad alta frequenza della lama che, una volta a contatto con il tessuto, provoca la dissezione per cavitazione e l'emostasi per mezzo della denaturazione delle proteine. Se confrontata con tecniche convenzionali quali sutura, applicazione clip vascolari, ed elettrocauterizzazione, questa tecnologia si propone di offrire vantaggi in termini di riduzione dei tempi chirurgici, riduzione del rischio di lesioni da calore sui tessuti adiacenti e riduzione dei fumi (che potrebbero limitare la visibilità durante le procedure endoscopiche).

Le forbici chirurgiche ad ultrasuoni rappresentano la tecnologia valutata all'interno di questo rapid HTA report. Il rationale della valutazione deriva dal considerevole volume di spesa di questi dispositivi registrato presso le strutture ospedaliere a livello nazionale. Fornire una guida per un utilizzo evidence-based di questa tecnologia potrebbe contribuire a migliorare l'allocazione dei fondi pubblici.

La valutazione è stata condotta secondo un approccio multidisciplinare e ha previsto l'analisi su diversi domini. L'analisi di contesto ha mostrato che sono quattro le aziende produttrici ad offrire questa tecnologia sul mercato italiano: Covidien (Sonicision), Ethicon Endo-surgery (forbici della famiglia Harmonic), Olympus Medical Systems (SonoSurgX, Thunderbeat e Sonicbeat) e SRA Developments (Lotus Series 4).

L'analisi dei consumi è stata effettuata per gli anni 2012 e 2013 incrociando i codici dei dispositivi di interesse, registrati sul Repertorio Dispositivi Medici (RDM), con i dati del database "Flusso consumi", istituito dal Ministero della Salute nel 2011. È stato rilevato un aumento dei consumi nel periodo di interesse (del 34,84% per le "forbici per chirurgia ad ultrasuoni a cielo aperto", del 29,86% per le "forbici per chirurgia ad ultrasuoni laparoscopica"). I volumi acquistati per tipi di chirurgia (a cielo aperto e laparoscopica) si sono mostrati grossomodo equivalenti, con leggera prevalenza per i dispositivi per procedure laparoscopiche. È stato inoltre possibile calcolare il range del prezzo d'acquisto relativamente a "forbici monouso per chirurgia ad ultrasuoni a cielo aperto", "forbici monouso per chirurgia ad ultrasuoni laparoscopica", "manipoli monouso per chirurgia ad ultrasuoni a cielo aperto" e "manipoli monouso per chirurgia ad ultrasuoni laparoscopica". A parte piccoli aumenti del prezzo massimo per alcuni dispositivi, non sono state rilevate differenze di prezzo significative tra i due periodi

presi in considerazione. L'impatto totale di questa tecnologia sulla spesa sanitaria nel 2013 può essere stimato in circa 30 milioni di Euro (dato sottostimato poiché non include la spesa relativa ai componenti accessori).

La revisione sistematica di studi di efficacia e sicurezza è stata condotta su studi comparativi che riportavano outcome relativi a pazienti trattati chirurgicamente (cielo aperto o laparoscopia) utilizzando uno dei dispositivi ad ultrasuoni identificati e pazienti trattati con tecniche emostatiche convenzionali (sutura, applicazione di clip vascolari elettrocauterizzazione) o altri dispositivi chirurgici a energia. Sono stati considerati studi secondari e primari pubblicati dal 2004. La sintesi delle evidenze è stata strutturata per sottogruppi, secondo procedura (o gruppi di procedure), ed è stata basata su 7 studi secondari e 42 studi primari raggruppati in 16 procedure (o gruppi di procedure). Solo per 2 delle procedure prese in esame è stato possibile fornire raccomandazioni conclusive a favore dell'utilizzo delle forbici chirurgiche ad ultrasuoni: chirurgia tiroidea (riduzione di: tempi operatori, perdite ematiche intra- e post-operatorie, periodo di degenza, dolore post-operatorio, tasso di ipocalcemia transitoria) e colecistectomia laparoscopica (riduzione di: tempi operatori, perdite ematiche, periodo di degenza, perforazione della cistifellea, dolore post-operatorio a 24 ore). Per la chirurgia della mammella e l'emorroidectomia gli studi primari identificati hanno mostrato diversi vantaggi (riduzione della formazione di sieroma e del volume di drenaggio nella chirurgia della mammella e riduzione del dolore post-operatorio nell'emorroidectomia) e pertanto ulteriori raccomandazioni potrebbero scaturire da un relativo approfondimento. Per tutte le altre procedure, la tecnologia è supportata solo da un numero limitato di studi primari, spesso su piccoli gruppi di pazienti e quindi, qualsiasi dichiarazione conclusiva richiede prudenza.

La revisione sistematica degli studi economici è stata condotta su studi comparativi, pubblicati dal 2004, che mettevano a confronto l'utilizzo delle forbici chirurgiche ad ultrasuoni con le tecniche emostatiche convenzionali e gli altri dispositivi chirurgici ad energia. Diciotto studi sono stati inclusi nell'analisi finale: 6 studi di costo-efficacia e 12 analisi di costi. Gran parte degli studi riguardava la chirurgia tiroidea (9 studi); altri studi erano su chirurgia coloretale (3 studi), chirurgia della mammella (2 studi), chirurgia su testa e collo (2 studi), chirurgia spinale (1 studio) e appendicectomia (1 studio). L'analisi degli studi economici ha mostrato che, in chirurgia tiroidea, il maggior costo legato all'utilizzo della tecnologia ad ultrasuoni è spesso compensato dalla riduzione dei tempi operatori. Nessuna conclusione in merito a tali aspetti può essere tratta per le altre procedure a causa della natura degli studi disponibili e della parziale copertura in termini di procedure valutate.

In conclusione, secondo le evidenze disponibili da studi secondari e rispetto alle tecnologie convenzionali o alternative, l'utilizzo delle forbici chirurgiche ad ultrasuoni è associabile ad un miglioramento di uno o più outcome nelle seguenti procedure:

- Colectomia laparoscopica;
- Chirurgia tiroidea.

Diversi studi primari hanno dimostrato che l'utilizzo della tecnologia in esame è altresì associabile ad alcuni vantaggi nelle seguenti procedure:

- Chirurgia della mammella;
- Emorroidectomia.

Le evidenze hanno mostrato invece l'inferiorità della tecnologia ad ultrasuoni rispetto alle tecnologie convenzionali o alternative nella chirurgia coloretale laparoscopica (in particolare resezione coloretale laparoscopica). Per tutte le altre procedure, data la scarsità di evidenze, non è possibile arrivare a conclusioni definitive circa l'utilizzo di questa tecnologia.

Si raccomanda pertanto l'utilizzo delle forbici chirurgiche ad ultrasuoni in quelle procedure per le quali l'evidenza a supporto sia stata documentata attraverso studi secondari e studi economici che abbiano dimostrato vantaggi reali. Si incoraggiano attività di approfondimento per quelle procedure in cui l'utilizzo della tecnologia in oggetto è supportato da studi primari. Si raccomandano attività di ricerca mirate alla produzione di evidenze a supporto dell'utilizzo di questa tecnologia, laddove queste siano ancora limitate e, una volta assodata l'efficacia clinica, si consiglia ai decisori di considerare con attenzione gli aspetti economici connessi all'utilizzo di questa tecnologia. Tra i dispositivi disponibili sul mercato, si raccomanda di preferire quelli per i quali siano stati pubblicati studi clinici, e prendere in considerazione l'uso degli altri solo nell'ambito di iniziative, percorsi e programmi atti a generare evidenze.

Abstract

Ultrasonic energy devices for surgery were developed in the early 1990s and are now available for both open and endoscopic surgical procedures. The operating principles of the ultrasonic energy devices for surgery are mainly related to the high-frequency vibration of the dissector's blade: once in contact with the tissue, it causes tissue dissection by cavitation and haemostasis by denaturation of protein. If compared with conventional techniques (e.g. suture ligation, vascular clips application, and electrocautery), this technology aims to offer benefits in terms of surgical time reduction, reduction of risk of local tissue heat injury and reduction of smoke (known for limiting the visibility during endoscopic procedures).

Ultrasonic energy devices for surgery are the technology assessed within this rapid HTA report. The rationale is represented by the significant volume of such devices purchased by the Italian hospitals. Providing guidance on the evidence-based use of this technology may contribute to improve the allocation of public funds.

We identified and described all the ultrasonic energy devices for surgery available on the Italian market and performed a context analysis to show their impact in terms of expenditure and consumption. We performed a systematic review of primary and secondary studies to synthesise the comparative evidence on effectiveness and safety on the use of the ultrasonic energy devices. We considered operating time, hospital stay, blood loss, post-operative complications, and any reported death as main outcomes. We performed a systematic review of economic studies comparing the ultrasonic energy devices to the conventional haemostatic techniques or other energy-based devices.

We concluded that, on the basis of the current evidence, the use of the ultrasonic energy devices in surgery can be linked to the improvement of some relevant outcomes. However, this statement cannot be extended to all the surgical procedures in which this technology is used. The evidence is clearly in favour of the ultrasonic energy devices (i.e., linked to benefits in one or more outcomes) in thyroid surgery and laparoscopic cholecystectomy. The use of the ultrasonic energy devices in some other procedures (breast surgery and haemorrhoidectomy) is supported by a number of primary studies that should be furtherly assessed and meta-analised to produce final clinical guidelines. In the context of tonsillectomy, the evidence from secondary studies showed little added benefits from the use of ultrasonic energy devices (i.e., equivalence to conventional or alternative techniques). The use of the technology in a variety of other

procedures is only supported by primary studies. These have a small sample size and are few in number, thus any conclusive statement requires caution.

Within the setting of thyroid surgery, the analysis of the economic literature showed several advantages related to the use of the ultrasonic energy devices. No statements about the economic aspects can be made for laparoscopic cholecystectomy or any other procedure.

In conclusion, we recommend the use of the ultrasonic energy devices in those procedures for which evidence from secondary studies is in their favour, and economic analyses have shown real advantages. We encourage research to support the use of this technology in those procedures for which evidence is still limited and, once evidence on clinical effectiveness has been made available, we recommend decision makers to consider carefully the economic aspects related to the use of this technology.

1. Technology description

1.1 Clinical problem

Surgical procedures are extremely common in the clinical practice of several medical specialties. Other than tissue dissection, that needs to be accurate, concomitant vessels sealing (haemostasis) needs also to be performed in the quickest way to avoid excessive bleeding. Conventional haemostatic techniques are suture ligation, vascular clips application, and electrocautery. These techniques showed pitfalls when used in some procedures and settings: suture ligation can be time consuming and technically complex in confined spaces and sutures may cause foreign body reactions; vascular clips may be susceptible to displacement during tissue manipulation in the surgical field or interfere with future CT or MRI examinations; electrocautery causes temperature rises up to 400 °C that may be dangerous for the collateral tissues and nerves²⁰. For these reasons, surgery is continuously moving toward better ways for dissection and haemostasis. In the last decades, several technologies for surgical dissection have been developed with the aim to simultaneously cut tissues and seal vessels. Bipolar radiofrequency devices, electrothermal bipolar vessel sealing devices, and ultrasonic energy devices are classified under the umbrella-term of “energy-based devices”⁹. These technologies allow controlled tissue and vessel alteration through the application of electrical, electrothermal, and mechanic energy, respectively. In particular they are intended to provide improved haemostasis and reduced heat transfer to collateral tissues during surgical procedures. Energy-based devices are commonly used in most of the surgical procedures of many surgical specialties such as colorectal surgery, hepato-biliary surgery, pancreatic surgery, thoracic surgery, urologic surgery, gynaecologic surgery, ENT surgery, endocrine surgery, gastro-oesophageal surgery, in both open and endoscopic setting^{31, 68}. This Rapid HTA Report focuses exclusively on the ultrasonic energy devices for surgery. The rationale is represented by the high volume of such devices purchased by the Italian hospitals (a total estimate expenditure of 26 million of Euro in 2012 – data owned by the Italian Ministry of Health). Providing guidance on the evidence-based use of this technology may contribute to improve the allocation of public funds.

1.2 Description and regulatory status of the technology

Ultrasonic energy devices are not newcomers in surgery as they were developed in the early 1990s³. During the decades, several improvements have been made and today's surgeons can choose from several devices on the market.

Ultrasonic energy devices are available for both open surgery and endoscopic procedures. Typically, the ultrasonic dissector, that is the device that performs cutting and haemostasis, is part of a system that includes also an ultrasonic transducer (often called hand piece, that converts the electric energy from the generator into ultrasonic energy), an ultrasonic generator, and sometimes also a foot switch (for controlling the activation of the device). A single-use torque wrench is also provided to fix together the dissector and the transducer.

Generally, the ultrasonic dissector and the torque wrench are disposable devices (single-patient use); the other components of the system (like the generator and the transducer) are reusable. The operating principles of the ultrasonic energy devices for surgery are mainly related to the high-frequency vibration of the dissector's blade: once in contact with the tissue, it causes tissue dissection by cavitation and haemostasis by denaturation of protein²⁰. If compared with traditional techniques like suture ligation, electrocautery and vascular clips application, this technology aims to offer benefits in terms of surgical time reduction, reduction of risk of local tissue heat injury and reduction of smoke (known to cause visibility problems, especially during endoscopic procedures)³¹.

2. Report's objectives: policy and research questions

This Rapid HTA Report has been developed to answer the following questions:

Policy question: What is the optimal use of the ultrasonic energy devices for surgery in terms of effectiveness, safety and economic costs compared to the alternatives?

Research question: Are the ultrasonic energy devices for surgery safe, effective and cost-effective?

3. Context overview

3.1 Ultrasonic energy devices for surgery on the Italian market

A search of the RDM was conducted on January 2014 using the National Classification of Medical Devices (CND) codes associated with those ultrasonic energy devices linked to high-volume expenditures:

- K020201 – Electrosurgical ultrasonic instrumentary, single-use (GMDN code: 18049);
- Z120108 – Ultrasound surgery instruments (GMDN code: 18049).

Results of this search, integrated with further searches on the internet (i.e., manufacturers' websites and regulators' databases) are summarised in Table 3.1. Four companies are sharing the market in this field; all the companies offer the technology, in different combinations, for both open and endoscopic procedures.

Table 3.1: Ultrasonic energy devices for surgery commercially available in Italy as at 20th January 2014 and registered within the General Repertory of medical devices (RDM). All the devices registered within the RDM are CE-marked.

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Manufacturer	Device name	Variants	Surgical setting
Covidien	Sonicision	-	Open and Endoscopic
Ethicon Endo-surgery	Harmonic	ACE + Shears ACE Shears FOCUS Curved Shears FOCUS + Curved Shears FOCUS Long Curved Shears LCSC5 WAVE Open Shears	Open and Endoscopic Open and Endoscopic Open Open Open Endoscopic Open
Olympus Medical Systems	SonoSurgX	-	Open Endoscopic
	Thunderbeat*	-	Open and Endoscopic
	Sonicbeat	-	Open and Endoscopic
SRA Developments	Lotus Series 4	Dissecting Shears Liver Resector Vessel Welder	Open and Endoscopic Open and Endoscopic Open and Endoscopic

* Ultrasonic energy is used for cutting; haemostasis is performed by an integrated bipolar electrothermal source.

Source: Data from General Repertory of medical devices and internet searches.

3.2 Technical description of the devices identified

We synthesised some of the main technical features for each device in alphabetical order by manufacturer:

Covidien

Sonicision

The Sonicision is a cordless ultrasonic dissector able to perform sealing of vessels up to 5 mm of diameter. The battery pack and the ultrasound generator are integrated in the hand piece. The device can be used as an adjunct to or substitute for electrosurgery, laser, and steel scalpel in general, plastic, paediatric, gynaecologic, urologic, exposure to orthopaedic structures (such as spine and joint space), and other open and endoscopic procedures⁹⁰. The Sonicision dissector is part of the Cordless Ultrasonic Dissection Device system that is composed of single use components (the ultrasonic dissector and the torque wrench) and reusable components (the generator, the battery pack, and the battery charger)¹⁶.

Ethicon Endo-surgery

Harmonic

All the devices from the Harmonic family are for single-patient use and activated by the Ethicon Endo-Surgery Generator G11 by a specific transducer (called hand piece). The same generator activates also all the devices from the Enseal family (bipolar energy devices for surgery; out of the scope of this Rapid HTA Report)²⁵.

The Harmonic ACE dissectors (ACE and ACE +) are hand-actuated devices with a shaft and tissue effector that can be rotated. The energy delivery can be activated with hand activation or with an optional generator foot switch. The devices can seal vessels up to 5 mm of diameter. The ACE devices can be used as an adjunct to or substitute for electrosurgery, lasers and steel scalpels in general, plastic, paediatric, gynaecologic, urologic, thoracic, exposure to orthopaedic structures (such as spine and joint space) and other open and endoscopic procedures⁹¹.

The Harmonic FOCUS dissectors (Curved Shears, + Curved Shears, and Long Curved Shears) consist of a soft grip scissor handle housing assembly with two hand power controls. The devices have a curved blade and clamp arm with Teflon pad. The devices allow for coagulation of vessels up to and including 5 mm in diameter. The FOCUS devices can be used as an adjunct to or substitute for electrosurgery, lasers, and steel scalpels in general, otorhinolaryngology (ENT), plastic, paediatric, gynaecologic, urologic, exposure to orthopaedic structures (such as spine and joint space), and other open procedures⁹².

The Harmonic WAVE dissector consists of a scissor handle housing assembly with hand control power buttons. The handle housing has an integrated audible/tactile mechanism for indicating full closure. The device has a straight blade and clamp arm and is designed to function through an incision without the use of a trocar. The WAVE device can be used as an adjunct to or substitute for electrosurgery, lasers, and steel scalpels in general, plastic, pediatric, gynecologic, urologic, exposure of orthopedic structures (such as spine and joint space) and other open procedures⁹³.

The Harmonic LCSC5 dissector is a device with a shaft and tissue effector that can be rotated. The device is designed to function through an incision with or without the use of a trocar. The LCSC5 device can be used as an adjunct to or substitute for electrosurgery, lasers and steel scalpels in abdominal, paediatric, gynaecologic, and other endoscopic procedures⁹⁴.

The Harmonic system is composed of single use components (any of the ultrasonic dissectors and the specific torque wrench, reusable only for the LCSC5 device) and reusable components (the generator and the hand piece)²⁵.

Olympus

SonoSurgX

The SonoSurg System is composed of reusable components: i) the ultrasonic dissector (available in different grip designs, for open or endoscopic surgery, different lengths and shape of the blade, and also compatible for use with an electrosurgical unit); ii) the ultrasonic transducer; iii) the generator⁵⁹. The SonoSurgX device can be used in bariatric procedures which include: laparoscopic and general (open) surgery in intra-abdominal, obstetric/gynaecologic, thoracic and urologic procedures⁹⁵.

Thunderbeat and Sonicbeat

The Thunderbeat is the only device integrating advanced bipolar and ultrasonic energy. Advanced bipolar energy is used for vessel sealing and tissue coagulation while ultrasonic energy perform the tissue cutting and dissection. The device is capable of 7 mm vessel sealing and can be used in "seal & cut" mode or only in "seal" mode. The Sonicbeat device is developed from the Thunderbeat device but works with ultrasonic energy alone and is able to seal and cut vessels up to and including 5 mm in diameter. Both the Thunderbeat and Sonicbeat are available in different lengths and grip designs and can be used for open and endoscopic surgical procedures. In particular, the Thunderbeat device can be used for open, laparoscopic (including single-site surgery) general surgery and gynaecological surgery (including urologic, thoracic, plastic and reconstructive, bowel resections,

cholecystectomies, Nissen fundoplication, adhesiolysis, oophorectomy, hysterectomies, etc.) and endoscopic surgery or in any procedure in which cutting vessel ligation (sealing and cuffing), coagulation, grasping, and dissection is performed. The Sonicbeat can be used in open, laparoscopic (including single-site surgery), and general surgery to cut (dissect), coagulate, or grasp soft tissue or to ligate (seal and cut) vessels in gynaecologic, thoracic, urologic, and endoscopic surgical procedures⁹⁶.

The Thunderbeat and the Sonicbeat are single-patient use devices and work as part of the Olympus Surgical Tissue Management System composed of reusable components (the ultrasonic generator, the electrosurgical generator, the Thunderbeat transducer, the Sonicbeat transducer) and single use components (the Thunderbeat dissector and the Sonicbeat dissector)⁶⁰.

SRA Developments

Lotus Series 4

The Lotus is the only system that uses torsional ultrasound, designed to direct the energy towards the target tissue (between the device's jaws) and avoiding stray energy lost at the distal tip of the jaws. Three dissectors are available, the Dissecting Shears, the Liver Resector (designed specifically for resecting liver tissue), and the Vessel Welder (that integrate the "Weld" mode only to seal, and "Cut" mode to seal and cut). The dissectors are for single-patient use and activated with hand activation or with foot switch by the LG4 generator by means of the Lotus transducer (specific for each dissector)⁷⁴.

The Series 4 Lotus Coagulation and Cutting System can be used as an adjunct to or substitute for electrosurgery, laser surgery and traditional scalpels in general, urological, gynaecological, bariatric, thoracic, hepatopancreaticobiliary surgery and exposure to orthopaedic structures (such as spine and joint space) and other endoscopic and open procedures⁹⁷. The Series 4 Lotus Coagulation and Cutting System is composed of reusable elements (the generator and the transducer) and single-use elements (the dissector)⁷⁴.

3.3 Consumption of ultrasonic devices in Italy

We analysed the national database "Flusso consumi" run by the Ministry of Health with the aim of identifying the real consumption of devices assessed in this report (in terms of number of devices purchased) in Italian public health structures, for the years 2012 and 2013.

The database is sustained by Italian Regions which gather data from public health care providers in their territory. The database was created in 2011 with a piloting phase in 2012 and its maintenance became mandatory in 2013. During the pilot phase the database was powered by about 87% of health care providers, while in the first half year of 2013 from 92%⁵².

We collected data related to:

- 1.** The consumption of ultrasonic devices, marketed within health national system, belonging to the following CND classes:
 - Single-use ultrasonic scissors for open surgery (K0202010101),
 - Single-use ultrasonic scissors for endoscopic surgery (K0202010102),
 - Single-use hand piece for ultrasound open surgery (K0202010201),
 - Single-use hand piece for ultrasound endoscopic surgery (K0202010202),
 - Single-use instruments for ultrasound surgery – Other (K02020199),
 - Devices for surgery with ultrasound generator – Accessories (K020280),
 - Ultrasonic scalpel (Z12010801),
 - Instruments for ultrasound surgery – hardware components (Z12010880),
 - Instruments for ultrasound surgery – specific materials (Z12010885).

- 2.** The contract price of the devices listed above.

The choice for the selection of the classes of devices listed above originated by cross checking the data with device names and the related components registered within the CND database. Within the “Flusso consumi” database data on the consumptions and contract prices were searched for in the reports CNS003 and CRT009 respectively. Concerning the first issue, the real national consumption of K classes and Z classes, in 2012, is reported in Table 3.2 and Table 3.3, in which detailed data for each Region are also shown. The same data for 2013, are presented in the Table 3.4 and Table 3.5.

Table 3.2: Devices consumptions of K classes (2012).

REGIONS	K0202010101	K0202010102	K0202010201	K0202010202	K02020199	K020280
ABRUZZO	1163	2425	0	0	0	0
BASILICATA	358	374	0	0	0	0
CALABRIA	85	516	0	0	0	0
CAMPANIA	1274	1577	0	0	0	0
EMILIA-ROMAGNA	3168	2921	0	0	0	1
FRIULI VENEZIA GIULIA	723	1140	0	0	0	0
LAZIO	12	30	0	0	0	0
LIGURIA	223	380	0	0	0	3
LOMBARDIA	2357	3230	8	21	0	4200
MARCHE	680	481	0	0	0	0
MOLISE	144	264	0	0	0	0
PA BOLZANO	128	276	0	0	0	0
PA TRENTO	156	0	0	0	0	0
PIEMONTE	735	567	0	12	0	0
PUGLIA	2363	1650	0	0	0	0
SARDEGNA						
SICILIA	1275	1353	0	0	0	0
TOSCANA	1283	2154	0	0	0	0
UMBRIA	282	204	0	0	0	0
VALLE D'AOSTA	84	36	0	0	0	0
VENETO	3298	4937	0	0	0	0
TOTAL	19791	24515	8	33	0	4204

Source: Agenas analysis based on national database "Flusso consumi", year 2012.

Table 3.3: Devices consumptions of Z classes (2012).

REGIONS	Z12010801	Z12010880	Z12010885
ABRUZZO	92	48	0
BASILICATA	0	0	0
CALABRIA	0	4	0
CAMPANIA	0	16	0
EMILIA-ROMAGNA	1	51	0
FRIULI VENEZIA GIULIA	4	7	0
LAZIO	0	0	0
LIGURIA	0	2	0
LOMBARDIA	18	19	0
MARCHE	0	4	0
MOLISE	11	1	0
PA BOLZANO	2	0	0
PA TRENTO	0	7	0
PIEMONTE	15	13	0
PUGLIA	0	66	0
SARDEGNA			
SICILIA	0	60	0
TOSCANA	0	14	0
UMBRIA	0	4	0
VALLE D'AOSTA	0	1	0
VENETO	7	68	6
TOTAL	150	385	6

Source: Agenas analysis based on national database "Flusso consumi", year 2012.

Table 3.4: Devices consumptions of K classes (2013).

REGIONS	K0202010101	K0202010102	K0202010201	K0202010202	K02020199	K020280
ABRUZZO	1003	2184	0	0	0	0
BASILICATA	348	744	0	0	0	0
CALABRIA	250	2202	0	0	0	0
CAMPANIA	1680	1596	0	36	0	0
EMILIA-ROMAGNA	3292	2784	0	48	0	30
FRIULI VENEZIA GIULIA	1310	813	0	0	0	0
LAZIO	2581	2152	31	458	0	3
LIGURIA	214	252	37	0	0	14
LOMBARDIA	2804	3302	62	51	0	0
MARCHE	846	906	0	580	0	0
MOLISE	108	288	0	0	0	0
PA BOLZANO	144	270	0	18	0	0
PA TRENTO	144	0	0	0	0	0
PIEMONTE	1571	4286	0	62	0	11
PUGLIA	3140	1936	0	0	0	0
SARDEGNA						
SICILIA	1710	1514	29	47	0	5
TOSCANA	1318	2105	0	48	0	0
UMBRIA	129	84	0	13	0	0
VALLE D'AOSTA	57	60	0	0	0	0
VENETO	4038	4356	0	20	0	1
TOTAL	26687	31834	159	1381	0	64

Source: Agenas analysis based on national database "Flusso consumi", year 2013.

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Table 3.3: Devices consumptions of Z classes (2013).

REGIONS	Z12010801	Z12010880	Z12010885
ABRUZZO	264	17	0
BASILICATA	0	0	0
CALABRIA	0	12	0
CAMPANIA	6	9	0
EMILIA-ROMAGNA	31	14	2
FRIULI VENEZIA GIULIA	0	3	0
LAZIO	21	15	0
LIGURIA	0	6	0
LOMBARDIA	17	27	15
MARCHE	0	1	2
MOLISE	13	2	4
PA BOLZANO	1	0	0
PA TRENTO	0	0	0
PIEMONTE	10	20	0
PUGLIA	0	81	0
SARDEGNA			
SICILIA	4	50	2
TOSCANA	4	14	0
UMBRIA	0	0	0
VALLE D'AOSTA	0	0	0
VENETO	2	58	0
TOTAL	373	329	25

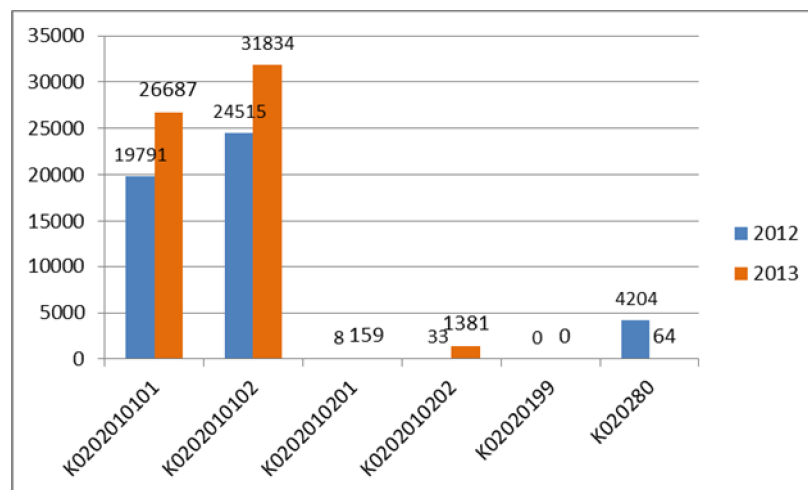
Source: Agenas analysis based on national database "Flusso consumi", year 2013.

Figure 3.1 shows graphically the consumption in 2012 and 2013 of the ultrasonic devices belonging to K Class. Specifically, device consumption in 2013, compared to 2012, increased by 34.84% for “single-use ultrasonic scissors for open surgery”, by 29.86% for “single-use ultrasonic scissors for endoscopic surgery” and the consumption of “hand pieces (for open and endoscopic surgery)” showed an exponential growth (from 1800% to 4000%). This trend could be only slightly influenced by partial data available for 2012 (piloting phase). However, “accessories for surgery with ultrasound generator” recorded a relevant decrease (98.48%) while no data were found on purchase in both years for the “single-use instruments for ultrasound surgery – other”.

Regarding the ultrasonic scalpel belonging to classes Z and relative hardware components and specific materials, the consumption is represented in Figure 3.2.

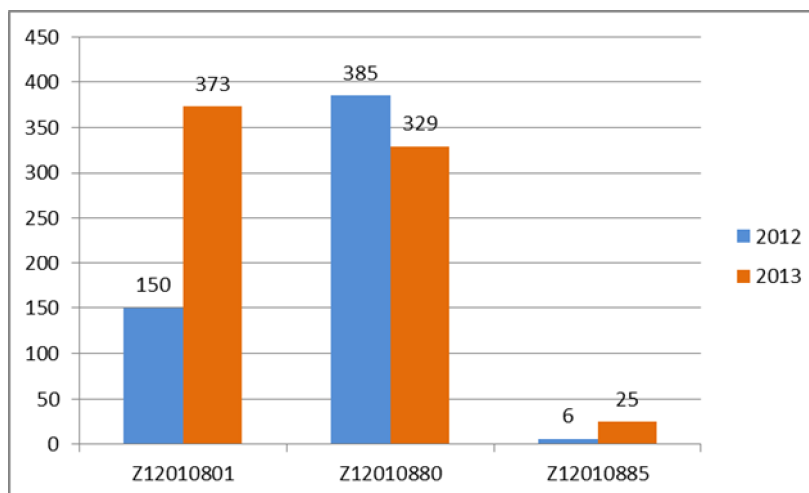
Ultrasonic scissors could be used both in open and endoscopic surgery; data from Italian national database “Flusso consumi” showed that the volumes of ultrasonic scissors purchased are equivalent for the two surgical procedures, with a slightly higher consumption of scissors for endoscopic surgery in 2012 and 2013 (Figure 3.3).

Figure 3.1: Consumption of K class devices in 2012 and 2013.



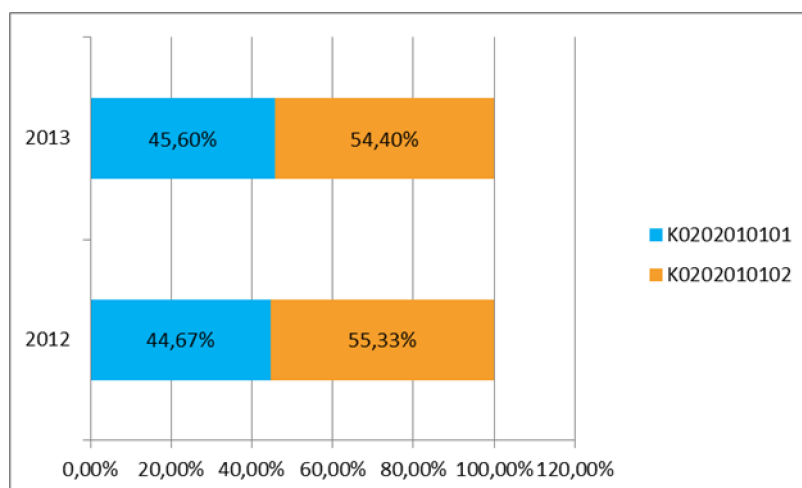
Source: Agenas analysis based on national database “Flusso consumi”, years 2012 and 2013.

Figure 3.2: Consumption of Z class devices in 2012 and 2013.



Source: Agenas analysis based on national database "Flusso consumi", years 2012 and 2013.

Figure 3.3: Distribution of ultrasonic scissors consumption for open and endoscopic surgery in 2012 and 2013.



Source: Agenas analysis based on national database "Flusso consumi", years 2012 and 2013.

We gathered the data on contract price of all devices in classes K and Z listed above, marketed in Italy. We identified the minimum and maximum price for 2012 and 2013.

We did not calculate the price range of the following CND classes:

- Single-use instruments for ultrasound surgery – Other (K02020199),
- Devices for surgery with ultrasound generator – Accessories (K020280),
- Instruments for ultrasound surgery – hardware components (Z12010880),
- Instruments for ultrasound surgery – specific materials (Z12010885).

The reason was mainly due to the wide heterogeneity of devices included in these classes. In the same class the categories of "accessories", "specific materials" and "components" were

completely different. For example footswitch and battery chargers or transducer and connecting cable had sizeably different prices. Calculation of the price range for each subgroup of these categories was beyond the aims of our study.

Table 3.4 reports the price range of ultrasonic scissors, for open and endoscopic surgery, in 2012 and 2013. No relevant difference in price range between the years considered was identified for both classes. The maximum price showed a slight increase of about 100 Euros for both classes, but the minimum price stayed relatively stable (Table 3.4). No data were available for ultrasonic hand pieces for 2012. Conversely, in 2013 the data showed a small variation between minimum and maximum price for both classes (Table 3.5). The class Z price range for both years is similar (Table 3.6).

Table 3.4: Price ranges of ultrasonic scissors in Euros.

CND Classes	2012		2013	
	min (€)	max (€)	min (€)	max (€)
K0202010101 - Single-use ultrasonic scissors for open surgery	245	600	258,4	712,5
K0202010102 - Single-use ultrasonic scissors for endoscopic surgery	313	675	300	760

Source: Agenas analysis based on national database "Flusso contratti", years 2012 and 2013.

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Table 3.5: Price ranges for ultrasonic hand pieces in Euros.

CND Classes	2012		2013	
	min (€)	max (€)	min (€)	max (€)
K0202010201 - Single-use hand piece for ultrasound open surgery	-	-	460	510
K0202010202 - Single-use hand piece for ultrasound endoscopic surgery	-	-	500	627

Source: Agenas analysis based on national database "Flusso consumi", years 2012 and 2013.

Table 3.6: Price ranges for ultrasonic scalpel in Euros.

CND Class	2012		2013	
	min (€)	max (€)	min (€)	max (€)
Z12010801 - Ultrasonic scalpel	2900	3000	2750.8	3000

Source: Agenas analysis based on national database "Flusso consumi", years 2012 and 2013.

A whole cost of about 30 million of Euro in 2013 can be calculated by the analysis of data on the volume of devices purchased by Italian hospitals. This amount is however underestimated as referred exclusively to the ultrasonic shears and does not take into account the other components and accessories.

4. Effectiveness and safety

4.1 Methods of literature review

A search strategy was conducted in February 2014 to identify studies in which the outcomes of patients that have been treated surgically (open or laparoscopic procedures) by using one of the ultrasonic energy devices identified, are compared to those of patients treated by conventional haemostatic techniques (suture ligation, standard electrocautery, vascular clips application) or other energy-based devices (radiofrequency or electrothermal surgical devices). No restrictions on the surgical procedures were applied. The search strategy is reported in Appendix 1. The main outcomes we considered were: operating time, hospital stay, blood loss, post-operative complications, and any reported death. We considered for inclusion secondary studies as well as comparative prospective primary studies published in English since January 2004.

Two authors (AM and CR) screened the records by title and abstract. Differences of opinion were resolved by discussion with a third author (TJ). Potentially included studies were retrieved in full-text and reconsidered for actual inclusion in the present evidence review. The evidence synthesis was structured by sub-groups, according to the surgical procedure (or groups of procedures) performed. When evidence overlaps in terms of intervention and population were identified, we included in our synthesis just the latest systematic reviews and update the evidence with the primary studies identified by our searches. Evidence on sub-groups of procedures for which no systematic reviews were retrieved was described using primary studies only. Data extraction was performed in double on standardised sheets.

Methodological quality of secondary studies was assessed by using the R-AMSTAR tool⁴³. Methodological quality of RCTs and CCTs was assessed using the criteria from the Cochrane Handbook for Systematic Reviews of Interventions³⁰.

4.2 Results of literature review

The PRISMA flow-chart of the studies is reported in Figure 4.1. The searches produced 365 records. Based on the relevance of titles and abstracts, 95 records were considered for full-text evaluation; two of them were not retrievable in full-text. This left 93 full-text studies assessed for eligibility. By cross-reference searches, we identified and included one further study. The first draft of the rapid HTA report, prepared according to such evidence, was available for public

consultation on the website of the Italian Ministry of Health for 60 days. Analysis of comments from reviewers allowed the inclusion of a further 7 primary studies.

Finally, 56 studies were actually included in the present evidence review (Figure 4.1). The list of excluded records with reasons for exclusion is reported in Appendix 2. Among the included studies, 14 were systematic reviews and 42 were primary studies. As among the systematic reviews, 7 were overlapping, we used only the most updated studies for our evidence synthesis (7 systematic reviews; see details in Appendix 3). The evidence synthesis was performed for the 16 surgical procedures (or groups of procedures) presented in Table 4.1. We described the evidence available for each procedure (or groups of procedures) following the alphabetical order. Secondary studies are described in Table 4.2; Primary studies are described in Table 4.3 to Table 4.6. We synthesised data on evidence tables only when more than two studies were available for the specific procedure.

Figure 4.1: Flow-chart of the studies according to PRISMA (adapted from: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097.

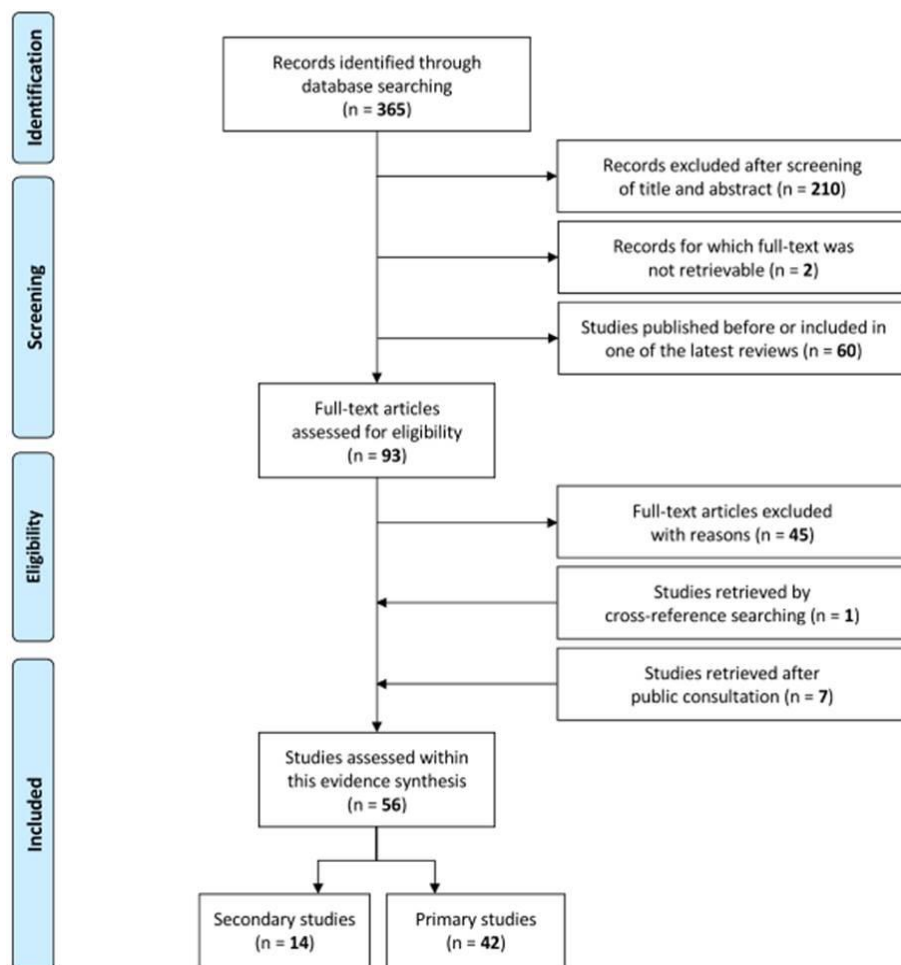


Table 4.1: Surgical procedures (or groups of procedures) identified for this evidence review (see Appendix 3).

Procedure (or group of procedures)	Action(s)
Abdominal surgical procedures (various)	Data extraction from the latest review (hepatic resection and laparoscopic adrenalectomy)
Breast surgery	Update of the latest review (mastectomy) and new synthesis of evidence (axillary lymph-node dissection)
Cardio-vascular surgery	Update of the latest review (radial artery harvest) and new synthesis of evidence (redo saphenous high ligation)
ENT oncologic surgery	New synthesis of evidence (neck dissection)
Gastrointestinal surgery (open procedures)	New synthesis of evidence (open total gastrectomy and left hemicolectomy, and gastrectomy with lymph node dissection)
Gynaecological surgery	New synthesis of evidence (various procedures)
Hemorrhoidectomy and ano-rectal surgery	New synthesis of evidence (haemorrhoidectomy and perineal rectosigmoidectomy with perineal levatorplasty)
Laparoscopic cholecystectomy	Update of the latest review (laparoscopic cholecystectomy)
Laparoscopic colorectal surgery	Data extraction from the latest review (laparoscopic colorectal resection)
Liver transplantation surgery	New synthesis of evidence (recipient hepatectomy with caval preservation)
Lung biopsy	New synthesis of evidence (lung parenchyma biopsy)
Orthopaedic surgery	New synthesis of evidence (total hip arthroplasty)
Pancreatic surgery	New synthesis of evidence (open pancreaticoduodenectomy or pylorus-preserving pancreaticoduodenectomy)
Plastic and reconstructive surgery	New synthesis of evidence (pectoralis major myocutaneous flap dissection and anterolateral thigh flap elevation)
Thyroid surgery	Update of the latest review (thyroid surgery)
Tonsillectomy	Update of the latest review (tonsillectomy)

Key: ENT = ear, nose, and throat.

4.2.1 Abdominal surgical procedures (various)

The latest review on abdominal surgical procedures, by Janssen et al., was aimed to report on available literature in a systematic manner with respect to the (cost) effectiveness of bipolar vessel-sealing devices in comparison to electrothermal or ultrasonic devices in laparoscopic and open abdominal procedures³⁷. Only RCTs were included. The authors identified 7 studies reporting on various surgical abdominal procedures. As evidence on laparoscopic colectomy has been reported separately within the present paragraph, we only report on hepatic resection (1 study, 24 cases) and laparoscopic adrenalectomy (1 study, 50 cases) from Janssen et al.³⁷. In both studies, the use of the ultrasonic energy device was linked to a longer mean operating

time (46.7 minutes longer in the hepatic resection and approximately 20 minutes longer per side in the laparoscopic adrenalectomy) and greater blood loss (485 ml vs. 210 ml in the hepatic resection, and 210 ml vs. 83 ml in the laparoscopic adrenalectomy). The mean difference in length of hospital stay among the various studies did not exceed one day, nor did it reach statistical significance in any of the procedures. None of the studies reported on quality of life or cost-effectiveness (Table 4.2). The device used in both the hepatic resection study was Harmonic (Ethicon Endo-Surgery) while a generic definition "Ultrasonic Shears" was reported in the adrenalectomy study.

4.2.2 Breast surgery

The latest review on breast surgical procedures, by Currie et al., was aimed to compare the operative outcomes of patients undergoing mastectomy for breast cancer between electrocautery and ultrasonic dissection¹⁷. All comparative trials were included. The authors identified 6 RCTs (287 cases) and reported on several outcomes, concluding that ultrasonic dissection and standard electrocautery appear to have similar outcomes, especially for postoperative drainage volume and seroma development, in the setting of mastectomy. The device used in all the RCTs included was Harmonic (Ethicon Endo-Surgery) (Table 4.2).

We included 6 primary studies reporting on the use of ultrasonic energy devices in breast surgical procedures for breast cancer^{11, 35, 50, 82, 83, 84}. Five of these studies were RCTs^{35, 50, 82, 83, 84}, one was CCT¹¹; the six studies reported on a total of 607 patients (Table 4.3). The outcomes for which a greater benefit was reported in the group underwent ultrasonic dissection were: operative time (reduced in 3 studies^{11, 83, 84}), drainage volume (reduced in 4 studies^{11, 50, 82, 83}), seroma formation (reduced in 5 studies^{11, 35, 50, 82, 84}), hospitalisation stay (reduced in 3 study^{35, 83, 83}), and intraoperative bleeding (reduced in 3 study^{50, 83, 84}). The device Harmonic Focus (Ethicon Endo-Surgery) was used in 4 studies^{11, 35, 82, 83}, while the other two studies^{50, 84} reported just Harmonic (Ethicon Endo-Surgery) without further specification.

4.2.3 Cardio-vascular surgery

The latest review on cardio-vascular surgical procedures, by Patel et al., was specific for radial artery harvest and aimed to address the question of whether radial arterial harvest with a harmonic scalpel produced a lower incidence of complications or was superior to conventional harvest with the diathermy or scissors and clip techniques⁶³. Both RCTs and CCTs were included. The authors identified 10 studies (5 RCTs and 5 CCTs for a total of 1,278 radial arteries harvested) and reported on incidence of complications, harvesting time, and any other relevant outcome, concluding that there is little convincing evidence in the literature to guide the decision to use an ultrasonic device over electrocautery for radial artery harvest (Table 4.2).

We identified 3 further primary studies in which ultrasonic artery harvest was compared to conventional or endoscopic technique. One study was CCT⁷ and two were RCT^{23, 85}; the three studies reported outcomes for a total of 138 cases (Table 4.4).

In the study by Brazio et al.⁷ the authors performed OCT examinations and reported less intimal defects and change in luminal volume of the harvested conduits when the ultrasonic device was used. In the study by Dumantepe et al.²³ the use of the ultrasonic device was linked to a shorter graft preparing time while blood flow parameters and endothelial cell structure were similar between the two groups. In the study by Shapira et al.⁸⁵ the endoscopic harvest associated with the use of the ultrasonic device was more time-consuming but not different from conventional techniques in terms of radial artery vasoreactivity or endothelial integrity compared with conventional harvest. The device Harmonic (Ethicon Endo-Surgery) was used in all the studies.

We identified also 2 primary studies on the use of ultrasonic energy devices for redo saphenous high ligation. A cohort of patients underwent the procedure within an RCT⁵⁴ and was then followed for 7 years⁵⁵ (Table 4.4). The patients were allocated in 3 groups: 12 underwent ultrasonic dissection; 12 underwent electrocoagulation; 12 underwent sharp dissection and ligation. At short-term, the authors concluded that there was no detectable advantage for the use of ultrasonic energy or electrocoagulation in recurrent saphenous high ligation. These findings were confirmed at the 7-years follow-up examinations. The device Harmonic (Ethicon Endo-Surgery) was used in the study.

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4.2.4 Ear, nose, and throat (ENT) oncologic surgery

No systematic reviews have been identified on ENT surgical procedures using ultrasonic energy devices.

We identified 2 primary studies both reporting on selective neck dissection for head and neck squamous cell carcinoma^{71, 79}.

In the study by Shin et al.⁷¹ 62 patients were enrolled in an RCT. After randomisation, 3 patients were excluded as they didn't meet the inclusion criteria. This left 59 patients allocated into the ultrasonic dissection group (29 patients; Harmonic Focus, Ethicon Endo-Surgery) and the conventional hand-tie group (30 patients). Since in the ultrasonic dissection group, 17 patients underwent bilateral neck dissection (thus, 46 neck dissections performed), and in the conventional hand-tie group, 14 patients underwent bilateral neck dissection (thus, 44 neck dissections performed) the authors reported comparative data in sub-groups: bilateral neck dissections and selective neck dissections. The analysis of bilateral neck dissections between the two groups showed that the mean operating time of the conventional group was

significantly longer than the ultrasonic group (158.6 ± 34.6 minutes vs. 112.1 ± 19.1 minutes; $P < 0.001$). Blood loss was significantly smaller in the ultrasonic group (163.8 ± 33.8 cc vs. 203.8 ± 36.5 cc; $P = 0.002$). The analysis of selective neck dissections between the two groups showed that the mean operating time was significantly shorter in the ultrasonic group (60.8 and 64.6 minutes vs. 76.2 and 85.7 minutes, depending on the level of the dissection). No significant difference was observed in the total amount of drainage, duration of drain placement, days of hospital stay, and perioperative complications.

In the study by Walen et al.⁷⁹ 31 patients (36 neck dissections performed) were enrolled in an RCT. Two subjects (one from each arm) were excluded from analysis and follow-up because of protocol violations. This left 34 neck dissections allocated in two groups: 17 dissections performed with the standard technique and 17 performed with an ultrasonic dissector (Harmonic Focus, Ethicon Endo-Surgery). The authors reported that the intraoperative blood loss was significantly lower in the ultrasonic group (62 ml vs. 158 ml; $P = 0.02$). There was no significant difference in operative time, total drain output, and hospital stay. None of the patients in both groups experienced any intraoperative complication (seroma, hematoma, wound infection).

4.2.5 Gastrointestinal surgery (open procedures)

No systematic reviews have been identified on gastrointestinal surgical procedures using ultrasonic energy devices.

We included 3 primary studies, one reporting on open total gastrectomy and left hemicolectomy⁸⁰, and two reporting on gastrectomy with lymph node dissection^{34, 86}.

In the study by Wilhelm et al.⁸⁰ 255 patients undergoing total gastrectomy for localised gastric cancer or hemicolectomy due to left-sided colonic cancer were enrolled in a multicentre RCT. After randomisation, 54 patients were excluded from the analysis since they did not meet inclusion criteria or were lost at follow-up. This left 100 patients in the ultrasonic dissection group (Harmonic Wave, Ethicon Endo-Surgery) and 101 patients in the conventional dissection group. The authors reported that the time-saving effect of ultrasonic dissection was noticeable in colonic resection (141 minutes vs. 160 minutes; $P = 0.133$), whereas operating times for gastric resection were almost equal. Median intraoperative blood loss was similar in the two groups. There was no significant difference in the total number of clips applied and the number of lymph nodes resected. Fewer sutures were required when the ultrasonic dissector was employed (median: 40 vs. 60 in the conventional group, $P < 0.001$). No relevant differences were observed in post-operative pain, median time until resumption of a normal diet, time to first mobilisation from bed, median overall hospital stay. Bowel movements resumed

significantly earlier in the ultrasonic dissection group (mean: 3.5 days vs. 4.0 days; $P=0.027$). No differences in quality of life (EORTC QLQ-30 questionnaire) were observed between the two groups.

In the study by Inoue et al.³⁴ 60 patients undergoing open gastric surgery were randomly assigned into two groups: ultrasonic group (Harmonic Focus, Ethicon Endo-Surgery), and conventional group. The authors reported that operative time was significantly shorter in the ultrasonic group (median: 238.5 minutes vs. 300.5 minutes; $P=0.0004$). Blood loss was also significantly lower in the ultrasonic group (median: 351.0 ml vs. 569.5 ml; $P=0.016$). No differences were observed in clinically significant blood loss (in terms of need for transfusions). Significantly fewer threads and gauzes were used in the ultrasonic group (5 packs vs. 11 packs, $P<0.0001$; 41 sheets vs. 60 sheets, $P=0.015$) while postoperative hospital stay did not differ between the two groups.

In the study by Choi et al.⁸⁶ 256 patients with gastric cancer who were to undergo gastrectomy with lymph node dissection were randomised in two groups: ultrasonic group (Harmonic, Ethicon Endo-Surgery) and conventional group. Three patients were excluded after randomisation leaving 128 and 125 patients, respectively. The authors reported a reduction of the mean operating time in the ultrasonic group (89.3 ± 15.6 minutes vs. 97.8 ± 17.2 minutes). No difference was found in the intraoperative blood loss and the amount of postoperative abdominal drainage. Rates of postoperative complications (postoperative bleeding, chylous drainage, pancreatitis and wound problems) were not different between the groups.

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4.2.6 Gynaecological surgery

No systematic reviews have been identified on gynaecological surgical procedures using ultrasonic energy devices.

We identified 6 primary studies reporting on the use of ultrasonic energy devices in gynaecological surgical procedures: three of them were CCTs^{38, 46, 48}, two were RCTs^{26, 49}, and one was a same-patient comparison study⁴; the six studies reported on a total of 614 patients within a wide range of procedures (Table 4.5).

In the study by Awadzi et al.⁴ 10 patients underwent open abdominal hysterectomy and bilateral salpingo-oophorectomy. In the same patient, the ultrasonic device (LOTUS Shears, SRA Developments) was used on one side and the bipolar diathermy device in the other side. The authors concluded that both devices were equally effective in securing haemostasis and no significant differences have been observed in terms of operating time and thermal damage.

In the study by Fitz-Gerald et al.²⁶ 40 women with benign lesions undergoing vaginal hysterectomy were randomised in two groups: ultrasonic dissection (21 patients; Harmonic,

Ethicon Endo-Surgery) and traditional suture ligations (19 patients). The authors reported on various outcomes concluding that the ultrasonic device offers no benefits in terms of operative time, reduction in clinically significant blood loss, and analgesic requirements.

In the study by Kartsionis et al.³⁸ 199 women with unsatisfactory colposcopy, positive endocervical curettage, discrepancies between pap smear and colposcopic examination, and suspicion of microinvasive disease undergoing cervical cone biopsy were divided in two groups: ultrasonic device (102 patients; Harmonic, Ethicon Endo-Surgery) and CO₂ laser device (97 patients). The authors reported on various outcomes concluding that, in terms of mean operating time, mean blood loss, mean cone volume and postoperative complications, the two technologies are substantially equivalent. The only benefit in favour of the ultrasonic device was related to the artefacts at the cone margins that were minimal.

In the study by Leblanc et al.⁴⁶ 14 women with BRCA mutation, scheduled for bilateral salpingo-oophorectomy (BSO) and undergoing ovarian transection, were divided into four groups: scissors and bipolar coagulation (4 patients); stapler straight or roticulator with vascular tape (3 patients); bipolar scalpel (4 patients); ultrasonic device (3; Harmonic, Ethicon Endo-Surgery). The authors reported on various outcomes concluding that scissors and bipolar coagulation, and stapler with vascular tape are the least traumatic methods to divide the ovaries, both providing the best tissue margins for a thorough pathological examination.

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In the study by Li et al.⁴⁸ 191 women undergoing laparoscopic excision of benign ovarian cysts were divided in three groups: bipolar device (64 patients), ultrasonic device (57 patients; Harmonic, Ethicon Endo-Surgery), conventional sutures (70 patients; open surgery). The authors reported on various outcomes concluding that bipolar or ultrasonic coagulation of the ovarian parenchyma during cystectomy adversely affect ovarian reserve.

In the study by Litta et al.⁴⁹ 160 pre-menopausal women with symptomatic uterine leiomyoma undergoing laparoscopic myomectomy were randomised in two groups: electrosurgery device with a vasoconstrictive solution (80 patients); ultrasonic device (80 patients; Harmonic, Ethicon Endo-Surgery). The authors reported on various outcomes concluding that the use of the ultrasonic device for laparoscopic myomectomy reduces the total operative time, the intraoperative blood loss, and postoperative pain without increasing the surgical difficulty.

4.2.7 Haemorrhoidectomy and ano-rectal surgery

No systematic reviews have been identified on haemorrhoidectomy and ano-rectal surgical procedures performed using ultrasonic energy devices.

We included 9 primary studies reporting on the use of ultrasonic energy devices in haemorrhoidectomy (8 studies) and perineal rectosigmoidectomy with perineal levatorplasty (1

study). All the 9 studies included were RCT; the 8 studies on haemorrhoidectomy reported on a total of 645 patients (Table 4.6).

In the study by Abo-hashem et al.¹ 64 patients with haemorrhoidal disease (Grade III and IV) were randomised in two groups of 32 patients respectively: ultrasonic device group (Harmonic, Ethicon Endo-Surgery) and bipolar electro-cautery group. The authors reported on pain and post-operative complications, concluding that, although the use of the ultrasonic device is linked to a prolonged learning curve and increased cost over the electro-cautery device, it carries several advantages: reduced postoperative pain, reduced doses of narcotic analgesia and diclofenac sodium postoperatively, and excellent haemostasis; moreover, significantly reduced incidence of postoperative urine retention and reduced time off-work for the patients have been observed.

In the study by Bulus et al.⁸⁷ 151 patients with haemorrhoidal disease (Grade III and IV) were randomised in two groups: ultrasonic device group (80 patients; Harmonic, Ethicon Endo-Surgery) and electrocautery group (71 patients). The authors reported on operating time, postoperative pain, number of issued analgesics, length of hospital stay, time to return to normal activity, and postoperative complications, showing that all the observed outcomes were significantly better in the ultrasonic group.

In the study by Chung et al.¹² 88 patients with haemorrhoidal disease (Grade III) were randomised in two groups: ultrasonic device group (45 patients; Harmonic, Ethicon Endo-Surgery) and stapling device group (43 patients). The authors reported on several outcomes concluding that stapled haemorrhoidopexy in Grade III haemorrhoidal disease patients is linked to reduced pain, shorter length of hospital stay, and earlier return to work.

In the study by Ivanov et al.³⁶ 67 patients with haemorrhoidal disease (Grade III and IV) were randomised in two groups: ultrasonic device group (35 patients; Harmonic, Ethicon Endo-Surgery) and standard Milligan-Morgan technique (32 patients). The authors reported mainly on post-operative pain and post-operative complications concluding that the use of the ultrasonic device statistically significantly reduced postoperative pain.

In the study by Kwok et al.⁴⁴ 47 patients with haemorrhoidal disease (Grade III and IV) were randomised in two groups: electrocautery device group (24 patients) and ultrasonic device group (23 patients; Harmonic, Ethicon Endo-Surgery). The authors reported on several outcome concluding that the electrocautery device has a shorter operating time and produces less postoperative pain than the ultrasonic device.

In the study by Omar et al.⁸⁸ 72 patients with haemorrhoidal disease (Grade III and IV) were randomised in two groups of 32 patients respectively: ultrasonic device group (Harmonic, Ethicon Endo-Surgery) and conventional monopolar diathermy group. The authors reported on

operative time, intraoperative blood loss, hospital stay, time off of work, postoperative pain and analgesics requirement showing that all the observed outcomes were better in the ultrasonic group.

In the study by Ozer et al.⁶² 87 patients with haemorrhoidal disease (Grade III and IV) were randomised in four groups: open ultrasonic procedure (22 patients; Harmonic, Ethicon Endo-Surgery); closed ultrasonic procedure (22 patients; Harmonic, Ethicon Endo-Surgery); Milligan-Morgan procedure (22 patients); Ferguson procedure (21 patients). The authors reported mainly on postoperative pain and analgesic consumption and concluded that the use of the ultrasonic device in haemorrhoidectomy reduces postoperative pain, analgesic consumption, operation time, and bleeding.

In the study by Peker et al.⁶⁴ 69 patients with haemorrhoidal disease (Grade III and IV) were randomised in three groups of 23 patients respectively: electrocautery device group, ultrasonic device group (Harmonic, Ethicon Endo-Surgery), conventional Milligan-Morgan technique group. The authors reported on several outcomes concluding that, even if the energy devices provide some advantages (such as reducing operation time and decreasing bleeding), there may be some disadvantages in terms of post-operative pain, analgesic requirement, and wound healing rate. They concluded that conventional surgical technique for haemorrhoidectomy remains safer and more accessible.

The study by Boccasanta et al.⁶ is the only reporting on perineal rectosigmoidectomy with perineal levatorplasty. Forty patients with full-thickness rectal prolapse and faecal incontinence were randomised in two groups of 20 patients respectively: conventional technique with monopolar electrocautery and hand-sewn anastomosis, and ultrasonic device and circular stapler (Harmonic, Ethicon Endo-Surgery). The authors reported on several outcomes, at short- and long-term, concluding that the clinical and functional long-term results were not influenced by surgical instruments and type of anastomosis; however, the use of the ultrasonic device and circular stapler was associated with less intra-operative blood loss, shorter operative time, and shorter hospital stay.

4.2.8 Laparoscopic cholecystectomy

The latest review on laparoscopic cholecystectomy, by Xiong et al., was aimed to investigate the safety and efficacy of ultrasonic energy and monopolar electrosurgical energy in the setting of laparoscopic cholecystectomy⁸¹. Only RCTs were included. The authors identified 11 RCTs (1,434 patients) and reported on several outcomes, concluding that differences in mean operation time, mean blood loss, mean hospital stay, gallbladder perforation, and postoperative abdominal pain score at 24 hours were statistically significant between the two groups, in

favour of the use of ultrasonic energy. However, there were no differences in operation conversion, bile leakage, intra-abdominal collections, and postoperative nausea at 24 hours (Table 4.2).

We identified a new primary study on laparoscopic cholecystectomy⁵¹ in which 60 patients were randomly assigned to either monopolar electrocautery or ultrasonic dissection. In accordance with the review by Xiong et al.⁸¹, the authors reported that ultrasonic dissection is associated with a statistically significant lower incidence of gallbladder perforation, and duration of surgery. Moreover, the study by Mahabaleswar et al.⁵¹ reported lower incidence of bile leakage and reduction of lens cleaning time in favour of the ultrasonic dissection. There was no statistical difference in stone spillage between the groups.

4.2.9 Laparoscopic colorectal surgery

The latest review on laparoscopic colorectal surgical procedures, by Di Lorenzo et al., was aimed to appraise the quality of evidence available in the literature and to provide insightful clinical information within the technology of choice (electrothermal bipolar vessel sealing versus ultrasonic energy) for elective laparoscopic colorectal resection in adults affected by either benign or malignant colorectal diseases²¹. Both RCTs and CCTs were included. The authors identified 2 RCTs and 2 CCTs (408 procedures) and reported on operative time and intraoperative blood loss. Even though findings were against the use of ultrasonic energy device (i.e., in favour of the bipolar vessel sealing device) in terms of operative time and intraoperative blood loss, several elements hamper the authors' conclusions (difference in study designs, small number of enrolled patients, difference in evaluated outcomes, lack of a large number of RCTs) and increased the heterogeneity of the meta-analysis. The authors suggest to use caution and solicit for more adequately designed RCTs with larger samples to confirm their results. The ultrasonic device used in the included studies was Harmonic (Ethicon Endo-Surgery) (Table 4.2).

4.2.10 Liver transplantation surgery

No systematic reviews have been identified on hepatic surgical procedures using ultrasonic energy devices.

We identified 1 primary study⁵⁸ in which 16 patients undergoing elective living donor liver transplantation were randomised in two groups: conventional technique group and ultrasonic group. Recipient hepatectomy with caval preservation was performed in all the patients. Among 144 short hepatic veins in 16 patients, 61 were transected using an ultrasonic device (Harmonic, Ethicon Endo-Surgery), 83 were ligated traditionally (i.e., knot tying). The authors reported similar overall bleeding rates between the two groups. Subgroup analysis regarding

vein diameter showed that the ultrasonic device was as safe as traditional ligation for veins of ≤ 2 mm diameter and that traditional ligation was safer for 3 mm or larger veins. With traditional knot tying, an increased risk of bleeding was observed with the decreasing of vein diameter. Both total and per vessel procedure time did not differ between the groups and no postoperative bleeding complications were observed.

4.2.11 Lung biopsy

No systematic reviews have been identified on lung biopsy using ultrasonic energy devices.

We identified 1 primary study⁵³ in which 40 patients undergoing surgical lung parenchyma biopsy for suspicion of diffuse parenchymal lung disease or multinodular appearances of unknown pathology were randomised in two groups: endostapler group, and ultrasonic device group (Harmonic, Ethicon Endo-Surgery). The authors reported that a significant advantage of 16 minutes in average operation time was found in favour of the ultrasonic device (30.75 minutes vs. 46.9 minutes). No differences were observed in average drainage duration, pleural fluid volume, minor complication rates, and in-hospital stays.

4.2.12 Orthopaedic surgery

No systematic reviews have been identified on orthopaedic surgical procedures performed by ultrasonic energy devices.

We identified 1 primary study⁷⁶ in which 30 consecutive patients undergoing total hip arthroplasty due to primary osteoarthritis were randomly assigned to either the ultrasonic group (i.e., the surgery was performed entirely using the Harmonic with sharp curved blade, Ethicon Endo-Surgery) or the conventional technique group (i.e., electrocautery and a standard blade). The authors reported that the mean operative time was longer in the ultrasonic group (61 minutes vs. 54 minutes; $P < 0.05$). No differences have been observed in postoperative pain or use of paracetamol; the use of tramadol was reduced in the ultrasonic group (at the 7th day: 83.3 mg vs. 113.3 mg; $P < 0.05$). Drainage volume was significantly lower in the ultrasonic group at 24 hours (332 ml vs. 429 ml; $P < 0.05$) and at 48 hours (429 ml vs. 537 ml; $P < 0.05$). Markers related to soft tissue damage were found lower in the ultrasonic group (C-reactive protein blood levels: 75 mg/l vs. 96 mg/l at the 3rd day, $P < 0.05$, and 26 mg/l vs. 54 mg/l at the 7th day, $P < 0.01$; Creatine kinase blood levels: 2.4 ukat/l vs. 5.3 ukat/l at the 3rd day, $P < 0.01$, and 1.1 ukat/l vs. 1.8 ukat/l at the 7th day, $P < 0.01$).

4.2.13 Pancreatic surgery

No systematic reviews have been identified on pancreatic surgical procedures performed by ultrasonic energy devices.

We identified 1 primary study⁷⁸ in which 255 patients undergoing open pancreatic surgery due to tumour of the pancreatic head were randomised in two groups: ultrasonic dissection and conventional dissection. After randomisation, 154 patients were excluded from the analysis since they did not meet inclusion criteria. This left 57 patients in the ultrasonic dissection group (Harmonic Wave, Ethicon Endo-Surgery) and 44 patients in the conventional dissection group. The authors reported that the difference in the operation time was not statistically significant between the two groups. No learning curve effect was observed comparing data between the first 20 patients and the remaining 37 in the ultrasonic dissection group. The median calculated blood loss was equal in both groups. No adverse events related to the ultrasonic device were recorded. The overall complication rate was comparable in both groups.

4.2.14 Plastic and reconstructive surgery

No systematic reviews have been identified on plastic and reconstructive surgical procedures performed by ultrasonic energy devices.

We identified 2 primary studies presenting outcomes for pectoralis major myocutaneous flap dissection¹⁹ and anterolateral thigh flap elevation²⁹.

In the study by Deo et al.¹⁹ 30 patients with oral cancer, for whom resection and reconstruction using a pectoralis major myocutaneous flap was planned, were recruited in a prospective RCT and assigned to electrocautery group (15 patients) or ultrasonic group (15 patients; Harmonic, Ethicon Endo-Surgery). The authors reported that the mean operative duration for flap dissection was found less in the ultrasonic group (84 minutes vs. 47 minutes; $P < 0.001$), as well as blood loss (129 ml vs. 36 ml; $P < 0.001$), and total drainage volume (551 ml vs. 302 ml; $P < 0.001$).

In the study by Hamahata et al.²⁹ 10 patients with head and neck cancer who had been scheduled for cancer resection and reconstruction with the free anterolateral thigh flap were randomised in two groups: the ultrasonic group (5 patients; Harmonic Focus, Ethicon Endo-Surgery) and the electrocautery group (5 patients). The authors reported differences in favour of the ultrasonic group in the operation time (63 minutes vs. 81.4 minutes; $P = 0.01$) and in the number of hand ligations (3.6 vs. 26; $P < 0.001$). Differences in intraoperative bleeding and postoperative drainage volume were not statistically significant.

4.2.15 Thyroid surgery

The latest review on thyroid surgery, by Contin et al., was aimed to conduct a three-way comparison between energised vessel sealing systems and conventional "clamp-and-tie" or traditional electro-surgical methods to evaluate operation time and post-operative complications¹⁵. Only RCTs were included. The authors identified 35 RCTs (4,061 patients) and

reported primarily on operation time concluding that using energised vessel sealing systems can significantly lead to its reduction. Additionally, the use of ultrasonic devices was associated with several small-scale benefits, i.e. reduced intra- and postoperative blood loss, reduced rates of transient hypocalcaemia and postoperative pain as well as a reduced duration of hospital stay. The conventional techniques for haemostasis were not superior in any outcome investigated. No differences were observed in the clinically important safety outcomes of recurrent nerve palsy and rates of clinically symptomatic hypocalcaemia. The devices used in the included RCTs were Harmonic and Harmonic Focus (both Ethicon Endo-Surgery) (Table 4.2).

We identified 3 further primary studies in which ultrasonic dissection was compared to conventional techniques in the setting of thyroid surgery. Two of these studies were CCTs^{13, 70} so they were excluded from the review by Contin et al.¹⁵, one was RCT⁶⁷; the three studies involved a total of 606 patients (Table 4.6). In accordance with the review by Contin et al.¹⁵, the operation time was shorter in the ultrasonic dissection group and this was observed, with statistical significance, in all the 3 studies. All the other clinical outcomes investigated, such as postoperative transient complications, transient/permanent hypocalcaemia, permanent laryngeal nerve palsy, were comparable between the two groups. The device Harmonic Focus (Ethicon Endo-Surgery) was used in one study¹³, while in the other 2 studies^{70, 67} this was not clearly reported.

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4.2.16 Tonsillectomy

The latest review on tonsillectomy, by Alexiou et al.², was aimed to systematically review evidence regarding modern technology-assisted tonsillectomy pertaining to operative time, intraoperative and postoperative bleeding, postoperative pain, and other outcomes. Only RCTs were included. The authors identified 33 RCTs (3,139 patients) reporting on several outcomes concluding that the ultrasonic and radiofrequency ablation devices that have been used during the past decade, in an attempt to decrease postoperative morbidity in terms of pain and bleeding, do not provide any significant advantage over the conventional techniques (cold steel and/or electrocautery dissection). The only outcome that differed significantly in tonsillectomies performed using ultrasonic devices compared with those using conventional techniques was perioperative bleeding. The device used in the included RCTs was Harmonic (Ethicon Endo-Surgery) (Table 4.2).

We identified a further primary study³⁹ in which 200 patients (age: 5-12 years) undergoing tonsillectomy were distributed in two groups: 100 patients in the ultrasonic dissection group (Harmonic, Ethicon Endo-Surgery) and 100 patients in the conventional group (cold dissection and haemostasis secured with unipolar diathermy). The authors reported, in clear contrast with

the review by Alexiou et al.², that intensity of pain was less for the ultrasonic dissection group (mean value of pain score at one day: 3.42 vs. 5.02, $P < 0.0001$; at three days: 4.59 vs. 6.32, $P < 0.0001$; at five days: 3.16 vs. 4.88, $P < 0.0001$; at ten days: 1.67 vs. 2.77, $P < 0.0001$) as well as that the return to normal diet was earlier in the ultrasonic dissection group: a mean of 5.06 days vs. 7.01 days ($P < 0.0001$). No significant differences were observed in wound healing and bleeding while significant collateral damages were observed in the conventional group: 14 cases (14%) of oedema of uvula and 2 cases (2%) of minor burns of tongue and angle of mouth.

Table 4.2: Synthesis of secondary studies reporting on the use of ultrasonic energy devices.

Authors [ref.] Year	Intervention(s)	Type of studies included	Number of studies included; Number of cases	Comparisons	Main Study Findings	Authors' Conclusions
Alexiou et al., 2011	Total tonsillectomy	RCT	33 RCTs; 3,139 patients.	Vessel sealing systems (VSS), Harmonic Scalpel (HS), Radiofrequency ablation (RFA) VS Conventional technique of cold steel and/or electrocautery dissection (CS/EC).	No significant difference was found between HS versus CS/EC regarding operative time (WMD, -0.10 minutes; 95% CI, -6.26 to 6.05 minutes; 655 cases), postoperative bleeding (OR, 0.78; 95% CI, 0.50 to 1.23; 1473 cases), and averaged postoperative pain (SMD, -0.38; 95% CI, -1.20 to 0.43; 517 cases). However, perioperative bleeding was significantly less in the HS group (WMD, -37.71 ml; 95% CI, -52.98 to -22.43 ml; 535 cases).	In conclusion, despite its limitations, this meta-analysis provides evidence that the use of HS for tonsillectomy is equivalent to the use of the conventional CS/ES technique.
Contin et al., 2013	Open partial and/or total thyroidectomy	RCT	35 RCTs; 4,061 patients.	Ultrasonic systems (HS) VS Electrothermal bipolar vessel sealing systems (LS) VS Conventional techniques for haemostasis (CH).	All trials comparing CH with HS (2,573 patients) demonstrated a significant reduction of operation time with HS. The pooled estimate was 23.6 min (95% CI, [19.5, 27.6]; $P < 0.001$; 24 studies, $I^2=89\%$). The comparison of HS with LS (673 patients) provided a reduction in operation time by 9.3 min when using HS (95% CI, [-17.8, -0.8]; $P = 0.032$; 6 studies, $I^2=91\%$). Intraoperative blood loss: The pooled value was lower by 28.5 ml for HS compared with CH ($P < 0.001$) but not significant for HS compared with LS ($P=0.448$). Statistical heterogeneity was high. Length of hospital stay: Lower by 0.28 days for the HS compared with the CH. High degree of heterogeneity. Amount of drainage fluid after 24 h was significantly higher for CH compared with HS by 11.2 ml. No differences in: transitory and definitive laryngeal palsy, transient and persistent hypocalcaemia, rate of hematoma/seroma, reoperation and wound infection. Postoperative pain and cosmetic result have not been pooled.	Using energised vessel-sealing systems can significantly reduce operation time. Additionally, the use of HS was associated with several small-scale benefits, i.e. reduced intra- and postoperative blood loss, reduced rates of transient hypocalcaemia and postoperative pain as well as a reduced duration of hospital stay. The conventional technique was not superior in any outcome investigated. The clinically important safety outcomes of recurrent nerve palsy and rates of clinically symptomatic hypocalcaemia were not negatively affected by using any of the energised vessel systems.

Currie et al., 2012	Mastectomy for breast cancer	Comparative trials	6 RCTs; 287 cases.	Ultrasonic dissection (UD) VS Standard electrocautery (SE)	Total postoperative drainage (6 studies): the mean drainage volume was 699 ml and 896 ml for UD and SE, respectively. There was no significant difference in total postoperative drainage between the two groups (statistical heterogeneity was significant). Seroma development (5 studies): no statistically significant difference between the two groups (no significant statistical heterogeneity). Intra-operative blood loss (5 studies): the mean blood loss volume was 236 ml and 365 ml for UD and SE, respectively (statistical heterogeneity was significant). Wound complications (5 studies): no statistically significant difference between the two groups (no significant statistical heterogeneity).	Ultrasonic dissection and standard electrocautery appear to have similar outcomes, especially for postoperative drainage and seroma development, in the setting of mastectomy. On the basis of current evidence, it appears that further cost-effectiveness investigation may be warranted in any future trial in order to establish the benefits of further introduction of this technology.
Di Lorenzo et al., 2012	Laparoscopic colorectal surgery	RCT; CCT	2 RCTs; 2 CCTs; 408 procedures.	Electrothermal bipolar vessel sealing (EBVS) VS Ultrasound energy (UE)	The time for dissection was significantly shorter with the use of EBVS compared to UE (P=0.013). However, when the two more complete series were considered, no statistically significant difference was obtained. The analysis shows a statistically significant difference in the combined mean of blood loss between the two instruments favouring EBVS.	The different study designs, the small number of enrolled patients with different evaluated outcomes, and the lack of a large number of RCTs increased the heterogeneity of our meta-analysis. Consequently, even if EBVS seems to be favoured in terms of intraoperative blood loss and operative time, our findings should be interpreted with caution. Nevertheless, more adequately designed RCTs with larger samples are required to confirm and enhance the results of this meta-analysis.

Janssen et al., 2012	Abdominal surgical procedures	RCT	7 RCTs; 554 patients.	Vessel sealing device (VS) VS Other electrothermal or ultrasonic haemostatic (US) devices	Operating time: In the laparoscopic adrenalectomy study, the mean operating time was approximately 20 min shorter per side in using VS versus US, with the difference statistically significant. In the hepatic resection study there was a trend toward shorter mean operating time (46.7 min shorter, p = 0.08) in using VS versus US. Blood loss: Total blood loss was less with the use of VS devices in comparison with US devices during laparoscopic adrenalectomies and hepatic resections, whereas the other RCTs found no differences in registered blood loss. None of the studies assessed quality of life or return to work. Cost-effectiveness or utility analyses were not performed.	We have to conclude that yet more well-designed studies are needed before giving appropriate advice on the preferred haemostatic device for abdominal surgery in terms of haemostatic effect, complications, and cost effectiveness.
Patel et al., 2006	Radial artery harvest	RCT; CCT	5 RCTs; 5 CCTs; 1,278 radial arteries.	Ultrasonic harvesting (US) VS Standard harvesting techniques (ST)	Of 5 studies reporting time to harvest, 3 report no difference and 2 report that US is quicker. Six studies reported the marked reduction in the number of clips used with the US. Two studies reported a small benefit in reducing spasm. Two studies looked at the artery electron microscopically but no significant differences were seen. Two studies reported less numbness and 2 studies no difference in numbness post-operatively. Three studies looked at the results angiographically or by flow assessment, 1 study showed no difference, 1 study reported US superiority, and 1 study reported that scissors and clips were superior. All studies were small and either used a single surgeon or a very small number of surgeons to harvest the radial artery. Highly subjective outcome measures to assess numbness and spasm were employed, together with poor or absent blinding of assessors.	We conclude that there is little convincing evidence in the literature to guide the decision to use an ultrasonic scalpel over electrocautery for radial artery harvest.

Xiong et al., 2012	Laparoscopic cholecystectomy	RCT	11 RCTs; 1,434 patients.	Ultrasonic energy device (US) VS Monopolar electrosurgical energy device (MP)	<p>Mean operation time (7 trials): significantly shorter mean operation time in the US group (WMD, - 17.86; 95% CI, - 21.72 to - 14.01; P < .00001). Inclusion of low-quality trials showed a similar effect (WMD, - 17.57; 95% CI, - 23.33 to - 11.80; P < .00001).</p> <p>Mean blood loss (3 trials): statistically significant reduction in the outcome measure using US (WMD, - 41.02; 95% CI, - 42.67 to - 39.38, P < .00001).</p> <p>Mean hospital stay (6 trials): significant reduction of mean hospital stay in the US group (WMD, - 0.43; 95% CI, - 0.76 to - 0.09, P = .01).</p> <p>Operation conversion (6 trials): No statistically significant difference was found between the two groups</p> <p>Gallbladder perforation (6 trials): The pooled result favoured the US (OR, 0.31; 95% CI, 0.22–0.44; P < .00001).</p> <p>Bile leakage (5 trials): US energy significantly reduced the incidence of bile leakage (OR, 0.31; 95% CI, 0.06–1.56; P = .16).</p> <p>Intra-abdominal collections (2 trials): No difference.</p> <p>Postoperative abdominal pain at 24 hours (4 trials): US energy resulted in a significant reduction in postoperative abdominal pain (WMD, - 1.13; 95% CI, - 1.23 to - 1.02; P < .0001).</p> <p>Postoperative nausea at 24 hours (2 trials): No difference.</p>	
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Key: = CCT = Controlled clinical trial; RCT = Randomised clinical trials.

Table 4.3: Synthesis of primary studies reporting on the use of ultrasonic energy devices in breast surgical procedures.

Authors [ref.] Year Study Design	Population	Intervention	Groups (num. of patients)	Ultrasonic Device Assessed	Main Study Findings	Authors' Conclusions
Böhm et al. 2012 RCT	Women with confirmed primary breast cancer or ductal carcinoma in situ (DCIS)	Breast-conserving surgery for primary breast cancer	Group A (52 F): ultrasonic dissection; Group B (54 F): conventional surgery using scalpel and electrocautery	Harmonic Focus	There was no difference in operative time between groups. Total drainage volume of the breast increased in group B: 60.0 ml (40.0-111.2) vs. 22.5 ml (11.3-40.0); p<0.001. Breast drainage removed earlier in group A: 3.3 days (±1.1) vs. 2.1 (±1.1); p<0.001. Total drainage volume of the axillary region increased in group B: 131.5 ml (72.8-283.8) vs. 82.5 ml (56.3-115.0); p<0.017. Axillary drainage removed earlier in group A: 3.5 days (3.0-4.3) vs. 2.0 (1.8-3.0); p=0.001. Median length of stay increased for group B: 4.5 days (4-6) vs. 4.0 days (3-5); p<0.001. Group A: less intramammary seroma (p=0.042), less pain in the breast (median pain score 1.0 (0.0-3.0) vs. 0.5 (0.0-2.0)) and axillary region (median pain score 2.0 (0.0-3.3) vs. 0.0 (0.0-2.0)); p<0.001. Less additional analgesics postoperatively in favour of group A: 15 (27.8%) vs. 5 (9.6%); p=0.024.	Despite higher costs for this device instead of conventional instruments, the Harmonic device is safe to use and provides key benefits in intraoperative technique, postoperative outcome, and rate of complications in breast cancer surgery. However, further randomized trials are needed to validate our results.
Cavallaro et al. 2011 CCT	Patients requiring ALND for breast cancer or suspected metastatic skin melanoma	Axillary lymph-node dissection (ALND)	Group A (33 F / 14 M): ultrasonic dissection; Group B (28 F / 17 M): conventional dissection (combination of clips, ties, and cautery).	Harmonic Focus	Operating time lower in group A (47.6 ± 22.1 vs. 55.4 ± 29.3 minutes; P<0.05). Total drain volume lower in group A (323.65 ± 221.7 vs. 454 ± 315.7; P<0.005). Drain removed earlier in group A (5.6 ± 0.8 vs. 7.1 ± 1.3 days; P<0.005). Seroma incidence: 8.5% (4 of 47) in group A vs. 15.5% (7 of 45) in group B (P<0.05).	Results of the present study, even though there were not many patients and the study was not randomized (because of the lack of regular availability of the device), are significant. The use of Harmonic Focus during ALND is effective in reducing operating time, drain volume and complications.

He et al. 2012 RCT	Women with confirmed T1-3 N1-2 breast cancer	Mastectomy (or breast-conserving) and axillary lymph node dissection	Group A (64 F): ultrasonic dissection Group B (64 F): electrocautery	Harmonic Focus	Significant statistical difference was found in operating time (92±15 min vs. 117±20 min; P<0.05), mean volume of blood loss (75.6±25.5 ml vs. 190.4±96.2 ml), mean total volume of drainage fluid (656.8±150.5 ml vs. 985.7±590.6 ml), and mean number of days until removal of the drain (8.9±1.5 days vs. 13.5±3.9 days). The average number of postoperative length of stay was also significantly less in group A (11.5 vs. 14.7 days, P<0.001). None of the patients in either group developed wound infection, postoperative bleeding, hematoma, pneumothorax, skin burns or flap necrosis.	Using Harmonic Focus significantly diminished operative time, blood loss, total drainage volume, days of stay, and visual analogue scale as compared with traditional electrocautery. There was no statistical difference between the 2 groups regarding seroma, hematoma, and flap necrosis.
Iovino et al. 2011 RCT	Patients with breast cancer	Breast surgery and axillary lymph-node dissection	Group A (30 F): traditional dissection; Group B (30 F): ultrasonic dissection.	Harmonic Focus	No significant differences observed in terms of operative time. A statistically significant benefit was observed in terms of: Intraoperative blood loss (median: 60 vs. 40 ml); Drainage volume (median for chest wall and axilla: 50 and 200 vs. 30 and 60 ml/day); Axilla seroma formation (30% vs. 3.3%); Hospital stay duration (median: 5 vs. 3 days). No postoperative hematoma, wound infections, and chest wall seroma were observed.	The use of the harmonic scalpel was shown to reduce the magnitude of seromas in axilla and hospitalization stay. Although statistically significant, our results are limited by the small number of patients enrolled; thus, further randomized controlled studies on larger series comparing this techniques with others conventional techniques are necessary.

Lumachi et al. 2013 RCT	Women with confirmed primary infiltrating ductal breast cancer	Modified radical mastectomy or breast-conserving surgery (partial mastectomy) and axillary lymph-node dissection (ALND)	Group A (68 F): ultrasonic dissection; Group B (71 F): conventional technique.	Harmonic	A statistically significant benefit was observed in terms of: Operative time (95.7 ± 22.4 vs. 109.1 ± 25.7 minutes; P=0.001); Intraoperative blood loss (56.1 ± 12.5 vs. 85.8 ± 15.5 ml; P<0.001); Drainage output (412.6 ± 83.7 vs. 456.9 ± 69.0 ml; P<0.001); Days of drain placement (5.2 ± 2.0 vs. 6.2 ± 1.2 days; P<0.001). Hospital stay and postoperative office visits were also reduced, but the differences were not significant. Cases of seroma formation were 9/59 vs. 20/51 (P=0.030).	Our study confirms that, in patients with breast cancer requiring ALND the use of ultrasonic dissector is more time efficient than conventional surgery, and reduces intraoperative bleeding, the amount of drainage, and the risk of seroma formation.
Yilmaz et al. 2011 RCT	Breast cancer patients	Modified radical mastectomy	Group A (27): scalpel dissection; Group B (26): electrocautery; Group C (29): ultrasonic dissection	Harmonic	Operation time was significantly higher in group A (min): 158.8±36.1 vs. 134±41.6 vs. 121±28.2 (p=0.001). Bleeding was significantly higher in group A (ml): 720.7±245 vs. 368±156 vs. 375±176 (p=0.001). Seroma incidence was higher in group B (%): 37.0 vs. 53.8 vs. 34.4 (p=0.003). No difference between groups with respect to hematoma, surgical site infections, ecchymosis, days needed for vacuum drain removal, the amount of seroma on the first postoperative day or total drainage levels.	Ultrasonic dissector was found to decrease the duration of surgery by diminishing the bleeding without increasing the seroma incidence. Ultrasonic dissector was as efficient as electrocautery in terms of hemostasis and decreasing the operation time yet it is as harmless as scissor in terms of seroma formation. In short, ultrasonic dissector was advantageous compared to the other two devices.

Key: ALND = Axillary lymph-node dissection; CCT = Controlled clinical trial; RCT = Randomised clinical trials.

Table 4.4: Synthesis of primary studies reporting on the use of ultrasonic energy devices in cardio-vascular surgical procedures.

Authors [ref.] Year Study Design	Population	Intervention	Groups (num. of patients)	Ultrasonic Device Assessed	Main Study Findings	Authors' Conclusions
Brazio et al. 2008 CCT	Patients undergoing coronary artery bypass grafting	Harvest of radial artery conduit for coronary artery bypass grafting	Group A (15): ultrasonic device; Group B (29): electrocautery and clips	Harmonic	Luminal volume after harvesting: 921 ± 80 vs. $559 \pm 69 \text{ mm}^3$ ($P=0.003$). Endothelial integrity measured by CD31 staining of random biopsy specimens did not show differences between harvesting techniques. OCT examination demonstrated that 11 (73%) of 15 RAs harvested in group A had a completely normal intimal layer, with no evidence on OCT imaging of focal intimal trauma, compared with 9 (31%) of 29 arteries harvested by means of electrocautery ($P=0.011$). No differences in blood flow measured intraoperatively but a trend toward an increased pulsatility index was observed in favour of group A (3.12 vs 2.26 ; $P=0.05$).	OCT images of the radial artery obtained after harmonic scalpel harvesting revealed significantly less intimal defects and change in luminal volume, suggesting less trauma-induced endothelial disruption and spasm. The most practical explanation for our findings is that the harmonic scalpel provides a more meticulous technique for handling the radial artery.
Dumantepe et al. 2011 RCT	Patients with coronary artery diseases operated for coronary artery revascularization	Harvest of radial artery conduit for coronary artery bypass grafting	Group A (20): ultrasonic device; Group B (20): high-frequency electrocautery	Harmonic	The graft preparing time was shorter in group B than in group A (10.9 ± 2.42 vs. 15.2 ± 1.31 min; $P < 0.01$). Second and third phase flows were similar between the groups. Free flow was increased in group A when comparing with group B (60.4 ± 9.83 vs. 40.8 ± 7.50 ml/min; $P < 0.001$). Scoring of the groups in terms of endothelial cell structure and mitochondrial morphological changes did not show any significant difference.	Our study suggested that harvesting by electrocautery, which yields similar blood flows comparing to ultrasonic cautery is an easy, fast and economic technique in the experienced hands of a careful surgeon.
Mouton et al. 2005 RCT	Patients with recurrent sapheno-femoral incompetence	Redo saphenous high ligation	Group A (12): ultrasonic dissection; Group B (12): electrocoagulation; Group C (12): sharp dissection and ligation	Harmonic	The mean drain output per patient was 13.5 ml in group A, 15.4 ml in group B and 8.3 ml in group C. Six minor cases of lymphatic leakage occurred in group A; this resulted in no clinical problem. There were no other significant differences between the three groups. No detectable complications were observed.	We conclude that there is no detectable advantage for the use of ultrasound or electrocoagulation in recurrent saphenous high ligation, and the choice of technique can be left to the discretion of the surgeon.

Mouton et al. 2011 Follow-up study	Patients with recurrent sapheno-femoral incompetence	Redo saphenous high ligation	Group A (12): ultrasonic dissection; Group B (12): electrocoagulation; Group C (12): sharp dissection and ligation	Harmonic	Duplex ultrasound showed neovascularisation with an average maximal diameter of the newly formed refluxing vessel of respectively 2.00 (\pm 0.63) mm, 1.00 (\pm 0.45) mm and 0.50 (\pm 0.50) mm after 3 months and 4.29 (\pm 1.41) mm, 3.32 (\pm 0.90) mm and 3.00 (0.83) mm after 7 years (no significant difference between groups). After 7 years no reflux was detected in 8/36 patients, no varicose veins were found in 14/36 patients. The patients were less symptomatic than before our redo operation and no one needed reoperation within the 7 years.	Dissection techniques in the groin did not influence the clinical and sonographic result at 3 months and at 7 years after redo surgery for recurrent varicose veins.
Shapira et al. 2006 RCT	Patients undergoing first-time isolated coronary artery bypass grafting with the use of the radial artery	Harvest of radial artery conduit for coronary artery bypass grafting	Group A (18): conventional; Group B (18): conventional + ultrasonic dissection Group C (18): endoscopic + ultrasonic dissection	Harmonic	Harvest time was longer in Group C (45 \pm 19 min vs. 41 \pm 10 min vs. 61 \pm 24 min; P=0.0005). Clinical outcomes were similar among the groups. Radial artery harvest-related outcomes were also similar, with no incidence of hand ischemia, motor deficits, hematoma, or wound infection. There was a significant difference with respect to sensory deficits (paresthesias and numbness), limited to the superficial radial nerve only in Group C. Cosmetic results were superior in Group C. Adhesion molecule expression and histologic changes were similar between the groups.	Endoscopic harvest does not alter radial artery vasoreactivity or endothelial integrity compared with conventional harvest techniques. Because the endoscopic technique is less invasive, it might prove to be the technique of choice to harvest the radial artery.

Key: CCT = Controlled clinical trial; OCT = optical coherence tomography; RA = radial artery; RCT = Randomised clinical trials.

Table 4.5: Synthesis of primary studies reporting on the use of ultrasonic energy devices in gynaecological surgical procedures.

Authors [ref.] Year Study Design	Population	Intervention	Groups (num. of patients)	Ultrasonic Device Assessed	Main Study Findings	Authors' Conclusions
Awadzi et al. 2005 SPC	Women with non-malignant conditions (fibroids and menorrhagia)	Open abdominal hysterectomy and bilateral salpingo-oophorectomy	Group A (10): ultrasonic dissection; Group B (10): bipolar diathermy dissection	LOTUS Shears	Differences were not statistically significant between the two techniques.	Both instruments were equally effective in securing haemostasis.
Fitz-Gerald et al. 2013 RCT	Women with benign lesions	Vaginal hysterectomy	Group A (21): ultrasonic dissection; Group B (19): traditional suture ligatures	Harmonic	Mean (SD) hysterectomy time and was similar in both groups, 28.66 (4.0) vs. 32.37 (3.18) minutes (P=0.47), as was total operating time, 97.38 (8.9) vs. 91.63 (7.69) minutes (P=0.63). Operative blood loss was significantly decreased in the ultrasonic group: 62.63 (12.46) vs. 136.05 (21.54) mL (P=0.006). No significant change in haemoglobin concentration between the 2 groups: 19.53 (1.79) vs. -16.72 (2.5) g/L. No significant difference in mean oxycodone use: 9.29 (2.66) vs. 8.06 (3.19) mg (P=0.77). Length of hospital stay was similar in both groups: 58.98 (3.27) vs. 60.05 (6.48) hours (P=0.88). No significant difference in overall complication rates between the groups.	Although the Harmonic Scalpel system, compared with the traditional suture ligation method, seems to be a safe alternative for securing the pedicles in vaginal hysterectomy, it offers no benefit insofar as operative time, reduction in clinically significant blood loss, and analgesic requirements. In a cash-poor public hospital system, it would be difficult to justify the use of the Harmonic Scalpel in vaginal hysterectomy.
Kartsiounis et al. 2011 CCT	Women with unsatisfactory colposcopy, positive endocervical curettage, discrepancies between pap smear and colposcopic examination, and suspicion of microinvasive disease.	Cervical conisation (cone biopsy)	Group A (102): ultrasonic device; Group B (97): CO ₂ laser device	Harmonic	No statistical significance regarding the mean operating time, mean blood loss, mean cone volume and postoperative complications in the two groups. Thermal artefacts at the cone margins were minimal in the harmonic group (2/102 cones, 1.96%), while in the laser group they were considerably more (18/97 cones, 18.5%) (P<0.05). In most cases, artefacts were mild, but in 7/18 cases in the laser group evaluation of the margins was not possible due to thermal destruction. The overall complication rate was 10.7% in the harmonic group vs. 9.5% in the laser group.	Conisation using the Harmonic scalpel is as safe and effective as the CO ₂ laser procedure. It is cheaper, produces less smoke, better visual field and less thermal artefacts in the cone margins.

Leblanc et al. 2011 CCT	Women with BRCA mutation, who were scheduled for bilateral salpingo-oophorectomy (BSO)	Ovarian transection	Group A (4): Scissors and bipolar coagulation; Group B (3): stapler straight or roticulator with vascular tape; Group C (4): bipolar scalpel; Group D (3): harmonic scalpel	Harmonic	Comfort of handling (1 very poor, 5 very good): A=4.75; B=3.3; C=3.2; D=3.6 Time (min) until complete haemostasis: A=2; B=1.3; C=4.4; D=1.6 Blood loss (ml): A<10; B<10; C<13; D<10 Rate of resected/total volume of ovary: A=19 (16–25); B=19 (4–36); C=36 (14–38); D=25 (21–32). Median depth of tissue damage (mm) (part of ovary attached to fimbria): A=0.2 (0.1–0.3); B=0 (staple line); C=0.8 (0.5–1.2); D=0.7 (0.4–1.1). Median depth of tissue damage (mm) (remaining part of ovary): A=0.3 (0.2–0.4); B=0 (staple line); C=0.9 (0.5–1.3); D=0.8	Sharp dissection (group A) and stapler (group B) are the least traumatic methods to divide the ovaries, both providing the best tissue margins for a thorough pathological examination.
Li et al. 2009 RCT	Women with benign ovarian cysts	Laparoscopic excision of ovarian cysts	Group A (64): bipolar device; Group B (57): ultrasonic device; Group C (70): conventional sutures (open surgery)	Harmonic	When comparing the bipolar group and ultrasonic group with the conventional group, a statistically significant increase of the mean FSH value was found in bilateral-cyst patients at 1-, 3-, 6-, and 12-month follow-up evaluations and in unilateral-cyst patients at the 1-month follow-up evaluation. Statistically significant decreases of basal antral follicle number and mean ovarian diameter were found during the 3-, 6-, 12-month follow-up evaluations as well as statistically significant decreases of peak systolic velocity at all of the follow-up evaluations.	Our study has demonstrated that bipolar or ultrasonic coagulation of the ovarian parenchyma during cystectomy adversely affect ovarian reserve.
Litta et al. 2010 RCT	Premenopausal women with symptomatic uterine leiomyoma	Laparoscopic myomectomy	Group A (80): electrosurgery devices with a vasoconstrictive solution; Group B (80): ultrasonic device	Harmonic	Operative time: 88.8 ± 35.5 vs. 71.8 ± 26.7 minutes (P=0.000). Intraoperative blood loss: 182.8 ± 116.8 vs. 135.2 ± 89.1 ml (P=0.004). No differences were noted with respect to the degree of surgical difficulty. Postoperative pain (visual scale, 0-10) at 24 hours: 5.6 ± 0.8 vs. 4.4 ± 1.1 (P=0.00); at 48 hours: 2.5 ± 0.8 vs. 2.4 ± 1.1 (P=0.2).	The use of the harmonic scalpel for laparoscopic myomectomy is associated with low total operative time, low intraoperative blood loss, and low postoperative pain, with no increase in surgical difficulty.

Key: CCT = Controlled clinical trial; RCT = Randomised clinical trials; SD = Standard deviation; SPC = Same-patient comparative study.

Table 4.6: Synthesis of primary studies reporting on the use of ultrasonic energy devices in haemorrhoidectomy and ano-rectal surgical procedures.

Authors [ref.] Year Study Design	Population	Intervention	Groups (num. of patients)	Ultrasonic Device Assessed	Main Study Findings	Authors' Conclusions
Abo-hashem et al. 2010 RCT	Patients with Grade III and Grade IV haemorrhoidal disease	Haemorrhoidectomy	Group A (32): ultrasonic device Group B (32): bipolar electrocautery	Harmonic	<p>Postoperative pain was found to be significantly less in group A in all days of postoperative follow up.</p> <p>The mean dose of narcotic analgesia (NA) used in the first three days postoperatively was significantly reduced in group A ($P < 0.01$). There was also significant difference between both groups in required Diclofenac Sodium (DS) with less doses needed in group A.</p> <p>Incidence of postoperative bleeding was nearly comparable in both groups. Post-procedure urine retention was markedly less in group A (3/32 patients) while in group B it occurred in 11/32 patients ($P < 0.05$).</p> <p>No difference was found between both groups regarding wound infection, major short-term incontinence and swelling of the skin bridges.</p> <p>For group A, 75% of patients reported full-time return to work within the 2nd week postoperatively; the remaining patients joined their jobs by the end of the 4th week. For group B this happened only for 45% of patients; other patients required more time to return to work extended up to 45 days ($P < 0.05$).</p>	<p>Although the use of the Harmonic Scalpel carries some disadvantages as prolonged learning curve and increased cost over the electrocautery haemorrhoidectomy, it carries several advantages: reduced postoperative pain, reduced doses of NA and DS postoperatively, excellent haemostasis.</p> <p>Also, secondary to the reduced postoperative pain there was significantly reduced incidence of postoperative urine retention and finally reduced time-off work for the patients.</p>

Boccasanta et al. 2006 RCT	Patients with full-thickness rectal prolapse and faecal incontinence	Perineal rectosigmoidectomy (Altemeier's procedure) with perineal levatorplasty	Group A (20): conventional technique with monopolar electrocautery and hand-sewn anastomosis Group B (20): ultrasonic device and circular stapler.	Harmonic	Short term: The mean operating time and blood loss were significantly lower in group B (P<0.001). There was no operative mortality or complications. Mean hospital stay was 3.9 ± 0.8 in group A and 3 ± 0.5 days in group B (P<0.001). The pattern of the means of VAS score in the 1st week was remarkably low, without significant difference among the two groups. No patient of either group exceeded the dose of 50 mg per day of dexketoprofene during the hospital stay. Long term: No significant difference in mean time of inability to normal activity. Preoperative symptoms and continence score improved, without differences between the two groups.	The clinical and functional long-term results of perineal rectosigmoidectomy with levatorplasty are not influenced by surgical instruments and type of coloanal anastomosis. The use of harmonic scalpel and circular stapler is associated with less blood loss during the operation, shorter operative time, and hospital stay.
Bulus et al. 2013 RCT	Patients with symptomatic Grade III and Grade IV hemorrhoids	Haemorrhoidectomy	Group A (80): ultrasonic device Group B (71): Ferguson's with electrocautery	Harmonic	Operating time was shorter in Group A: 25.5±7.7 min vs. 16.8±4.1 min; p=0.001). Postoperative complications were lower in Group A: haemorrhage (2% vs. 4.2%; p=0.10) urinary retention (16.3% vs. 28.2%; p=0.05). Postoperative hospital stay was also lower for Group A (1.0±0.1 days vs. 1.2±0.4 days; p=0.001). Time of return to normal activity was less for Group A (10.6±2.1 days vs. 16.0±6.3 days; p=0.001). Postoperative VAS pain scores (p=0.001): Day 1: 5.4±0.7 vs. 6.8±5.3 Day 7: 4.0±0.8 vs. 5.2±1.2 Day 28: 0.01±0.1 vs. 1.4±0.2 Need for total postoperative analgesic was correlated with VAS scores.	In conclusion, hemorrhoidectomy with Harmonic scalpel is preferred for surgical treatment of Grade III or Grade IV hemorrhoids. It is safe and effective, and causes less blood loss, postoperative pain, and complications compared to Ferguson's with electrocautery.

Chung et al. 2005 RCT	Patients with Grade III haemorrhoidal disease	Haemorrhoidectomy	Group A (45): ultrasonic device Group B (43): stapling device	Harmonic	No significant observable difference in operation time, blood loss, or postoperative day when the first bowel movement occurred. Despite a similar parenteral and oral analgesic requirement, patients in group B had a significantly better mean VAS score (P=0.002) and also a shorter length of stay (P=0.02) and on average resumed work approximately 9 days earlier than those in group A (6.7 vs. 15.6 days; P=0.002). There was no difference in complication rate between the two groups. At all follow-up visits there was no observable difference in incontinence scores between the two groups. Patients in group B had significantly better satisfaction scores than those in group A (P=0.001).	Stapled haemorrhoidopexy is a safe and effective procedure for patients suffering from Grade III haemorrhoidal disease. Patients undergoing the stapled procedure derive greater short-term benefits, with reduced pain, shorter length of hospital stay, and earlier return to work.
Ivanov et al. 2007 RCT	Patients with Grade III and Grade IV haemorrhoidal disease	Haemorrhoidectomy	Group A (35): ultrasonic device Group B (32): standard Milligan- Morgan technique	Harmonic	On each of the three days, the average pain score was statistically significantly higher in group B. No statistically significant link was found between the complications and the operative techniques.	Harmonic Scalpel haemorrhoidectomy statistically significantly reduced postoperative pain compared with Milligan-Morgan's method of treating haemorrhoidal disease.
Kwok et al. 2005 RCT	Patients with Grade III and Grade IV haemorrhoidal disease	Haemorrhoidectomy	Group A (24): electrocautery device Group B (23): ultrasonic device	Harmonic	The postoperative pain score (median 2.6 vs. 4.8; P<0.001) and postoperative oral analgesic requirement (median 5 vs. 13; P=0.001) were significantly less in group A. The operating time (median 11 vs. 18 minutes; P<0.001) was significantly less in group A. The hospital stay, patient satisfaction score, percentage of patients requiring pethidine injection, percentage of patients with first bowel movement on or before the first postoperative day, and complication rates were similar between the two groups.	Electrocautery haemorrhoidectomy is safe and effective. It has a shorter operating time and produces less postoperative pain than ultrasonic haemorrhoidectomy.

Omar et al. 2011 RCT	Patients with symptomatic grade III & IV hemorrhoids	Haemorrhoidectomy	Group A (36): ultrasonic device Group B (36): Conventional monopolar diathermy	Harmonic	Operative time, intraoperative blood loss and hospital stay were significantly less in Group A (p<0.001). Operative time (minutes): 11±3 vs. 20±4; Intraoperative blood loss (cc): 13±3 vs. 25±4; Hospital stay (hours): 24-48 vs. 36-96. Time off of work was significantly longer in Group B (p<0.001). At 1 week: 18 (50%) vs. 3 (8.3%) At 3 weeks: 4 (11.1%) vs. 11 (30.6%) At 4 weeks: 4 (11.1%) vs. 9 (25%) Severity of pain assessed with VAS was significantly lower in Group A during the first 28 days. Daily requirements of analgesics showed significant difference in favour of Group A.	Harmonic scalpel haemorrhoidectomy can be used safely for treatment of grade III & IV hemorrhoids and is better in most of aspects than conventional diathermy. Its cost is overcome by shorter operation, rapid healing and early return to work.
Ozer et al. 2008 RCT	Patients with Grade III and Grade IV haemorrhoidal disease	Haemorrhoidectomy	Group A (22): open ultrasonic procedure Group B (22): closed ultrasonic procedure Group C (22): Milligan-Morgan procedure Group D (21): Ferguson procedure	Harmonic	Bleeding volume was significantly lower in groups A and B (P<0.001). Operation time was significantly shorter in group A (p<0.001). Postoperative pain and pain at the time of first defecation, was significantly lower in groups A and C (p<0.001) and lower during days 2-6 in group A compared to group C (p<0.004). VAS results were similar in Groups B and D. Analgesic consumption in groups A and C was significantly lower than groups B and D (p<0.001). Oral analgesic consumption during 2-5 postoperative days was lower in group A than in group C (p<0.007) and similar in group B and D.	Ultrasonic haemorrhoidectomy reduces postoperative pain, analgesic consumption, operation time, and bleeding. Ultrasonic haemorrhoidectomy is an effective, comfortable, and safe procedure.

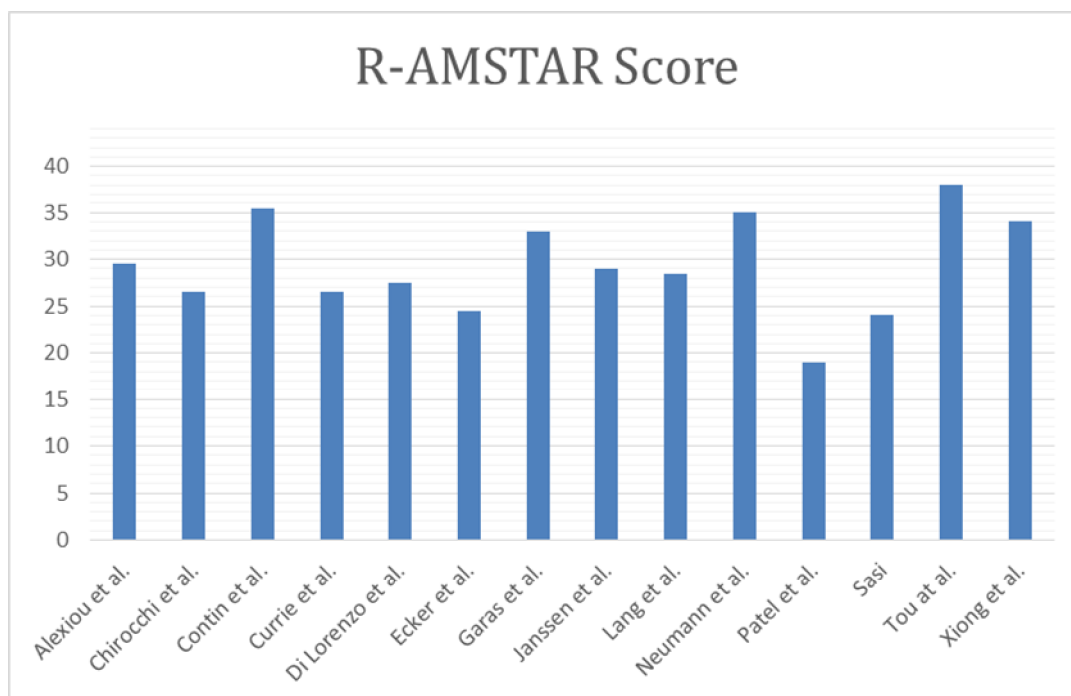
Peker et al. 2013 RCT	Patients with Grade III and Grade IV haemorrhoidal disease	Haemorrhoidectomy	Group A (23): electrocautery device Group A (23): ultrasonic device Group C (23): conventional technique (Milligan- Morgan)	Harmonic	Mean operative time for group A and B was significantly shorter ($P<0.001$). Perioperative bleeding rates were significantly higher for group C ($P<0.001$). When degree of pain was compared according to VAS scale, the results of group C and B were close to each other; degree of pain was significantly higher in group A ($P<0.001$). Analgesic consumption was least in group C and most for group A ($P<0.001$). Wound healing rate was the highest for group C ($P<0.001$).	These new cauterization devices provide some advantages such as reducing operation time and decreasing amount of bleeding. However, there may be some disadvantages for these devices; degree of pain is higher during postoperative period, analgesic requirement is quite higher and wound healing rates are worse. We suggest that conventional surgical technique for haemorrhoidectomy remains to be safer and more accessible.
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Key: CCT = Controlled clinical trial; RCT = Randomised clinical trials.

4.3 Methodological quality of the studies

The assessment of the methodological quality of the studies is reported in Appendix 4. The summary of the methodological quality of the systematic reviews initially considered in the present evidence review is reported in Figure 4.2. The most critical R-AMSTAR's items, for which most of the studies failed in fulfilling most of the criteria, were *item 5* (i.e., availability of the list of included and excluded studies), *item 8* (i.e., use of the scientific quality of the included studies in formulating conclusions), and *item 10* (i.e., assessment of the likelihood of publication bias).

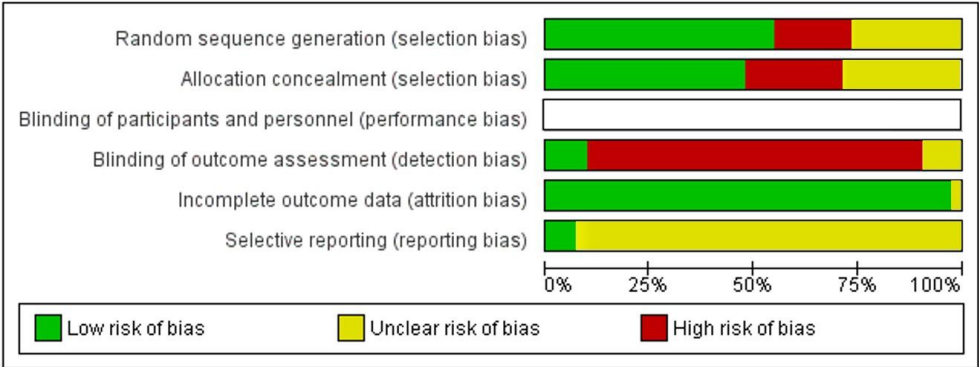
Figure 4.2: Average R-AMSTAR scores across two independent assessors of the review studies initially considered for inclusion in the present evidence review.



The summary of the methodological quality of the primary studies actually included in the present evidence review is reported in Figure 4.3. All the non-randomised studies or all the studies for which randomisation was not properly performed were considered at high risk of bias by default for what concern selection bias and allocation concealment. Given the nature of the technology, blinding of the surgeon was not believed practicable and thus, for all the

studies, we decided to consider "not applicable" the item "blinding of participants and personnel". Other types of bias were not assessed thus the judgement was not reported.

Figure 4.3: Risk of bias graph: authors' judgements about each risk of bias item presented as percentages across all included primary studies.



4.4 Safety

Thermal spread from the instrument blade is the main concern when ultrasonic energy devices or other surgical energy-based devices are used⁵⁷. The included studies did not report a specific and detailed analysis of the safety profile in such terms. Events such as thermal effects on the tissues, skin burns, nerve damages, thermal artefacts at the sample margins, depth of tissue damage, etc. were generally reported across the studies as intraoperative complications and thus have been discussed, together with the other clinical outcomes, in the previous paragraphs and tables. However, in the majority of the included studies, even with some exceptions (e.g., ovarian transection⁴⁶, laparoscopic excision of ovarian cysts⁴⁸), no difference in the complication rate was reported between the groups. Even though nerve injury due to thermal spread is a well-known risk in the setting of thyroid surgery⁷³, the studies included did not report any significant difference in the occurrence of such complication¹⁵.

4.5 Discussion of results of literature review

We stratified the evidence on the use of ultrasonic energy devices for surgery versus conventional haemostatic techniques or other energy-based devices by procedure or group of procedures.

4.5.1 Abdominal surgical procedures (various)

We identified only evidence from primary studies on hepatic resection and laparoscopic adrenalectomy³⁷. In both studies, findings were against the use of ultrasonic energy device in terms of operating time and blood loss (i.e., in favour of the bipolar vessel sealing device). The difference in length of hospital stay was not statistically significant. We believe further, more robust, evidence is needed to give a conclusive statement on the use of ultrasonic energy devices for hepatic resection and laparoscopic adrenalectomy.

4.5.2 Breast surgery

We identified evidence from secondary studies on mastectomy¹⁷. Findings showed equivalence between ultrasonic dissection and standard electrocautery in term of postoperative drainage and seroma development.

We identified further evidence from six primary studies^{11, 35, 50, 82, 83, 84}. Findings were clearly in favour of the ultrasonic energy device in term of seroma formation (reduced in 5 studies) and drainage volume (reduced in 4 studies), while no conclusive statements can be done in terms of operative time, hospitalisation stay, and intraoperative bleeding (all reduced in 3 out of 6 studies).

4.5.3 Cardio-vascular surgery

We identified evidence from secondary studies on radial artery harvest⁶³. Findings were contradictory in terms of incidence of complications, harvesting time, and other relevant outcomes related to the use of ultrasonic energy device versus diathermy or scissors and clip techniques. We identified 3 further primary studies in which findings were in favour of the ultrasonic energy device in terms of intimal defects and change in luminal volume of the harvested conduits⁷, and graft preparation time²³. We believe that further, more robust, evidence is needed to give a conclusive statement on the use of ultrasonic energy devices for radial artery harvest.

We identified only evidence from primary studies on redo saphenous high ligation^{54, 55}. Findings, confirmed by a follow-up study at 7 years, showed equivalence between the different techniques in terms of neovascularisation and recurrence of varicose veins. We believe that further, more robust, evidence is needed to give a conclusive statement on the use of ultrasonic energy devices for redo saphenous high ligation.

4.5.4 ENT oncological surgery

We identified only evidence from primary studies on selective neck dissection^{71, 79}. Findings were clearly in favour of the ultrasonic energy device in term of blood loss (reduced in both

studies). Operating time was reduced by the use of the ultrasonic energy device only in one of the studies. Both studies showed equivalence of the techniques in terms of total amount of drainage, duration of drain placement, days of hospital stay, and perioperative complications. We believe that further, more robust, evidence is needed to give a conclusive statement on the use of ultrasonic energy devices for selective neck dissection.

4.5.5 Gastrointestinal surgery (open procedures)

We identified only evidence from primary studies on open total gastrectomy and left hemicolectomy⁸⁰, and gastrectomy with lymph node dissection^{34, 86}.

In the total gastrectomy and left hemicolectomy study, findings were in favour of the ultrasonic energy device in terms of operative time (reduced only in colonic resection; no differences in gastric resection), number of sutures required, and resumption of bowels movements. Equivalence was observed in terms of intraoperative blood loss, number of clips applied, postoperative pain, time until resumption of a normal diet, time to first mobilisation from bed, overall hospital stay, quality of life. We believe further, more robust, evidence is needed to give a conclusive statement on the use of ultrasonic energy devices for total gastrectomy and left hemicolectomy.

In the gastrectomy with lymph node dissection studies, findings were in favour of the ultrasonic energy device in terms of operative time in both studies. Equivalence of the two techniques was observed in terms of intraoperative blood loss, postoperative hospital stay, amount of postoperative abdominal drainage, and rate of complications. We believe further, more robust, evidence is needed to give a conclusive statement on the use of ultrasonic energy devices for gastrectomy with lymph node dissection.

4.5.6 Gynaecological surgery

We identified only evidence from primary studies on a wide range of gynaecological surgical procedures^{4, 26, 38, 46, 48, 49}.

Findings were in favour of the use of the ultrasonic energy device for laparoscopic myomectomy in terms of operative time, intraoperative blood loss, and postoperative pain.

Findings showed equivalence between the ultrasonic energy device and the comparative techniques for open abdominal hysterectomy and bilateral salpingo-oophorectomy (in terms of haemostasis, operating time and thermal damage), vaginal hysterectomy (in terms of operative time, reduction in clinically significant blood loss, and analgesic requirements), cervical cone biopsy (equivalence in terms of operating time, blood loss, cone volume and postoperative complications; findings were in favour of the ultrasonic energy device only in terms of reduced artefacts at the cone margins).

Findings were against the use of the ultrasonic energy device for ovarian transection (in terms of provision of good tissue margins for pathological examination) and laparoscopic excision of benign ovarian cysts (in terms of preservation of the ovarian reserve).

As the six studies reported on a total of 624 procedures within a wide range of procedures, any kind of generalisation would be questionable. We believe further, more robust, evidence is needed to give a conclusive statement on the use of ultrasonic energy devices for gynaecological surgical procedures.

4.5.7 Haemorrhoidectomy and ano-rectal surgery

We identified only evidence from primary studies on haemorrhoidectomy^{1, 12, 36, 44, 62, 64, 87, 88}.

Findings were in favour of the use of the ultrasonic energy device in terms of reduction of post-operative pain (5 studies out of 8) and this was the only outcome reported in all the studies. Bleeding was reported in 7 studies (4 in favour of ultrasonic energy device; no difference in 3). Analgesic requirement was reported in 5 studies (4 were in favour of ultrasonic energy device) as well as operative time (4 were in favour of ultrasonic energy device) and time to return to work (3 in favour of ultrasonic energy device). Other outcomes were not uniformly reported across the studies or, when reported, such as hospital stay, were linked to contradictory findings.

We identified only evidence from primary studies on perineal rectosigmoidectomy with perineal levatorplasty⁶. Findings showed that, while clinical and functional long-term results were not influenced by the technique used, benefits in terms of intra-operative blood loss, operative time, and hospital stay are associated to the use of the ultrasonic energy device. We believe further, more robust, evidence is needed to give a conclusive statement on the use of ultrasonic energy devices for perineal rectosigmoidectomy with perineal levatorplasty.

4.5.8 Laparoscopic cholecystectomy

We identified evidence from secondary studies on laparoscopic cholecystectomy⁸¹. Findings were in clear favour of the ultrasonic energy device in terms of operation time, blood loss, hospital stay, gallbladder perforation, and postoperative abdominal pain score at 24 hours. Equivalence between the two techniques was observed in terms of operation conversion, bile leakage, intra-abdominal collections, and postoperative nausea at 24 hours. We identified concordant evidence from a further primary study that showed, in addition, lower incidence of bile leakage and reduction of lens cleaning time in favour of the ultrasonic energy device⁵¹.

4.5.9 Laparoscopic colorectal surgery

We identified evidence from secondary studies on laparoscopic colorectal resection²¹. Even though electrothermal bipolar vessel sealing seems to be favoured, findings should be interpreted with caution due to the heterogeneity of the studies included in the review. More adequately designed and larger RCTs are needed to give a final statement on this procedure.

4.5.10 Liver transplant surgery

We identified only evidence from primary studies on elective living donor liver transplantation⁵⁸. Findings showed equivalence between the two techniques in terms of total and per vessel procedure time, and bleeding rates. While traditional ligation appeared to be safer for 3 mm or larger veins, the harmonic scalpel appeared to be as safe as conventional ligation and even safer in especially narrow areas to transect hepatic veins with a diameter ≤ 2 mm during liver transplantation. We believe further, more robust, evidence is needed to give a conclusive statement on the use of ultrasonic energy devices for elective living donor liver transplantation.

4.5.11 Lung biopsy

We identified only evidence from primary studies on lung parenchyma biopsy⁵³. Findings were in favour of the ultrasonic energy device in terms of operation time. Equivalence was observed in terms of drainage duration, pleural fluid volume, minor complication rates, and in-hospital stays. We believe further, more robust, evidence is needed to give a conclusive statement on the use of ultrasonic energy devices for lung parenchyma biopsy.

4.5.12 Orthopaedic surgery

We identified only evidence from primary studies on total hip arthroplasty⁷⁶. Findings were in favour of the ultrasonic energy device in terms of soft tissue damage, use of tramadol, drainage volume at 24 hours. Equivalence was observed in terms of postoperative pain or use of paracetamol while a longer operative time was linked to the use of the ultrasonic device. We believe further, more robust, evidence is needed to give a conclusive statement on the use of ultrasonic energy devices for total hip arthroplasty.

4.5.13 Pancreatic surgery

We identified only evidence from primary studies on pancreatic surgery⁷⁸. Equivalence was observed between the ultrasonic energy device and the conventional technique in terms of operation time, blood loss, complication rate, and adverse events. We believe further, more robust, evidence is needed to give a conclusive statement on the use of ultrasonic energy devices for pancreatic surgery.

4.5.14 Plastic and reconstructive surgery

We identified only evidence from primary studies on pectoralis major myocutaneous flap dissection¹⁹ and anterolateral thigh flap elevation²⁹. For both procedures, findings were in favour of the ultrasonic energy device in terms of operation time. Findings on other outcomes, such as blood loss and drainage volume, were in contrast (favouring the ultrasonic device in one study and showing equivalence in the other).

4.5.15 Thyroid surgery

We identified evidence from secondary studies on thyroid surgery¹⁵. Findings were in clear favour of the ultrasonic energy device in terms of operation time, intra- and postoperative blood loss, rate of transient hypocalcaemia, postoperative pain, and duration of hospital stay. Equivalence was observed in the two clinically important safety outcomes: recurrent nerve palsy and rates of clinically symptomatic hypocalcaemia. We identified concordant evidence from three further primary studies^{13, 67, 70} in terms of operation time, while equivalence was observed for all the other outcomes investigated, such as postoperative transient complications, transient/permanent hypocalcaemia, permanent laryngeal nerve palsy.

4.5.16 Tonsillectomy

We identified evidence from secondary studies on tonsillectomy². Equivalence was observed between the ultrasonic energy device and the conventional technique in terms of post-operative pain and post-operative bleeding. Findings on intra-operative bleeding were in favour of the ultrasonic energy device. We identified contradictory findings from a further primary study³⁹ in terms of post-operative pain, while equivalence was observed in terms of bleeding and wound healing.

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4.6 Ongoing trials

We performed searches on www.clinicaltrial.gov in March 2014 to identify those ongoing registered trials on the devices identified. We used the name of the devices as keyword and reported our findings in Table 4.7.

Table 4.7: Summary of the ongoing trials registered on www.clinicaltrials.gov assessing the ultrasonic energy devices identified within this Rapid HTA Report on humans living subjects (ex-vivo studies are not reported) versus conventional haemostatic techniques. Searches performed on 12th March 2014.

Trial number	Procedure(s)	Intervention model	Arms		Enrolment [patients]	Start Completion
			Experimental	Active comparator		
RECRUITING						
NCT01929928	General surgery procedures (any).	Prospective cohort	Sonicision	NA	150	Jan 2013 Dec 2013
NCT01717794	Laparoscopic total hysterectomy with pelvic lymphadenectomy.	Randomised; Parallel ass.	Thunderbeat	Standard bipolar electrosurgery.	36	Oct 2012 Oct 2014
NCT01717781	Laparoscopic radical hysterectomy with pelvic lymphadenectomy.	Randomised; Parallel ass.	Thunderbeat	Standard bipolar electrosurgery	26	Oct 2012 Oct 2014
NCT01999296	Laparoscopic visceral or gynaecologic surgery (any).	Patient registry	Thunderbeat	NA	250	Oct 2013 Dec 2015
NCT01812395	Thyroidectomy.	Randomised; Parallel ass.	Harmonic FOCUS	Classic scalpel or scissors	100	Mar 2013 Apr 2014
NCT01551914	Total thyroidectomy.	Randomised; Parallel ass.	Harmonic FOCUS	Bi/monopolar electrosurgical instruments or clip coagulation techniques	1,350	Mar 2012 May 2014
NCT02017834	Neck dissection and tumour resection.	Randomised; Parallel ass.	Harmonic FOCUS	Standard technique	36	Feb 2012 Feb 2015
ONGOING BUT NOT RECRUITING						
NCT01565486	Conventional thyroidectomy.	Randomised; Parallel ass.	Harmonic ACE	LigaSure Precise	304	Aug 2011 Aug 2017
NCT01658085	Total thyroidectomy.	Case control	Harmonic FOCUS	Harmonic ACE	56	Feb 2009 Aug 2012

Key: *ass.* = assignment; *NA* = not applicable.

5. Economic analysis

5.1 Methods of economic analysis

The economic analysis comprised mainly a systematic review of economic evidence. We considered the economic studies about the ultrasonic energy devices comparing them to conventional haemostatic techniques (suture ligation or vascular clips application) or other energy-based devices (radiofrequency or electrothermal surgical device). Studies were included whether they met the following inclusion criteria: the ultrasonic energy devices were used in patients underwent surgery (open or laparoscopic procedure) without restrictions on the surgical specialty. We considered economic studies - cost-effectiveness, cost-utility, cost-benefit and cost analyses - published in the last 10 years, in English or Italian languages. Details of the search strategy are reported in Appendix 5.

Titles and abstracts of records identified, resulting from the electronic databases' search, were screened for potential eligibility by two reviewers independently (MC and MRP). The full-text of relevant papers were then retrieved and two reviewers (MC and MRP) formally assessed them, independently, with respect to their potential relevance according to the inclusion criteria. If it was unclear from an abstract or title whether a study was relevant, the full paper of the study was obtained for further information. Disagreements were resolved by discussion and when agreement was not reached, a third reviewer (TJ) was consulted.

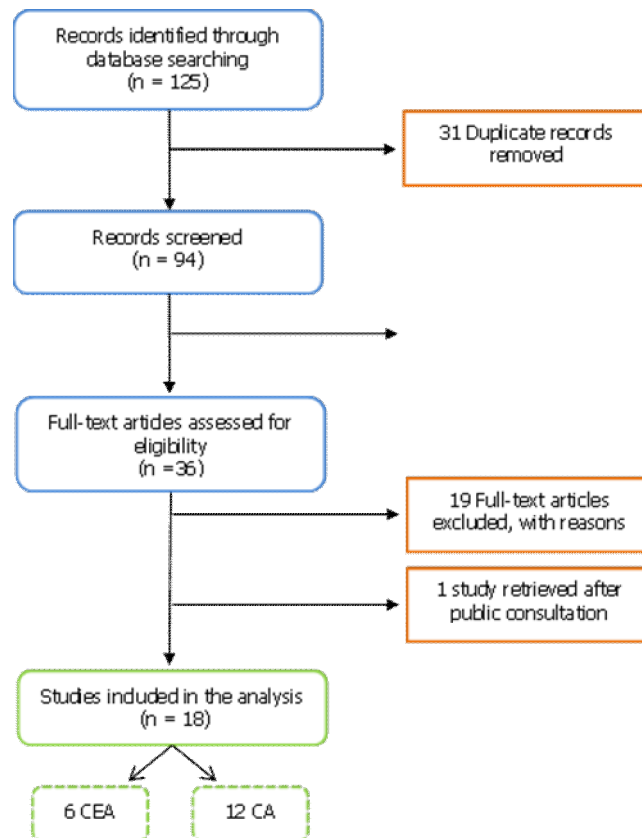
Data extraction was planned to be performed, independently and in duplicate, by two reviewers (MC and MRP). We intended to extract economic data related to the ultrasonic energy devices with an ad hoc form (Appendix 6). The methodological quality of economic studies was appraised using the CHEERS statement³³.

5.2 Results

Through electronic searches we identified 125 titles/abstracts and selected 17 as relevant to our systematic review (Figure 5.1). Thirty-one records out of 125 were duplicates. Based on the relevance of titles and abstracts, 36 articles underwent full-text screening. After reading the full-text of the studies, we included 17 studies. The first draft of the rapid HTA report, prepared according to such evidence, was available for public consultation on the website of the Italian Ministry of Health for 60 days. Analysis of comments from reviewers allowed the inclusion of

one further study. Full references of the excluded studies, with reason for exclusion, are listed in Appendix 7.

Figure 5.1: Flow-chart of the economic evidence.



The included studies performed a cost-effectiveness analysis (6/18) or a cost analysis (12/18) of ultrasonic energy devices compared to conventional or other energy-based techniques. Most of the studies (9/18) investigated the use of ultrasonic scalpel in thyroid surgery, specifically total or partial thyroidectomy, 3 studies regarded colorectal surgery, 2 studies focused in breast and 2 in head/neck surgery, 1 study was about spinal surgery and 1 about appendectomy.

As regards the surgical techniques used, open or endoscopic, in 9 studies open procedure was used while in 6 endoscopic procedure; 3 studies reported no information about this issue.

Economic data were collected on the basis of clinical trial with different study design: 3 retrospective studies, 9 randomised controlled trials, 2 prospective controlled trials and 1 prospective cohort study; as regards 3 studies the design was not clear. Nine studies compared the ultrasonic energy devices with conventional techniques while 11 studies with other energy-

based devices. Ultrasonic energy devices were compared both with conventional and other energy based devices in four studies. Four studies were funded by manufacturers, 10 did not declare the source of funding while 4 stated to have not received any funding. The main information on the cost-effectiveness and cost-analyses included were reported in Table 5.1.

Table 5.1: Cost-effectiveness and cost analysis studies.

Surgery specialty (n° of studies)		Surgery Procedure	Comparison	Study ID	Objective	Economic analysis (Study design)	Country	Funding
Appendectomy (1)		endoscopic	US vs other Energy based (monopolar electrocautery) vs Conventional (endoclip)	Lee et al 2014	A theoretical model of disposable cost was constructed for each method to compare cost-effectiveness	CEA (Retrospective study)	Korea	Not declared
Breast surgery (2)	Radical, simple, skin sparing mastectomy; wide excision and axillary clearance	open	US vs other Energy-Based (electrocautery)	Kontos et al 2008	To investigate the role of harmonic scalpel (HS) in reducing postsurgical seroma formation, complications, pain and consequent cost in breast surgery	CA (RCT)	UK	Not declared
	Breast reduction surgery			Burdette et al 2011	The authors also compared the learning curves, operative time versus specimen weights, complication, and costs for the devices	CA (RCT)	USA	Ethicon EndoSurgery
Colon rectal surgery (3)	Transanal endoscopic	endoscopic	US vs other Energy based (monopolar scalpel)	Gracia et al 2011	To compare the costs of performing TEM with harmonic scalpel and classic monopolar scalpel and to analyze complications	CA (NC)	Spain	Not declared
	Colon surgery		US vs other Energy Based (monopolar electrosurgery scissors) vs other Energy based (bipolar vessel sealing)	Hubner et al 2008	To compare MES, BVS and UCS in laparoscopic colorectal surgery with regard to dissection time, blood loss, technical aspects, surgeon comfort and costs	CEA (RCT) 68	NC	No financial support was received from the manufacturer
	Colon surgery		US vs Energy based (electrosurgery) vs Energy based (bipolar vessel sealing)	Targarona et al 2005	This trial compared the effectiveness of three different energy sources on the laparoscopic performance of a left colectomy	CA (RCT)	Spain	Not declared
Head/neck surgery (2)	Head/neck surgery	open	US vs Conventional or other Energy based (clamp – cut – tie or bipolar electrocautery)	Koch et al 2011	To investigate the use of ultrasonic shears as a means to decrease operative time and increase surgical	CA (Prospective cohort study)	USA	None

					efficiency in the harvest of microvascular free flaps			
	Tonsillectomy - Adenotonsillectomy		US vs other Energy based (electrocautery) vs surgical dissection	Shinhar et al 2004	To compare the surgical efficacy, practical utility, safety and cost-effectiveness of ultrasonic harmonic scalpel tonsillectomy, hot electrocautery and cold surgical dissection	CA (Retrospective study)	USA	Not declared
Spinal Surgery (1)		open posterior	US vs other Energy based (electrocautery)	Cakir et al 2006	To determine if blood loss was lower using the HS than electrocauterization (EC) and to evaluate the cost effectiveness of the HS in reducing the need for transfusion in patients undergoing posterior instrumentation of the spine	CEA (NC)	NC	None
Thyroid surgery (9)	Total thyroidectomy	open	US vs Conventional (cut and ligature)	Kowalski et al 2012	To improve the flaws of previous studies by designing a multicenter RCT with a large sample size and the inclusion of safety and economic variables to assess the effectiveness of ultrasonic scalpels in total thyroidectomy	CA (RCT)	Brazil (coordinating center)	Ethicon EndoSurgery
	Thyroidectomy		US vs other Energy Based (bipolar energy sealing)	Rahabari et al 2011	To determine if there was a difference in operative time or cost of thyroidectomy (operative and total) between the two surgical devices independent of the procedure and thyroid disease type and to determine if there was a difference in complication rates between the two surgical devices	CA (RCT) 69	USA	Covidien
	Total thyroidectomy and hemithyroidectomy		US vs Conventional (clamp and tie)	Ortega et al 2004	To study whether the use of the UHS could have advantages in thyroid surgery in terms of operative time, length of hospitalization, morbidity, and general costs	CEA (Prospective controlled trial)	Spain	Not declared

Total thyroidectomy		US vs Conventional (knot-tying)	Ruggeri et al 2012	To assess cost-effectiveness of the use of ultrasound scalpel in total thyroidectomy from an hospital, third payer and societal perspective	CEA (RCT)	Italy	J&J Medical
Unilateral thyroid lobectomy using MIVAT	endoscopic	US vs Conventional (clip – ligation)	Barczyński et al 2008	The primary endpoint of this study was the operating time, whereas the secondary endpoints included blood loss, complications, the length of the scar, patients' cosmetic satisfaction; and cost-effectiveness	CEA (RCT)	Poland	Not declared
Total and partial thyroidectomy with or without lymphadenectomy		US vs Conventional vs other Energy-Based (Energy vessel sealing)	Bersi da Silva et al 2012	To analyze the operative time, length of hospitalization and cost	CA (Retrospective study)	Brazil	Not declared
Total thyroidectomy for multinodular goiter		US vs Conventional (clamp-and-tie and bipolar electrocautery) vs other Energy Based (bipolar energy sealing)	Pons et al 2009	To compare the efficiency (operative time), safety (hemostasis quality and postoperative complications: bleeding, hematomas, infections, recurrent palsies, and hypocalcemia), and cost (the cost of the consumables and the total operative cost) of the different methods of hemostasis currently available for thyroid surgery	CA (RCT)	NC	None
Total or near total thyroidectomy for multinodular goiter (MNG)	-	US vs Conventional (tie and clip)	Sebag et al 2009	To evaluate the potential advantages of the HS in surgery for multinodular goiter (MNG) and to conduct the first economic evaluation based on prospective individual data, as well as a detailed observation of consumed resources during a surgical intervention. The economic evaluation was a CMA aimed to determine which of the two surgical procedures with comparable efficiency permitted a reduction in the global cost	70 CA (Prospective controlled trial)	NC	Not declared

	Thyroidectomy		US vs conventional (no instruments)	Lucchini et al 2013	To evaluate the opportunity to introduce routine use in thyroid surgery of the ultrasonic dissector	CA (NC)	Italy	Not declared
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Key: *US: ultrasound scalpel; MIVAT: minimally invasive video-assisted thyroidectomy; TEM: transanal endoscopic microsurgery; MES: monopolar electro-surgery scissors; BVS: bipolar vessel sealing; UCS: ultrasonically coagulating scissors; CA: cost-analysis; CEA: cost-effectiveness analysis; RCT: randomised control trial; NC: not clear.*

5.2.1 Appendectomy

One study⁴⁷ focused on laparoscopic appendectomy surgery comparing the cost effectiveness of ultrasonic device (HS) with another energy based device (monopolar, ME) and conventional technique (endoclip, EC) (Table 5.2). In this retrospective study, carried out on 1,178 patients, a cost-effectiveness model was built and based on cost model for each method including the EC applier, the HS and disposable surgical supplies such as surgical gowns, gloves, draping material and trocars; surgeon's fees, anaesthesia fees and hospital room costs were not included in the models. The perspective of the economic analysis was not reported. The effectiveness' measures considered were: operation time, hospital stay, complications and conversions. The study reported the total cost of each theoretical model and concluded that the cost effectiveness model showed ME to have the lowest disposable costs, with less than half of the cost for the HS group. Nevertheless no cost effectiveness measure was estimated in the study. The main limits of this study are its design (retrospective), the lack of randomisation of the dissection methods and since the study centre is a military hospital, the one of most important cost parameter (hospital stay) to evaluate the total cost of the treatment is not generalisable and transferable to other contexts. Funding was not declared.

5.2.2 Breast surgery

Two cost-analyses were included regarding breast surgery comparing ultrasonic device with other energy based, specifically electrocautery, with open procedure (Table 5.3). Kontos et al.⁴¹ investigated the role of ultrasonic scalpel in reducing post-surgical seroma formation, complications, pain and consequent costs related to mastectomy. Burdette et al.⁸ compared the learning curves, operative time versus specimen weights, complication, and cost for the devices in breast reduction surgery. Both studies were randomized controlled trials, enrolled 32 and 31 women respectively.

Kontos et al.⁴¹ considered the operating room and hospital stay costs and the disposable elements costs related to the devices used. The use of the ultrasonic scalpel did not result in reduction of operating time and hospital stay, through the decreased of total drained and aspirated volume. So the procedure using the ultrasonic device was more expensive due to the higher cost of this device. No study limitation and funding source were reported by the authors. Burdette et al.⁸ considered several cost elements for both procedures aimed at highlighting the difference between start-up cost and each subsequent case.

They measured the following costs: generator box, hand piece, grounding pad, tip (disposable); besides they calculated the total cost for first case and for each subsequent case.

It resulted that the start-up cost for both devices was similar, but the per-case cost for the ultrasonic device was significantly higher. The main limit of this study was the unknown effectiveness of the blinding of subjects. The study was funded by Ethicon EndoSurgery.

5.2.3 Colorectal surgery

Three studies focused on colorectal surgery analysing the endoscopic procedure (Table 5.4). Gracia et al.²⁸ compared the costs of ultrasonic device with those of the monopolar scalpel in transanal endoscopic microsurgery. Two hundred and twenty nine patients were enrolled in the trial, the study design was unclear. They measured the following cost per unit: hospital stay/day, intensive care unit stay/day, ultracision per use, whole blood transfusion and surgical room price/hour. The mean cost per procedure was reduced by 143 € when harmonic scalpel was used, but this difference had no statistical significance. The additional cost of ultracision was compensated with the decrease in the hospital stay resources. The authors not reported limits of study and funding sources.

Hubner et al.³² assessed the ultrasonic device (UCS), monopolar scissor (MES) and bipolar vessel sealing (BVS) in laparoscopic colorectal surgery with regard to dissection time, blood loss, technical aspects, surgeon comfort and costs (Table 5.5). The study enrolled 61 patients and randomized them among in three study groups. As regards clinical outcomes dissection time, intraoperative blood loss and post-operative complications were measured. The authors analysed the costs of operating theatre, allocated device and additional instruments used for haemostasis or dissection. The device related costs comprised a capital charge for the generator, maintenance charge and disposals. Costs were calculated for four different centre volumes (20, 50, 100 and 200 cases). Despite being expensive devices, the higher material related costs for BVS and UCS are balanced by a reduced operating time and a decreased need for additional material. In addition increasing the number of procedures performed yearly BVS and UCS incurred significantly lower costs than MES. BVS and UCS were cost-effective compared with MES. Nevertheless no cost effectiveness measure was estimated in the study. According to the authors the sample size was not sufficiently large to detect or exclude minor differences. . The study did not receive financial support from the manufacturer.

In the study of Targarona et al.⁷⁵, 38 patients were randomised to electrosurgery or bipolar electrosurgery or ultrasonic dissection. This trial aimed at comparing the effectiveness of such different energy sources on the laparoscopic performance of a left colectomy, as well as analysing their costs. In particular, intraoperative economic costs were assessed including operating room cost, disposable instruments' cost and final price. The analysis of operative

costs showed no significant differences between the three groups. The authors did not report any limits of the study and funding sources.

5.2.4 Head/neck surgery

Two studies, Koch et al.⁴⁰ and Shinhar et al.⁷², focused on head/neck surgery using open surgical procedure (Table 5.6). In particular Koch et al.⁴⁰ carried out a prospective cohort study where 69 and 39 patients underwent fibula or anterolateral thigh respectively, using conventional dissection or ultrasonic device, with the aim to investigate the use of ultrasonic shears as a means to decrease operative time and increase surgical efficiency in the harvest of microvascular free flaps. A cost analysis was conducted that considered the cost of devices, the anaesthesia time and operating room time including facilities fee, nursing and surgical staff. Since the study provided evidence that ultrasonic shears increased the efficiency of harvesting some flaps, the use of ultrasonic shears can lead to decreased costs associated to the procedure. They observed an average cost savings when using ultrasonic shears for the harvest of anterolateral thigh free flaps and for fibula free flaps when compared to traditional dissection using hemoclips, electrocautery or clamp-cut-tie technique. The authors specified that the study was designed as a prospective study but the patients were not randomized to the use of a specific device, and the surgeons performing the procedure was not able to be blinded to the method of dissection and haemostasis. Besides, the costs referred to only 1 institution and could widely vary. Finally no funds have been received to perform the study.

Shinhar et al.⁷² performed a retrospective study of 316 patients who underwent tonsillectomy or adenotonsillectomy with ultrasonic device (HS) or hot electrocautery (EC) or cold surgical dissection (SD) to compare the surgical efficacy, practical utility, safety and cost-effectiveness. However as regards the evaluation of the economic consequences, actually a cost analysis was performed. The authors measured the mean per patient institutional cost of surgery for the three treatment groups based on operating room time and the use of disposable and no disposable equipment. The study showed that ultrasonic device is clearly more expensive than either electrocautery or surgical dissection when considering only the operating room costs. However operating times using ultrasonic device were shorter than those of more established modalities implying a reduction in risks for patients and in variable costs. In addition the gain of experience with HS would make the HS-based procedure further faster. The complication rates among HS patients were lower although the differences were not statically significant; so, according to the authors, it is likely that savings, in terms of reduction of medical direct and indirect costs, could be realized due to lower complication rates and the use of US could be

considered cost-effective. The study did not take into consideration any evaluation of postoperative pain or return to normal activity. Funding was not declared.

5.2.5 Spinal surgery

The study of Cakir et al.¹⁰, with 100 patients, aimed to determine whether ultrasonic device (HS), is beneficial in reducing intra and post-operative blood loss and therefore in reducing the need for predonation/transfusion of blood products compared to electrocauterization (EC) in open posterior spinal instrumentation. The cost-effectiveness of ultrasonic device compared to electrocauterization was evaluated (Table 5.7). For intraoperative phase, the blood loss was measured by washing blood-soaked sponges/drapes and measuring the volume of salvaged blood. For post-operative phase, blood loss was measured by means of post-operative drains. Regarding the costs, the study considered the capital (depreciation, imputed interests) and operating costs, such as material, maintenance, occupancy costs and personnel, except the personnel employed in pre-donation autologous blood. The cost for HS was calculated per operation, considering an economic life of 8 years and an interest rate of 5%. Besides the costs of the HS handpiece were calculated on an estimated economic life of 100 operations, the hand-switching adaptor on an estimated economic life of 30 operations and the knife itself on an estimated economic life of 6 operations. The depreciation on the Ultracision HS and the interest were estimated for 50 operations. The study showed that the use of HS resulted in statistically significantly less intra-operative and post-operative blood loss than EC. The overall costs, including the cost of devices, were similar between the two treatments. Although the ultrasonic was more expensive its use led to lower blood loss and less need for and cost of blood products compared to electrocauterization technique in procedures with major expected blood loss as spinal surgery. Nevertheless no cost effectiveness measure was estimated in the study. According to the authors one significantly limit of this study was the inability to establish strict control of the criteria used in giving transfusions or even the total lack of these data. No funds have been received to perform the study.

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5.2.6 Thyroid surgery

Eight studies focused on thyroid surgery; specifically total or partial thyroidectomy.

Open thyroid surgery

In four studies thyroidectomy was performed with open procedure; in particular two of them^{42, 66} analysed only the costs (Table 5.8), while the other two^{67, 61} developed a cost-effectiveness analysis (Table 5.9). Ortega et al.⁶¹, Kowalski et al.⁴² and Ruggeri et al.⁶⁷ compared ultrasonic devices (US) versus conventional techniques, Rahabari et al.⁶⁶ investigated US versus other energy based devices.

Kowalski et al.⁴² in their RCT with 261 patients enrolled, assessed the effectiveness of US in total thyroidectomy taking into account safety and economic variables. They considered direct costs of resources (antiemetic medications, intraoperative resources, operative time, length of stay, devices) used in the surgical procedures in both treatment groups. The main difference in costs between the two treatments groups was due to the costs of the intraoperative resources which were in favour of US group, bringing to a decrease in the overall operative costs of about 14%. Although a decrease either in operative times and costs, the total costs related to the US procedure were higher (about 100US\$) than conventional technique due to the cost of the US device. However the study results showed that the use of ultrasonic scalpel could provide an economic advantage allowing more surgical procedures to be performed in the same amount of time compared to conventional techniques. No study limitation was pointed out by the authors. The study was funded by Ethicon EndoSurgery.

The study of Rahabari et al.⁶⁶, based on a prospective randomized trial with a total 90 patients, compared the ultrasonic device with bipolar energy sealing in terms of operative times, complications rates and costs. As regards the cost analysis, the authors measured the operative costs of thyroidectomy in both procedures and other costs including supply/device, laboratory tests, anaesthesia, pharmacy and recovery room. Although the study highlighted a significantly difference in operating room supply cost, due mainly to device cost, there was no significant difference in total costs between the procedures. The use of the billing charges of the study centre to value the costs of the two device-based procedures limits the transferability of results; however it was pointed out by the authors that cost difference would be expected to be similar across different institutions. The study was funded by Covidien.

Ortega et al.⁶¹ in their prospective controlled trial comparing two groups of 100 patients underwent total thyroidectomy or hemi-thyroidectomy with ultracision harmonic scalpel (UHS) or conventional technique, assessed the differences in cost-effectiveness and clinical outcomes. Economic analysis perspective was not described. Effectiveness analysis focused on the following clinical outcomes: operative time, hospital stay and complications (intra-operative and post-operative). Concerning the costs, the total cost per patient was calculated multiplying all the resources consumed per patient (medication, operating room time in minutes, disposable material, hospitalization time in days) by the hospital cost for each resource. Cost estimates were based on disposing of every unit after each patient. As regards the operative time, differences were significant between the two groups in both interventions (total thyroidectomy and hemi-thyroidectomy) with shorter operative time in UHS group. The mean length of hospitalization was similar in UHS group and conventional group. In both interventions there were none intra-operative complications whereas there were differences not statistically

significant for post-operative complications. The reduction of 15-20% in operating room time using UHS implied that the global cost of the procedure for patient was significantly lower, although ultrasonic shears were more expensive. So the use of the UHS for thyroid surgery resulted to be safe and cost-effectiveness. Nevertheless no cost effectiveness measure was estimated in the study. According to the authors the device could, in most cases, be shared by 3 to 5 patients with the same performance and safety, increasing the cost-effectiveness. In addition the shorter operative time implies the chance to treat more patients in the same operating session besides improving surgeons' comfort. No limitation and funding source were reported.

Ruggeri et al.⁶⁷ performed a cost-effectiveness analysis on the use of ultrasonic scalpel compared to conventional knot-tying technique on the side of a randomized controlled trial in which 203 patients were involved. Hospital, third party payer and social perspective were simultaneously adopted in the economic analysis. Data on the use of resources per patient during hospitalization for the thyroidectomy surgery, were recorded during the hospital stay, while data on the use of health care resources after discharge (follow up) and on productivity losses were collected through phone interview at 1 and 3 months. The value of healthcare resources used for the treatment and follow up was calculated using costs and data from hospital management control database, national/regional health system price lists and national administrative data. As regards effectiveness, patient's perception of pain was measured through a visual analogue scale at 6, 24 and 48 hours after surgery, while patient's quality of life was evaluated at discharge, 1 month and 3 months after discharge with the EuroQoL 5D questionnaire. The analysis showed that the use of US did not affect length of hospital stay, however significantly reduce operation time of about 20 minutes. This resulted in a decrease of overall hospitalization costs. Total medical direct costs at 3 months of follow up were lower (-140.18 Euros) for US treatment, whereas direct non-medical costs were not significantly different. Taking into account that indirect costs were similar, the overall costs of using ultrasonic scalpel were lower than conventional technique. Pain perception was similar between the two groups, while QoL was higher for US group both at discharge and during follow up. In base case the US was dominant compared to knot-tying since it cost less with a higher QoL which resulted in a QALY gain of 0.07. One-way and multi-way sensitivity analyses were carried out to test the validity of the study findings. The ultrasonic scalpel resulted dominant in 65 percent of the simulations based on bootstrap analysis and ICER remains below 30,000 euros/QALY in 90 percent of cases. However, the authors highlighted that the transferability of study findings to different settings could be limited since the randomized trial was carried out in

one centre. In addition training costs were not considered so the introduction of US could not be cost-effective in settings with smaller volume of activity. All authors reported receiving an unrestricted grant from the manufacturer (J&J Medical) **through** their institution.

Endoscopic thyroid surgery

Two of the eight studies on thyroid surgery focused on endoscopic procedures.

In particular, Barczyński et al.⁵ assessed in their randomised controlled trial (76 patients) the effectiveness and cost effectiveness of ultrasonic device compared with conventional technique (clip ligation) in minimally invasive video-assisted thyroidectomy (MIVAT) (Table 5.10). Effectiveness was measured through the following outcomes: operating time, intraoperative blood loss, complications, length of scar, postoperative stay and patients' cosmetic satisfaction. They considered the costs of operating room, general anaesthesia, clip and ligature, ultrasonic shears and bipolar coagulation. The perspective of the economic analysis was not reported. The result of cost-effectiveness analysis showed that the use of ultrasonic device in the MIVAT lobectomy was slightly more expensive (20-30 euros per procedure). No cost effectiveness measure was estimated in the study. The authors neither reported limits of the study nor declared the funding.

Da Silva et al.¹⁸ carried out a retrospective study, on 460 procedures, comparing the ultrasonic device with conventional techniques and other energy based device (energy vessel sealing) to analyse the total costs of thyroidectomy surgery (partial, total and total + lymphadenectomy) associated to different techniques/devices (Table 5.11). The cost and type of resources, used to perform the thyroid surgeries, were not specified. The authors considered the partial thyroidectomy with the conventional technique as the reference value for the analysis of procedure costs. So, for partial procedures no significant difference resulted between groups; for total thyroidectomy with lymphadenectomy the costs were similar, while for total thyroidectomy procedure there was a significant difference among the conventional group and ultrasonic or vessel sealing groups. Despite of reduced surgery time with ultrasonic device the total cost of procedure reflected a mean increase of 28% compared with conventional procedure. The cost of ultrasonic procedure resulted higher than that of other treatments. One limitation of the study is that the physician chose which technology to use and it was not possible to differentiate between the effect of the surgeon and the effect of the chosen technology in the evaluated outcomes. Funding was not declared.

Thyroid surgery with surgical access not reported

The last three studies Pons et al.⁶⁵,Sebag et al.⁷⁰ and Lucchini et al.⁸⁹ did not report the surgery procedure used to perform thyroid surgeries (Table 5.12).

Pons et al.⁶⁵ compared three different methods of haemostasis currently available for thyroid surgery: ultrasonic device, conventional technique (clump and tie and bipolar electrocautery) and other energy based device (vessel sealing system) to assess efficiency, safety and costs. Sixty patients were equally and randomly assigned to the three treatment groups. In the cost-analysis the authors measured the overall operative costs collecting the data on quantities and costs of the following resources: consumables, annual investment in materials and staff cost in the operative theatre. The study showed that the use of ultrasonic and vessel sealing system generate more consumable costs respect to conventional technique but their overall operative cost was lower because of the reduction of operative time and staff costs. No study limitation was reported related to the cost-analysis.

Sebag et al.⁷⁰ conducted a cost analysis based within a prospective controlled trial (100 patients enrolled) comparing ultrasonic device with conventional technique (tie and clip). They carried out a micro-cost evaluation to collect the resources used and the direct medical costs of surgical interventions for each patient which considered consumable, operating room use, and awakening room use (including equipment, staff and overheads). Only the cost of the surgical procedure was analysed because no difference between both groups in terms of hospitalization was hypothesized. Real costs incurred by study centre, instead of tariffs, were used to measure the value of resources used. The study showed no significant difference of total cost between the two groups; the higher cost of ultrasonic device was compensated by lower equipment and staff costs due to the reduction of operating time room. According to the authors, the increasing experience and staff expertise related to ultrasonic device use could provide potential improvements in terms of reduction of staff, further decrease of operative time and additional cases that could be treated in the same operating session. The main limitation was that allocation to different treatments groups was not a blind randomisation but depended on the availability of the HS equipment. However the authors stated that the hazard allocation reached two comparable groups. Funding was not declared.

Lucchini et al compared the use of ultrasonic dissector in thyroid surgery with standard procedure (no instruments) to estimate the total cost for each procedure. Two hundred and twenty patients were assigned to the intervention group (ultrasonic dissector) and an equal number of patients was treated with the standard procedure. The cost analysis considered: the technology purchasing cost, the involved staff cost, the cost of the operating room and the cost of hospitalization. It resulted that the reduction of operating time and hospitalization makes the cost of single intervention with ultrasonic dissector lower than traditional one. Study limitations and source of funding were not reported.

Table 5.2: Appendectomy cost-effectiveness.

Study ID	Comparison	Economic analysis type	Perspective	Model/Time horizon	Effectiveness				Costs				Economic results	
					Outcome			Follow up	Source	Item				Source
					Type	Device	Value			Type	Device	Value		
Lee et al 2014	US vs Monopolar (energy based) vs Conventional	CEA	-	-	Operation time	EC	58.1±24.9	-	Trial	Total cost	EC	620,350 KRW (571 USD)	Report of Hospital	"It seems that all three methods are safe to perform, considering the complication rates and conversion rates. HS was the fastest method, by about 6 minutes. ME was the most cost-effective method. EC did not have any obvious advantages."
						HS	51.4±25.6	-						
						ME	57.8±25.7	-						
					Hospital stay	EC	11.8±6.8	-			HS	1,041,230 KW (959 USD)		
						HS	11.9±4.5	-						
						ME	11.4±4.5	-						
					Complications [n %]	EC	8 (1.7)	-			ME	491,230 KRW (452 USD)		
						HS	5 (1.3)	-						
						ME	4 (1.2)	-						
					Conversion [n %]	EC	1 (0.2)	-						
						HS	1 (0.3)	-						
						ME	0 (0)	-						

Key: US: ultrasound scalpel; EC: electrocautery; HS: harmonic scalpel; ME: monopolar electrocautery; KRW: South Korean won.

Table 5.3: Breast surgery costs.

Study ID	Comparison	Costs				Economic results
		Item			Source	
		Type	Device	Value		
Kontos et al 2008	US vs other energy based (Electrocautery)	Theatre time (operating room)	HS	£720/h	institution	80 "In the present study no difference in operating time could be detected between HS and EC groups. In addition no potential reduction in the hospital stay could be identified through the decrease of the volume drained; thus the higher cost of HS (due to disposable elements) is not compensated by earlier discharge."
			EC			
		Disposable element	HS	£85/blade	institution	
			EC	£2.43/spatula		
		Hospital stay	HS	£650/night	-	
			EC			
Burdette et	US vs other	Generator Box	HS	\$ 18,950	Ethicon sales representatives	"Though the Harmonic Scalpel may be an excellent device for

al 2011	energy based (Electrocautery)		EC	\$ 27,984	OR Purchasing Depart	other surgical procedures, its higher per-case costs suggest that surgeons and institutions can confidently forgo this new technology for breast reduction surgery."
		Hand Piece	HS	\$ 895 (reusable)	Ethicon sales representatives	
			EC	\$ 3.09 (disposable)	OR Purchasing Depart	
		Grounding pad	HS	Not applicable	Ethicon sales representatives	
			EC	\$ 2.82	OR Purchasing Depart	
		Tip (disposable)	HS	\$ 275	Ethicon sales representatives	
			EC	\$ 5.54	OR Purchasing Depart	
		Total for first case (capital purchase)	HS	\$ 20,120	Ethicon sales representatives	
			EC	\$ 27,905.45	OR Purchasing Depart	
		Per subsequent case	HS	\$ 275	Ethicon sales representatives	
			EC	\$ 11.45	OR Purchasing Depart	

Key: US: ultrasound scalpel; HS: harmonic scalpel; EC: electrocautery; OR: operating room; Depart: department.

Table 5.4: Colorectal surgery costs.

Study ID	Comparison	Costs			Source	Economic results
		Item				
		Type	Device	Value		
Gracia et al 2011	US vs other energy based (Monopolar scalpel)	Hospital stay/day	HS	406.98 €	The price of each unit was kindly supplied by the Economical Department of hospital	"The clinical results were obtained without increasing the cost for treatment to the hospital. The financial sustainability of a health publishes is a major interesting fact in developed countries when facing new technologies. In our series the mean cost per procedure reduced by 143 € when harmonic scalpel was used, although this difference had no statistical significance. In this sense, the additional cost of UC was compensated with the decrease in the resource used (mainly hospital stay). The results are stable in the hospital stay reduction but they are not definitive in the cost per procedure, a although in most of the patients (up to 75%) this cost decreases to."
			MS	406.98 €		
		Intensive care unit stay/day	HS	1082.05 €		
			MS	1082.05 €		
		Ultracision per use	HS	519 €		
			MS	-		
		Whole blood transfusion	HS	122.30 €		
			MS	122.30 €		
		Surgical room price/hour	HS	361.95 €		
			MS	361.95 €		
		Mean cost	HS	2,91 €		
			MS	3,06 €		

Targarona et al 2005	US vs other energy based (electrosurgery) - other energy based (Bipolar vessel sealing)	Intraoperative costs: Hourly cost of the operating room	Electrosurgery	1.204 €	-	Company price lists	"Analysis of operative costs showed no significant differences between the three groups. The final costs were similar with all three procedures."
			Bipolar	860 €			
			HS	946 €			
		Cost of the disposable instruments	Electrosurgery	1.569 €	-		
			Bipolar	1.804 €			
			HS	1.907 €			
		Final price	Electrosurgery	2.995 €	-		
			Bipolar	2.664 €			
			HS	2.928 €			

Key: HS: Harmonic Scalpel; MS: monopolar scalpel.

Table 5.5: Colorectal surgery cost-effectiveness.

Study ID	Comparison	Economic analysis type	Perspective	Model/Time horizon	Effectiveness					Costs				Economic results				
					Outcome			Follow up	Source	Type	Item		Source					
					Type	Device	Value				Device	Value						
Hubner et al 2008	US vs Other energy based (Monopolar electrosurgery scissors) vs Other energy based (Bipolar vessel sealing)	Cost-analysis	not reported	August 2005 - December 2007	Dissection time	MES	137	Phase A	Operation nurses	Instrument cost	MES	180 €	Institutional accounting department (value year 2007)	"Costs for operations depend mainly on operating time and material costs. Despite being expensive devices, BVS and UCS may be cost-effective compared with MES, as shown in the present study. The higher material-related costs for BVS and UCS are balanced by a reduced operating time and a decreased need for additional material such as clips. For BVS and UCS the material-related costs per patient decrease with a higher annual caseload, whereas costs for MES remain the same. With an annual caseload of more than 200 patients, BVS and UCS incur significantly lower costs than MES."				
						BVS	105	Phase A	Operation nurses		BVS	549 €						
						UCS	90	Phase A	Operation nurses		UCS	620 €						
						Intraoperative blood loss	MES	125 ml		Surgeon	Theatre time cost	MES	1.045 €		Institutional accounting department (value year 2007)			
							BVS	50 ml		Surgeon		BVS	812 €					
							UCS	50 ml		Surgeon		UCS	699 €					
					Post-operative complications	MES	10 pz	30 days	Surgeon	Additional cost	MES	102 €	Institutional accounting department (value year 2007)					
						BVS	10 pz	30 days	Surgeon		BVS	0 €						
						UCS	6 pz	30 days	Surgeon		UCS	13 €						
															Comprehensive costs per patient for each device	MES	1.382 €	Institutional accounting department (value year 2007)
																BVS	1.364 €	
																UCS	1.323 €	

* The value refer to centre volume of 20 cases

Key: BVS: bipolar vessel sealing; MES: monopolar electrcautery scissor; UCS ultrasonic device.

Table 5.6: Head/neck surgery costs.

Study ID	Comparison	Costs			Source	Economic results
		Item		Value		
		Type	Device			
Koch et al 2011	US vs conventional (Hemoclips or Clamp – cut – tie) or other energy based (Electrocautery)	Estimated Cost	Ultrasonic	450 \$	Office of Financial Analysis at Mayo Clinic	<p>“Ultrasonic shears: \$1747 ± \$117 Fibula Free Laps ; Ultrasonic shears: \$1606 ± \$147 Anterolateral Thigh Free Flaps.”</p> <p>“No Ultrasonic shears: \$2239 ± \$243 Fibula Free Laps; Ultrasonic shears: \$2149 ± \$192 Anterolateral Thigh Free Flaps.”</p> <p>“The estimated cost for harvesting the fibula free laps in which ultrasonic shears were used was \$ 1747 ± \$117, which was significantly decreased compared to cases in which ultrasonic shears were not used at \$2239±\$243. The estimated cost for harvesting the anterolateral thigh free flaps in which ultrasonic shears were used was \$1606 ± \$147, which was significantly decreased compared to cases in which ultrasonic shears were not used at \$2149 ± \$192.”</p>
			LigaClip (average 5 clip)	111 \$/ pz		
		Anesthesia	both	6 \$/ minute		
		Operating room	both	21 \$ / minute		
Shinhar et al 2004	US vs other energy-based (Electrocautery) vs cold surgical dissection	Mean cost of surgery	HS	US\$460.00	-	<p>“HS is clearly more expensive than either EC or SD from strictly an operating room standpoint. However, we must also consider the tangential savings that can be realized by using the HS in terms of lower complication rates. We conclude that the use of the HS is cost-effective as the time-tested methods. AS the use of the HS becomes more commonplace, we expected that its cost will decrease, which will further enhance its cost-effectiveness.”</p>
			EC	US\$310.75		
			SD	US\$300.00		

Key: US: ultrasound scalpel; HS: harmonic scalpel; EC: electrocautery; SD: cold surgical dissection.

Table 5.7: Spinal surgery cost-effectiveness.

Study ID	Comparison	Economic analysis type	Perspective	Model/Time horizon	Effectiveness					Costs				Economic results	
					Outcome			Follow up	Source	Item			Source		
					Type	Device	Value			Type	Device	Value			
Cakir et al 2006	US vs other energy-based (Electrocauterization)	CEA	-	-	Blood loss intra-operative (ml)	HS	803±758	-	Trial	Blod products	HS	€72.07±82.54	-	"Adding the costs of blood products, the total cost per operation was 729.98 with the HS and €749.55 with EC. Because of reduced need for autologous blood products and less frequent use of intraoperative autologous transfusion device the overall costs of HS remained neutral although it is expensive device. It is important specify that this device is only cost-neutral in surgery with major blood loss."	
						EC	1580±1458	-			EC	€219.08±193.25	-		
						Blood loss post-operative (ml)	HS	303±316		-	Operating team	HS	€477.28		-
							EC	596±535		-		EC	€530.47		-
					Total blood loss (ml)	HS	1106±985	-		Materials	HS	€101.83	-		
							EC	2176±1764			-	EC	NR		-
					Device	HS	78.80	-		Device	HS	78.80	-		
							EC	NR			EC	NR	-		
					Total	HS	€729.98	-		Total	HS	€729.98	-		
							EC	€749.55			EC	€749.55	-		

Key: US: ultrasound scalpel; CEA: cost-effectiveness analysis; HS: harmonic scalpel; EC: electrocautery.

Table 5.8: Open thyroid surgery costs.

Study ID	Comparison	Costs			Source	Economic results
		Item				
		Type	Device	Value		
Kowalski et al 2012	US vs conventional (Cut and ligature)	Analgesic	US	US\$2.9±1.9	Hospital and simulation	"The most important difference in costs was for the intraoperative resources, which demonstrated a difference of almost 14% in favor of the harmonic group. After cost simulation, results were U.S. \$2554.7 for the ultrasonic scalpel group versus U.S. \$2470.1 for the conventional group (p = 0.5)."
			CL	US\$2.6±2.4		
		Antiemetic	US	US\$9.7±9.7		
			CL	US\$6.2±8.4		
		Antiulcer	US	US\$0.7±1.9		
			CL	US\$0.9±1.0		
		Intraoperative resources	US	US\$387.2±127.3		
			CL	US\$442.7±113.1		
		Operative time	US	US\$1,333.1±476.9		
			CL	US\$1,596.1±838.7		
		Length of stay	US	US\$419.4±168.7		
			CL	US\$383.6±75.7		
Ultrasonic scalpel	US	US\$370				
	CL	US\$0				
Total	US	US\$2,554.7±525.1				
	CL	US\$2,470.1±923.9				
Rahabari et al 2011	US vs other energy based (Bipolar energy sealing)	Operating room	UC	US\$11,510.9	Medical center billing charges	"There was also no significant difference in total cost, operative cost, or operative time between the two groups (UC vs. B groups). The only significant difference in cost was in the operating room supply cost. The majority of the supply cost was due to the device cost."
			B	US\$11,196.05		
		Operating room supply (device)	UC	US\$3,885.71 (US\$2007.43)		
			B	US\$2,763.61 (US\$1,036.57)		
		Anesthesia	UC	US\$3,921.19		
			B	US\$4,074.27		
		Lab	UC	US\$314.76		
			B	US\$292.57		
		Pathology	UC	US\$1,418.2		
			B	US\$1,555.03		
		Pharmacy	UC	US\$1,119.64		
			B	US\$947.67		
		Pain medication	UC	US\$59.21		
			B	US\$90.74		
Recovery room	UC	US\$1,540.3				
	B	US\$2,280.14				
Total	UC	US\$24,005.96				
	B	US\$23,355.89				

Key: HS: harmonic scalpel; CT: clamp and tie; UC: ultrasonic coagulation; B: bipolar energy sealing.

Table 5.9: Open thyroid surgery cost-effectiveness.

Study ID	Comparison	Economic analysis type	Perspective	Model/Time horizon	Effectiveness				Costs				Economic results		
					Outcome			Follow up	Source	Item				Source	
					Type	Device	Value			Type	Device	Value			
Ortega et al 2004	US vs Conventional (clamp and tie)	CEA		NO/NC	operative time (minutes)	UHS	86±20 (TT) 61±6 (HT)	-	RCT	Global per patient	HS	€985.77±107.08	Hospital	"The difference in cost between the two groups was statistically significant. The use of ultrasonically activated shears is more expensive than resorbable sutures, but taking account of charges for operating room times, the results are cost-effective, with a significant mean difference of fifteen minutes for cases operated on with UHS."	
						C	101±16(TT) 78±10 (HT)	-							
					intraoperative complications (n)	UHS	0	-							
						C	0	-							
					length of hospitalization (days)	UHS	1.07	-							
						C	1.15	-							
					transient postoperative complications (n)	UHS	3	-							
						C	2	-							
sequelae (n)	UHS	0	-												
	C	0	-												
Ruggeri et al 2012	US vs Conventional (knot tying)	CEA	Hospital/Third payer/Social	NO/NC	Pain	-	-	6-24-48 h	RCT	Total hospital	HS	€2,292.52	hospital purchasing price; hospital management control data	"The use of the ultrasound scalpel does not affect duration of hospitalization and reduces operation time by more than 20 minutes, thus reducing the costs associated with the surgical team and OT use. This saving compensates the higher cost of OT equipment and ultrasound scalpel cost. The improvement in QoL results in a QALY gain of 0.07. Cost-effectiveness ratio is dominant in 65 percent of the scenarios considered in the bootstrap simulation. Moreover, the threshold analysis shows 90 percent of the scenarios considered below an ICER of 30,000 euros per QALY."	
						C	€2,411.49								
					QoL	discharge	HS	0.83		1 month	Total direct medical	HS	€2,400.34		All the above sources
							C	0.78				C	€2,540.52		
						3 month	HS	0.90		Total direct non medical	HS	€342.77	Bank of Italy data		
							C	0.83			C	€535.51			
					Total	HS	0.91	Total indirect		HS	€464.49	All the above sources			
						C	0.84			C	€456.93				
					HS	€3,207.60	Total	HS		€3,207.60	All the above sources				
					C	€3,535.96		C		€3,535.96					

Key: US: ultrasound scalpel; CEA: cost effectiveness analysis; NC: not clear; QoL: quality of life; HS: harmonic scalpel; C: conventional; RCT: randomized controlled trial; ICER: incremental cost effectiveness ratio.

Table 5.10: Endoscopic thyroid surgery cost-effectiveness.

Study ID	Comparison	Economic analysis type	Perspective	Model/Time horizon	Effectiveness				Costs				Economic results	
					Outcome			Follow up	Source	Item				Source
					Type	Device	Value			Type	Device	Value		
Barczyński et al 2008	US vs conventional (Clip ligation)	CEA	-	January 2006-December 2007	Operating time (min)	US	31.4±7.7		RCT	Operating theater use	US	4 €/per minute	Official in-hospital price-list for medical procedures of hospital	
						CL	47.5±13.2				CL	4 €/per minute		
					Intraoperative blood loss (ml)	US	12.9±5.7			General anesthesia	US	4 €/ per minute		
						CL	32.8±13				CL	4 €/ per minute		
					Complications (number): Wound seroma	US	0			Ultrasonic shears	US	280 €/single use		
						CL	1				CL	0		
					Transient hypocalcemia	US	2			Clip	US	0		
						CL	1				CL	3 €/single use		
					Transient RLN paresis	US	0			Ligature	US	0		
						CL	1				CL	3 €/single use		
					Length of scar (mm)	US	15.6±1.4	1 month after surgery		Bipolar coagulation	US	0		
						CL	21.5±1.9				CL	100 €/single use		
					Postoperative stay (days)	US	1.3±0.5				US	0		
						CL	1.4±0.6				CL	100 €/single use		
					Patients' cosmetic satisfaction	US	88.9±9.7	1 month						
						CL	96.7±3.2	6 months						
	US	81.9±5.4	1 month											
	CL	95.4±3.9	6 months											

Key: US: ultrasound scalpel; CEA: cost effectiveness analysis; CL: clip ligation; RCT: randomized controlled trial.

Table 5.11: Endoscopic thyroid surgery costs.

Study ID	Comparison	Costs			Source	Economic results
		Item				
		Type	Device	Value		
Bersi da Silva et al 2012	US vs Conventional	-	-	-	-	"Considering the per-minute costs associated with using the operating room, this shortened duration should result in a 4% reduction in the total cost of procedures by using this technology. However, the incremental cost increase due to the use of the harmonic scalpel more than compensates for the savings achieved through a shorter period of time in the operating room. The use of the harmonic scalpel in surgical thyroidectomy reflected a mean increase of 28% in the total cost of the procedure."

Key: US: ultrasound scalpel.

Table 5.12: Thyroid surgery costs (surgical access not reported).

Study ID	Comparison	Costs			Source	Economic results
		Item				
		Type	Device	Value		
Pons et al 2009	US vs conventional (Clump and tie + Bipolar electrocautery) vs other energy based (LigaSure vessel sealing system)	Consumable	CH	US\$563±97	-	"The cost of consumables was 375 and 407 US\$ lower in group one (CH) than in groups two (LVSS) and three (HS), respectively (P=0.001). The overall operative cost was 11 and 85 US\$ more expensive in group one than in groups two and three (P=ns and 0.001), respectively."
			LVSS	US\$938±24		
			HS	US\$970±23		
		Overall operative	CH	US\$2,571±296		
			LVSS	US\$2,560±157		
			HS	US\$2,486±153		
Sebag et al 2009	US vs conventional (Tie and clip)	Operating room use	HS	€584±136	Hospital data from ad hoc micro-costing analysis	"In the cost-minimization analysis, we showed that mean estimated total costs were not statistically different between both groups. Major cost factors were surgical consumables (UAS in the HS group and sutures, clips, and, especially, automatic clips in the TC group) and cost induced by operating room use (equipment and staff). This latter factor is totally dependent on the length of time of surgery. The cost analysis showed that the additional cost of HS use was almost entirely compensated for by the avoided consumption of a part of surgical consumables, as well as the cost reduction of equipment and staff mobilization, due to the reduction in operative times."
			TC	€655±121		
		Surgical consumables	HS	€428±15		
			TC	€323±104		
		Awakening use	HS	€12±3		
			TC	€12±5		
		Total	HS	€1,024±143		
			TC	€990±191		
Lucchini et al 2013	US vs Standard procedure	Device	US	€560.45	-	"According to the economic point of view, the cost of the single intervention with US is less than traditional one." 89
			SP	€36.15		
		Staff	US	€247.55		
			SP	€334.29		
		Operating room use	US	€940.30		
			SP	€1,185.34		
		Hospitalization	US	€1,020.00		
			SP	€1,500.00		
Total	US	€2,768.00				
	SP	€3,055.80				

Key: US: ultrasound scalpel; LVSS: LigaSure vessel sealing system; CH: conventional hemostasis; TC: tie and clip; UAS: ultrasonically activated shear; HS: harmonic scalpel; SP: standard procedure.

5.3 Methodological quality appraisal

The methodological quality of included economic studies was appraised through the CHEERS (Consolidated Health Economic Evaluation reporting Standards) checklist developed by ISPOR³³. The checklist aims at providing detailed guidance on the appropriate reporting of health economic evaluations. It comprises 24 recommendations (for 3 of them exist a two options alternately excludable, two in the Methods category and one in the Results category) divided into six main categories: title/abstract (2); introduction (1); methods (16); results (5); discussion (1) and other (2)³³.

A simplified tool, adapting the CHEERS checklist, was developed to assess the quality of the 12 cost-analyses described above. Recommendations judged to be pertinent only to cost-effectiveness, cost-utility or cost-benefit analyses were not applied (e.g. economic model based recommendations). As regards cost-effectiveness analysis included overall quality reaches middle level; in 4 studies^{47,61,10,32} half items (12-13/24) are fully or partially satisfied; only one economic evaluation⁶⁷ has a higher level of quality (18/24) while the last one⁵ is under average (10/24). The overall quality of all cost-analysis studies^{8,18,28,40,41,42,65,66,70,72} is average with 10/20 items fully or partially satisfied except two^{75,89}, whose quality is very low (5/20 and 6/20 respectively).

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5.4 Discussion of results of economic literature review

We found a body of economic evidence of average quality, mostly based on prospective studies, especially trials with uneven coverage of procedures. All economic studies considered the medical direct costs (e.g. visits, medications, surgical intervention, etc.), except one⁶⁷ that estimated also the indirect costs (patients' loss of productivity). Concerning the 6 cost-effectiveness analyses included, 4^{5,10,32,47} of them measured the direct medical costs of the surgical intervention, 1⁶¹ added the hospitalization costs and the last one⁶⁷ considered the whole healthcare procedure to calculate the average total cost of admission. Similarly the majority of cost analyses (8/12)^{18,40,42,65,66,70,72,75} assessed only the surgical procedure costs, 3 studies^{28,41,89} also considered the hospitalization costs while the last one⁸ took into account only the device system cost. About the cost-effectiveness evaluations only one study⁶⁷ estimated the cost effectiveness measure; in particular the authors estimated the ICERs resulting from multi-varied sensitivity analysis. The evidence suggests that despite the high cost of the ultrasonic energy devices *vis a vis* with their traditional comparators, in complicated procedures, especially those entailing considerable loss of blood and time, the balance was neutral or in favour of

index devices because of shorter operation times, higher quality of life and diminished length of hospital stay.

6. Conclusions

Based on the current evidence of effectiveness and safety, the use of the ultrasonic energy devices in surgery can be linked to the improvement of some relevant outcomes. However, this statement cannot be extended to all the surgical procedures in which the ultrasonic energy devices are currently used. Extrapolations based on clinical plausibility are out of the scope of the present rapid HTA report and, within the present assessment, would be highly speculative. However, it is important to acknowledge that published evidence, identified by our searches, comes *de facto* from one single ultrasonic system (Harmonic, Ethicon Endo-Surgery).

According to our analysis, in a limited number of procedures (Group A), the evidence is clearly in favour of the ultrasonic energy devices (i.e., linked to benefits in one or more outcomes) and comes from secondary studies. The use of the ultrasonic energy devices in some other procedures (Group B) is supported by a number of primary studies that should be furtherly assessed and meta-analysed to produce final clinical guidelines (out of the scope of the present rapid HTA report). In one procedure (Group C), the evidence from secondary studies showed little added benefits from the use of ultrasonic energy devices (i.e., equivalence to conventional or alternative techniques). The use of the technology in a variety of other procedures (Group D) is only supported by primary studies. These have a small sample size and are few in number, thus any conclusive statement requires more evidence.

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Procedures in Group A:

- *Laparoscopic cholecystectomy;*
- *Thyroid surgery;*

Procedures in Group B:

- *Breast surgery (breast surgical procedures for breast cancer);*
- *Haemorrhoidectomy and ano-rectal surgery (haemorrhoidectomy);*

Procedures in Group C:

- *Tonsillectomy;*

Procedures in Group D:

- *Abdominal surgical procedures (hepatic resection; laparoscopic adrenalectomy);*
- *Cardio-vascular surgery (radial artery harvest);*
- *Cardio-vascular surgery (redo saphenous high ligation);*

- *ENT oncological surgery (selective neck dissection);*
- *Gastrointestinal surgery (open total gastrectomy and open left hemicolectomy; gastrectomy with lymph node dissection);*
- *Gynaecological surgery (laparoscopic myomectomy; open abdominal hysterectomy and bilateral salpingo-oophorectomy; vaginal hysterectomy; cervical cone biopsy; ovarian transection; laparoscopic excision of benign ovarian cysts);*
- *Haemorrhoidectomy and ano-rectal surgery (perineal rectosigmoidectomy with perineal levatorplasty);*
- *Laparoscopic colorectal surgery (laparoscopic colorectal resection);*
- *Liver transplantation surgery (living donor liver transplantation);*
- *Lung biopsy (lung parenchyma biopsy);*
- *Orthopaedic surgery (total hip arthroplasty);*
- *Pancreatic surgery (pancreatic resection);*
- *Plastic and reconstructive surgery (pectoralis major myocutaneous flap dissection; anterolateral thigh flap elevation).*

Moreover, the analysis of the economic literature showed advantages in the use of the ultrasonic energy devices in thyroid surgery. No statements about such aspects can be made for laparoscopic cholecystectomy due to the lack of economic studies.

We are aware (*Alessiani M - Personal communication; 5 July 2014*) that the ultrasonic technology is widely used for several other surgical procedures (e.g., laparoscopic hiatal hernia, Heller myotomy, bariatric surgery). However, our searches failed to identify systematic reviews or primary studies related to these procedures. Moreover, other procedures are being studied within registered clinical trials. No statements about these procedures can be done before the results of such studies will be published.

7. Recommendations

We believe in innovation in healthcare and we aim to promote those technologies that have been proved to be more effective or cost-effective than others. We are conscious that the final choice of the most suitable surgical instrument, for the specific procedure, lies in the hands of surgeons (and there it should stay) and we are sure that cautious surgeons will rely on evidence to take the final decision. We thus propose the present rapid HTA report as an “informative tool” to guide that decision. It may also serve as basis to further research in local or national contexts aimed to develop a more comprehensive set of guidelines and indications for the use of the technology in the clinical practice. We encourage the dialogue among stakeholders to reach the common target.

In conclusion, we recommend the use of the ultrasonic energy devices in those procedures for which evidence from secondary studies is in their favour, and economic analyses have shown real advantages. We encourage research to support the use of this technology in those procedures for which evidence is still limited and, once evidence on clinical effectiveness has been made available, we recommend decision makers to consider carefully the economic aspects related to the use of this technology.

Among the ultrasonic energy devices available on the market, we recommend **privileging those** devices for which clinical studies have been published, and consider the use of the other ultrasonic energy devices only within evidence-generation frameworks. New evidence would lead to new recommendations on this technology.

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9. Competing interests declaration

The Authors declare that they will not receive either benefits or harms from the publication of this report.

None of the Authors has or has held shares, consultancies or personal relationships with any of the manufacturers of the devices assessed in this report.

Bibliography

1. Abo-hashem AA, Sarhan A, Aly AM. Harmonic Scalpel compared with bipolar electro-cautery hemorrhoidectomy: a randomized controlled trial. *Int J Surg* 2010; 8(3):243-7.
2. Alexiou VG, Salazar-Salvia MS, Jervis PN, Falagas ME. Modern technology-assisted vs conventional tonsillectomy: a meta-analysis of randomized controlled trials. *Arch Otolaryngol Head Neck Surg* 2011; 137(6):558-70.
3. Amaral JF (1994) The experimental development of an ultrasonically activated scalpel for laparoscopic use. *Surg Laparosc Endosc* 4:92-99.
4. Awadzi G, Frappell J, Oriolowo A, Sibanda T. A clinical evaluation of the LOTUS ultrasonic shears in gynaecological surgery. *Gynecol. Surg.* 2005; 2(3):183-6.
5. Barczynski, M.; Konturek, A., and Cichon, S. Minimally invasive video-assisted thyroidectomy (MIVAT) with and without use of harmonic scalpel--a randomized study. *Langenbecks Arch Surg.* 2008 Sep; 393(5):647-54.
6. Boccasanta P, Venturi M, Barbieri S, Roviario G. Impact of new technologies on the clinical and functional outcome of Altemeier's procedure: a randomized, controlled trial. *Dis Colon Rectum* 2006; 49(5):652-60.
7. Brazio PS, Laird PC, Xu C et al. Harmonic scalpel versus electrocautery for harvest of radial artery conduits: reduced risk of spasm and intimal injury on optical coherence tomography. *J Thorac Cardiovasc Surg* 2008; 136(5):1302-8.
8. Burdette, T. E.; Kerrigan, C. L., and Homa, K. Harmonic scalpel versus electrocautery in breast reduction surgery: a randomized controlled trial. *Plast Reconstr Surg.* 2011 Oct; 128(4):243e-249e.
9. CADTH Rapid Response Report – Alternative Energy Devices for Adults Undergoing General Surgery: A Review of Clinical Effectiveness and Evidence-Based Guidelines. 11 December 2012.
10. Cakir, B.; Ulmar, B.; Schmidt, R.; Kelsch, G.; Geiger, P.; Mehrkens, H. H.; Puhl, W., and Richter, M. Efficacy and cost effectiveness of harmonic scalpel compared with electrocautery in posterior instrumentation of the spine. *Eur Spine J.* 2006 Jan; 15(1):48-54.
11. Cavallaro G, Polistena A, D'Ermo G et al. Usefulness of harmonic focus during axillary lymph node dissection: A prospective study. *Surg. Innov.* 2011; 18(3):231-4.
12. Chung CC, Cheung HY, Chan ES, Kwok SY, Li MK. Stapled hemorrhoidopexy vs. Harmonic Scalpel hemorrhoidectomy: a randomized trial. *Dis Colon Rectum* 2005; 48(6):1213-9.
13. Cirocchi R, Boselli C, Guarino S et al. Total thyroidectomy with ultrasonic dissector for cancer: multicentric experience. *World J Surg Oncol* 2012; 10:70.
14. Cirocchi R, D'Ajello F, Trastulli S et al. Meta-analysis of thyroidectomy with ultrasonic dissector versus conventional clamp and tie. *World J Surg Oncol* 2010; 8:112.
15. Contin P, Goossen K, Grummich K et al. ENERgized vessel sealing systems versus CONventional hemostasis techniques in thyroid surgery - The ENERCON systematic review and network meta-analysis. *Langenbeck's Arch. Surg.* 2013; 398(8):1039-56.
16. Covidien website - www.covidien.com/sonicision/pages.aspx (accessed on 13th Feb 2014).

17. Currie A, Chong K, Davies GL, Cummins RS. Ultrasonic dissection versus electrocautery in mastectomy for breast cancer - a meta-analysis. *Eur J Surg Oncol* 2012; 38(10):897-901.
18. da Silva, F. B.; Limoeiro, A. C.; Del Bianco, J.; Teich, V.; Teich, N.; Teixeira, J. C.; Vasconcelos, A. L., and Sardenberg, C. Impact of the use of vessel sealing or harmonic scalpel on intra-hospital outcomes and the cost of thyroidectomy procedures. *Einstein (Sao Paulo)*. 2012 Jul-2012 Sep 30; 10(3):354-9.
19. Deo S, Hazarika S, Shukla NK, Kar M, Samaiya A. A prospective randomized trial comparing harmonic scalpel versus electrocautery for pectoralis major myocutaneous flap dissection. *Plast Reconstr Surg* 2005; 115(4):1006-9.
20. Dhepnorrarat RC, Witterick IJ. New technologies in thyroid cancer surgery. *Oral Oncol*. 2013 Jul;49(7):659-64.
21. Di Lorenzo N, Franceschilli L, Allaix ME, Asimakopoulos AD, Sileri P, Gaspari AL. Radiofrequency versus ultrasonic energy in laparoscopic colorectal surgery: a metaanalysis of operative time and blood loss. *Surg Endosc* 2012; 26(10):2917-24.
22. Dibidino, R.; Ruggeri, M.; Marchetti, M.; Lombardi, N.; Raffaelli, M.; Attina, G., and Cicchetti, A. Harmonic study: A cost-effectiveness evaluation of ultrasonically activated shears for total thyroidectomy. [Italian]. *PharmacoEconomics - Italian Research Articles*. 2010; 12(3):143-155.
23. Dumantepe M, Kehlibar T, Gullu AU et al. Comparison of ultrasonically activated scalpel and traditional technique in radial artery harvesting; an electron microscopic evaluation. *Anadolu Kardiyol Derg* 2011; 11(3):250-6.
24. Ecker T, Carvalho AL, Choe JH, Walosek G, Preuss KJ. Hemostasis in thyroid surgery: harmonic scalpel versus other techniques--a meta-analysis. *Otolaryngol Head Neck Surg* 2010; 143(1):17-25.
25. Ethicon Endo-surgery website - www.ethicon.com/healthcare-professionals/products/energy-devices/#!/harmonic-portfolio (accessed on 13th Feb 2014).
26. Fitz Gerald AL, Tan J, Chan K W et al. Comparison of ultrasonic shears and traditional suture ligation for vaginal hysterectomy: Randomized controlled trial. *Journal of Minimally Invasive Gynecology*.
27. Garas G, Okabayashi K, Ashrafian H et al. Which hemostatic device in thyroid surgery? A network meta-analysis of surgical technologies. *Thyroid* 2013; 23(9):1138-50.
28. Gracia, J. A.; Ramirez, J. M.; Callejo, D.; Elia, M.; Maeso, S.; Aguilera, V., and Martinez, M. Efficiency and outcomes of harmonic device in transanal endoscopic microsurgery compared with monopolar scalpel. *Surg. Endosc. Interv. Tech*. 2011; 25(10):3209-3213.
29. Hamahata A, Saitou T, Kubo K, Beppu T, Yamaki T, Sakurai H. Usefulness of harmonic focus during anterolateral thigh flap elevation. *J Reconstr Microsurg*.
30. Higgins JPT, Green S (editors). *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.0.2 [updated September 2009]. The Cochrane Collaboration. Available from www.cochrane-handbook.org 2009.
31. Homayounfar K, Meis J, Jung K, Klosterhalfen B, Sprenger T, Conradi LC, Langer C, Becker H. Ultrasonic scalpel causes greater depth of soft tissue necrosis compared to monopolar electrocautery at standard power level settings in a pig model. *BMC Surg*. 2012 Feb 23;12:3.
32. Hubner, M.; Demartines, N.; Muller, S.; Dindo, D.; Clavien, P.-A., and Hahnloser, D. Prospective randomized study of monopolar scissors, bipolar vessel sealer and ultrasonic shears in laparoscopic colorectal surgery. *Br. J. Surg*. 2008; 95(9):1098-1104.

33. Husereau D, Drummond M, Petrou S, et al. Consolidated health economic evaluation reporting standards (CHEERS) – Explanation and elaboration: A report of the ISPOR health economic evaluations publication guidelines good reporting practices task force. *Value health* 2013;16:231-50.
34. Inoue K, Nakane Y, Michiura T et al. Ultrasonic scalpel for gastric cancer surgery: a prospective randomized study. *J Gastrointest Surg* 2012; 16(10):1840-6.
35. Iovino F, Auriemma PP, Ferraraccio F, Antoniol G, Barbarisi A. Preventing seroma formation after axillary dissection for breast cancer: a randomized clinical trial. *Am J Surg* 2012; 203(6):708-14.
36. Ivanov D, Babovic S, Selesi D, Ivanov M, Cvijanovic R. Harmonic Scalpel hemorrhoidectomy: a painless procedure? *Med Pregl* 2007; 60(9-10):421-6.
37. Janssen PF, Brolmann HA, Huirne JA. Effectiveness of electrothermal bipolar vessel-sealing devices versus other electrothermal and ultrasonic devices for abdominal surgical hemostasis: a systematic review. *Surg Endosc* 2012; 26(10):2892-901.
38. Kartsionis C, Koutlaki N, Evaggelinos D et al. Comparison of the ultrasonic scalpel to CO(2) laser in cervical conization. *Minim Invasive Ther Allied Technol* 2011; 20(3):185-8.
39. Khan AA, Aasim MU, Saeed I. Ultrasonic scalpel tonsillectomy versus cold dissection/electrocautery tonsillectomy: A Pakistani perspective. *Pak. Paediatr. J.* 2012; 36(1):23-6.
40. Koch, C. A.; Olsen, S. M.; Martin, E. J., and Moore, E. J. Ultrasonic shears in free-tissue transfer: Increased efficiency and cost savings. *Otolaryngol. Head Neck Surg.* 2011; 144(2):201-205.
41. Kontos, M.; Kothari, A., and Hamed, H. Effect of harmonic scalpel on seroma formation following surgery for breast cancer: a prospective randomized study. *J BUON.* 2008 Apr-2008 Jun 30; 13(2):223-30.
42. Kowalski, L. P.; Sanabria, A.; Vartanian, J. G.; Lima, R. A.; Toscano De Mendonca, U. B.; Roberto Dos Santos, C.; Boldrini Junior, D.; Barbalho De Mello, L. E.; Pinto, F. P.; Lehn, C. N.; Correa, L. A. C.; Deditis, R. A.; Guimaraes, A. V.; Pedruzzi, P. A. G.; Ramos, G. H. A.; Goncalves, A. J.; Suehara, A. B.; Kanda, J. L.; De Castro Capuzzo, R.; Carlos De Oliveira, J.; Curado, M. P.; Francisco De Gois Filho, J.; Fukuyama, E.; Beserra Junior, I. M.; Bentes De Carvalho Neto, P., and Carvalho, A. L. Total thyroidectomy with ultrasonic scalpel: A multicenter, randomized controlled trial. *Head Neck.* 2012; 34(6):805-812.
43. Kung J, Chiappelli F, Cajulis OO, Avezova R, Kossan G, Chew L, Maida CA. From Systematic Reviews to Clinical Recommendations for Evidence-Based Health Care: Validation of Revised Assessment of Multiple Systematic Reviews (R-AMSTAR) for Grading of Clinical Relevance. *The Open Dentistry Journal*, 2010, 4, 84-91.
44. Kwok SY, Chung CC, Tsui KK, Li MK. A double-blind, randomized trial comparing Ligasure and Harmonic Scalpel hemorrhoidectomy. *Dis Colon Rectum* 2005; 48(2):344-8.
45. Lang BH, Ng SH, Lau LL, Cowling BJ, Wong KP. A systematic review and meta-analysis comparing the efficacy and surgical outcomes of total thyroidectomy between harmonic scalpel versus ligasure. *Ann Surg Oncol* 2013; 20(6):1918-26.
46. Leblanc E, Narducci F, Farre I et al. Radical fimbriectomy: a reasonable temporary risk-reducing surgery for selected women with a germ line mutation of BRCA 1 or 2 genes? Rationale and preliminary development. *Gynecol Oncol* 2011; 121(3):472-6.
47. Lee, J. S. and Hong, T. H. Comparison of various methods of mesoappendix dissection in laparoscopic appendectomy. *J. Laparoendosc. Adv. Surg. Techn.* 2014; 24(1):28-31.

48. Li CZ, Liu B, Wen ZQ, Sun Q. The impact of electrocoagulation on ovarian reserve after laparoscopic excision of ovarian cysts: a prospective clinical study of 191 patients. *Fertil Steril* 2009; 92(4):1428-35.
49. Litta P, Fantinato S, Calonaci F et al. A randomized controlled study comparing harmonic versus electrocautery in laparoscopic myomectomy. *Fertil Steril* 2010; 94(5):1882-6.
50. Lumachi F, Basso SMM, Santeufemia DA, Bonamini M, Chiara GB. Ultrasonic dissection system technology in breast cancer: A case-control study in a large cohort of patients requiring axillary dissection. *Breast Cancer Res. Treat.* 2013; 142(2):399-404.
51. Mahabaleswar V, Kaman L, Iqbal J, Singh R. Monopolar electrocautery versus ultrasonic dissection of the gallbladder from the gallbladder bed in laparoscopic cholecystectomy: a randomized controlled trial. *Can J Surg* 2012; 55(5):307-11.
52. MdS 2013 - Rapporto sulla spesa del SSN per l'acquisto di dispositivi medici, I semestre 2013
http://www.salute.gov.it/portale/news/p3_2_1_1_1.jsp?lingua=italiano&menu=notizie&p=dalministero&id=1418
53. Molnar TF, Benko I, Szanto Z, Laszlo T, Horvath OP. Lung biopsy using harmonic scalpel: a randomised single institute study. *Eur J Cardiothorac Surg* 2005; 28(4):604-6.
54. Mouton WG, Bessell JR, Zehnder T, Wirth R, Naef M, Wagner HE. A randomised trial of ultrasonic dissection versus electrocoagulation to reduce lymphatic complications after surgery for recurrent sapheno-femoral incompetence. *Eur J Vasc Endovasc Surg* 2005; 29(3):313-5.
55. Mouton WG, Marklewitz MM, Friedli S et al. Neovascularisation after surgery for recurrent saphenofemoral incompetence: does surgical dissection technique matter? *Vasa* 2011; 40(4):296-301.
56. Neumann C, Street I, Lowe D, Sudhoff H. Harmonic scalpel tonsillectomy: a systematic review of evidence for postoperative hemorrhage. *Otolaryngol Head Neck Surg* 2007; 137(3):378-84.
57. Newcomb WL, Hope WW, Schmelzer TM, et al. Comparison of blood vessel sealing among new electrocautery and ultrasonic devices. *Surg Endosc.* 2009;23:90–6.
58. Olmez A, Karabulut K, Aydin C, Kayaalp C, Yilmaz S. Comparison of harmonic scalpel versus conventional knot tying for transection of short hepatic veins at liver transplantation: prospective randomized study. *Transplant Proc* 2012; 44(6):1717-9.
59. Olympus Medical website (Italy) -
www.olympus.it/medical/en/medical_systems/products_services/product_details/product_details_10121.jsp (accessed on 13th Feb 2014).
60. Olympus Medical website (UK & Ireland) -
www.olympus.co.uk/medical/en/medical_systems/products_services/rigid_endoscopy/energy_systems_1/productselector_surgical_systems_energy_systems.jsp (accessed on 13th Feb 2014).
61. Ortega, J.; Sala, C.; Flor, B., and Lledo, S. Efficacy and cost-effectiveness of the UltraCision harmonic scalpel in thyroid surgery: an analysis of 200 cases in a randomized trial. *J Laparoendosc Adv Surg Tech A.* 2004 Feb; 14(1):9-12.
62. Ozer MT, Yigit T, Uzar AI et al. A comparison of different hemorrhoidectomy procedures. *Saudi Med J* 2008; 29(9):1264-9.

63. Patel A, Asopa S, Dunning J. Does radial artery harvest with a harmonic scalpel result in fewer complications than standard electrocautery methods? *Interact Cardiovasc Thorac Surg.* 2006 Feb;5(1):36-41.
64. Peker K, Inal A, Gullu H et al. Comparison of vessel sealing systems with conventional. *Iran. Red Crescent Med.J.* 2013; 15(6):488-96.
65. Pons, Y.; Gauthier, J.; Ukkola-Pons, E.; Clément, P.; Roguet, E.; Poncet, J. L., and Conessa, C. Comparison of LigaSure vessel sealing system, harmonic scalpel, and conventional hemostasis in total thyroidectomy. *Otolaryngology--Head and Neck Surgery : Official Journal of American Academy of Otolaryngology-Head and Neck Surgery.* 2009; 141(4):496-501.
66. Rahbari, R.; Mathur, A.; Kitano, M.; Guerrero, M.; Shen, W. T.; Duh, Q.-Y.; Clark, O. H., and Kebebew, E. Prospective randomized trial of ligasure versus harmonic hemostasis technique in thyroidectomy. *Ann. Surg. Oncol.* 2011; 18(4):1023-1027.
67. Ruggeri M, Dibidino R, Marchetti M, Lombardi CP, Raffaelli M, Cicchetti A. The harmonic study: cost-effectiveness evaluation of the use of the ultrasonic scalpel in total thyroidectomy. *Int J Technol Assess Health Care* 2012; 28(3):259-64.
68. Sankaranarayanan G, Resapu RR, Jones DB, Schwaitzberg S, De S. Common uses and cited complications of energy in surgery. *Surg Endosc* 2013;27:3056-3072.
69. Sasi W. Dissection by ultrasonic energy versus monopolar electrosurgical energy in laparoscopic cholecystectomy. *JLS* 2010; 14(1):23-34.
70. Sebag, F.; Fortanier, C.; Ippolito, G.; Lagier, A.; Auquier, P., and Henry, J. F. Harmonic scalpel in multinodular goiter surgery: impact on surgery and cost analysis. *J Laparoendosc Adv Surg Tech A.* 2009 Apr; 19(2):171-4.
71. Shin YS, Koh YW, Kim SH, Choi EC. The efficacy of the harmonic scalpel in neck dissection: a prospective randomized study. *Laryngoscope* 2013; 123(4):904-9.
72. Shinhar, S.; Scotch, B. M; Belenky, W.; Madgy, D., and Hauptert, M. Harmonic scalpel tonsillectomy versus hot electrocautery and cold dissection: an objective comparison (Structured abstract). *Ear Nose and Throat Journal.* 2004; 83(10):712-715.
73. Smith C, Zarebczan B, Alhefdhi A, Chen H. Infrared Thermographic Profiles of Vessel Sealing Devices on Thyroid Parenchyma. *Journal of Surgical Research.* 2011. Vol.170 (1) 64-68.
74. SRA Developments website - www.lotusultrasonicscalpel.net/technology/ (accessed on 13th Feb 2014).
75. Targarona, E. M.; Balague, C.; Marin, J.; Neto, R. B.; Martinez, C.; Garriga, J., and Trias, M. Energy sources for laparoscopic colectomy: a prospective randomized comparison of conventional electrosurgery, bipolar computer-controlled electrosurgery and ultrasonic dissection. Operative outcome and costs analysis. *Surg Innov.* 2005 Dec; 12(4):339-44.
76. Tomas T, Janicek P, Nachtnabl L, Ondrusek S, Kunovsky R. Use of the harmonic system in total hip arthroplasty: a prospective, comparative, observational study. *Hip Int* 2010; 20(3):314-9.
77. Tou S, Malik AI, Wexner SD, Nelson RL. Energy source instruments for laparoscopic colectomy. *Cochrane Database Syst Rev* 2011; (5):CD007886.
78. Uzunoglu FG, Stehr A, Fink JA et al. Ultrasonic dissection versus conventional dissection techniques in pancreatic surgery: a randomized multicentre study. *Ann Surg* 2012; 256(5):675-9; discussion 679-80.

79. Walen SG, Rudmik LR, Dixon E, Matthews TW, Nakoneshny SC, Dort JC. The utility of the harmonic scalpel in selective neck dissection: a prospective, randomized trial. *Otolaryngol Head Neck Surg* 2011; 144(6):894-9.
80. Wilhelm D, Szabo M, Glass F, Schuhmacher C, Friess H, Feussner H. Randomized controlled trial of ultrasonic dissection versus standard surgical technique in open left hemicolectomy or total gastrectomy. *Br J Surg* 2011; 98(2):220-7.
81. Xiong J, Altaf K, Huang W et al. A meta-analysis of randomized clinical trials that compared ultrasonic energy and monopolar electrosurgical energy in laparoscopic cholecystectomy. *J. Laparoendosc. Adv. Surg. Techn.* 2012; 22(8):768-77.
82. Böhm D, Kubitz A, Lebrecht A, Schmidt M, Gerhold-Ay A, Battista M, Stewen K, Solbach C, Kölbl H. Prospective randomized comparison of conventional instruments and the Harmonic Focus[®] device in breast-conserving therapy for primary breast cancer. *Eur J Surg Oncol.* 2012; 38(2):118-24.
83. He Q, Zhuang D, Zheng L, Fan Z, Zhou P, Zhu J, Lv Z, Chai J, Cao L. Harmonic focus versus electrocautery in axillary lymph node dissection for breast cancer: a randomized clinical study. *Clin Breast Cancer.* 2012; 12(6):454-8.
84. Yilmaz KB, Dogan L, Nalbant H, Akinci M, Karaman N, Ozaslan C, Kulacoglu H. Comparing scalpel, electrocautery and ultrasonic dissector effects: the impact on wound complications and pro-inflammatory cytokine levels in wound fluid from mastectomy patients. *J Breast Cancer.* 2011; 14(1):58-63.
85. Shapira OM, Eskenazi BR, Anter E, et al. Endoscopic versus conventional radial artery harvest for coronary artery bypass grafting: functional and histologic assessment of the conduit. *J Thorac Card Surg.* 2006; 131:388–94.
86. Choi MG, Oh SJ, Noh JH, Sohn TS, Kim S, Bae JM. Ultrasonically activated shears versus electrocautery in open gastrectomy for gastric cancer: a randomized controlled trial. *Gastric Cancer.* 2014 Jul; 17(3):556-61.
87. Bulus H, Tas A, Coskun A, Kucukazman M. Evaluation of two hemorrhoidectomy techniques: Harmonic scalpel and Ferguson's with electrocautery. *Asian J Surg.* 2014; 37(1):20-3.
88. Omar W, Mahmoud S, Farid M. Harmonic scalpel[®] versus conventional diathermy hemorrhoidectomy; gain or pain? *Egyptian Journal of Surgery,* 2011, 30(3):111–118.
89. Lucchini R, Sanguinetti A, Monacelli M, Triola R, Avenia S, Conti C, Santoprete S, Avenia N, Health technology assessment and thyroid surgery *G Chir,* 2013, 34(7/8):198-201.
90. www.accessdata.fda.gov/cdrh_docs/pdf/K993054.pdf
91. www.accessdata.fda.gov/cdrh_docs/pdf10/K100597.pdf
92. www.accessdata.fda.gov/cdrh_docs/pdf10/K101797.pdf
93. www.accessdata.fda.gov/cdrh_docs/pdf11/K111202.pdf
94. www.accessdata.fda.gov/cdrh_docs/pdf12/K121550.pdf
95. www.accessdata.fda.gov/cdrh_docs/pdf5/K050885.pdf
96. www.accessdata.fda.gov/cdrh_docs/pdf6/K062000.pdf
97. www.accessdata.fda.gov/cdrh_docs/pdf6/K063531.pdf

List of acronyms and abbreviations

CND: Classificazione Nazionale Dispositivi medici – national classification of medical devices.

CCT: controlled clinical trial.

CE mark: conformity marking for certain products sold within the European Economic Area.

CT: computed tomography.

ENT: ear, nose, and throat.

GMDN: global medical device nomenclature.

HTA: health technology assessment.

ICER: incremental cost-effectiveness ratio.

MRI: magnetic resonance imaging.

NOS: Newcastle-Ottawa Scale.

OCT: optical coherence tomography.

QALY: quality-adjusted life year.

QoL: quality of life.

RAAS: renin-angiotensin-aldosterone system

RCT: randomised clinical trial.

RDM: general repertory of medical devices.

SSN: Servizio Sanitario Nazionale – the Italian national health service.

Appendix 1 – Search strategy (effectiveness and safety)

Searches have been performed on 10th February 2014 in the following databases: MEDLINE, Embase, and The Cochrane Library (all databases).

Searches started from January 2004. Only full-text in English. Only studies on humans.

MEDLINE

Ultrasonic Surgical Procedures/instrumentation (MESH) OR Ultrasonic Surgical Procedures/methods (MESH) OR Ultrasonic Surgical Procedures/adverse effects (MESH) OR "ultrasonic surgical procedure*" OR "surgical instruments" OR "ultrasound surgery"	AND	harmonic scalpel" OR "harmonic shears" OR "ultrasonic shears" OR "ultrasonic scalpel" OR "ultrasonic coagulator" OR Dissector OR Cauterization, OR Cutting, OR Ablation, OR Coagulation, OR Dissection, OR Dissector OR Vessel sealing, OR Resection, OR Incision. OR Scalpel OR "surgical energy device" OR "Ultrasonic energy device" OR Sonicision OR SonoSurg OR Thunderbeat OR Sonoca OR "Bipolar radiofrequency devices" OR "Energy based device*" OR Sonication OR Sonicision OR Ultracision OR Ultra* scalpel OR Vaporization
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OR

"Energy device*" OR Ultrasonic AND procedure* OR "energy based" OR "harmonic scalpel OR Ultrasoni AND device* OR Ultrasonic AND scalpel OR Ultrasonic AND shears	AND	Surgery OR surgical
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Clinical Trial; Comparative Study; Meta-Analysis; Review; Systematic Reviews; Randomized Controlled Trial; Controlled Clinical Trial.

Embase

<p>Ultrasound surgery (EMTREE TERM) OR</p> <p>(Ultrasonic Surgical Procedures).exp OR</p> <p>(ultrasonic surgical procedure).exp OR</p> <p>(surgical instruments).exp OR</p> <p>(ultrasound surgery).exp</p>	<p>AND</p>	<p>(harmonic scalpel) OR</p> <p>(harmonic shears) OR</p> <p>(ultrasonic shears) OR</p> <p>(ultrasonic scalpel) OR</p> <p>(ultrasonic coagulator) OR</p> <p>Dissector OR</p> <p>Cauterization, OR</p> <p>Cutting, OR</p> <p>Ablation,OR</p> <p>Coagulation, OR</p> <p>Dissection, OR</p> <p>Dissector OR</p> <p>(Vessel sealing) OR</p> <p>Resection, OR</p> <p>Incision.OR</p> <p>Scalpel OR</p> <p>(surgical energy device) OR</p> <p>(Ultrasonic energy device) OR</p> <p>Sonicision OR</p> <p>SonoSurg OR</p> <p>Thunderbeat OR</p> <p>Sonoca OR</p> <p>(Bipolar radiofrequency devices) OR</p> <p>(Energy based device) OR</p> <p>Sonication OR</p> <p>Sonicision OR</p> <p>Ultracision OR</p> <p>(Ultra scalpel) OR</p> <p>Vaporization</p>
<p>"Energy device*" OR</p> <p>Ultrasonic AND procedure*OR</p> <p>"energy based" OR</p> <p>"harmonic scalpel OR</p> <p>Ultrasoni AND device* OR</p> <p>Ultrasonic AND scalpel OR</p> <p>Ultrasonic AND shears</p>	<p>AND</p>	<p>Surgery OR surgical</p>

([cochrane review]/lim OR [controlled clinical trial]/lim OR [meta analysis]/lim OR [randomized controlled trial]/lim OR [systematic review]/lim) AND ([article]/lim OR [review]/lim OR [short survey]/lim) AND ([english]/lim AND [humans]/lim AND [embase]/lim

Cochrane Library (all databases)

<p>Ultrasonic Surgical Procedures/instrumentation (MESH) OR Ultrasonic Surgical Procedures/methods (MESH) OR Ultrasonic Surgical Procedures/adverse effects (MESH) OR "ultrasonic surgical procedure*" (ti,ab,kw) OR "surgical instruments" (ti,ab,kw) OR "ultrasound surgery" (ti,ab,kw)</p>	<p>AND</p>	<p>"harmonic scalpel" (ti,ab,kw) OR "harmonic shears" " (ti,ab,kw) OR "ultrasonic shears" " (ti,ab,kw) OR "ultrasonic scalpel" " (ti,ab,kw) OR "ultrasonic coagulator" " (ti,ab,kw) OR Dissector " (ti,ab,kw) OR Cauterization, " (ti,ab,kw) OR Cutting, " (ti,ab,kw) OR Ablation, " (ti,ab,kw) OR Coagulation, " (ti,ab,kw) OR Dissection, " (ti,ab,kw) OR Dissector " (ti,ab,kw) OR Vessel sealing, " (ti,ab,kw) OR Resection, " (ti,ab,kw) OR Incision. " (ti,ab,kw) OR Scalpel " (ti,ab,kw) OR "surgical energy device" " (ti,ab,kw) OR "Ultrasonic energy device" " (ti,ab,kw) OR Sonicision " (ti,ab,kw) OR SonoSurg" (ti,ab,kw) OR Thunderbeat" (ti,ab,kw) OR Sonoca " (ti,ab,kw) OR "Bipolar radiofrequency devices" " (ti,ab,kw) OR "Energy based device*" " (ti,ab,kw) OR Sonication " (ti,ab,kw) OR Sonicision " (ti,ab,kw) OR Ultracision " (ti,ab,kw) OR Ultra* scalpel" (ti,ab,kw) OR Vaporization " (ti,ab,kw)</p>
<p>"Energy device*" OR Ultrasonic AND procedure*OR "energy based" OR "harmonic scalpel OR Ultrasoni AND device* OR Ultrasonic AND scalpel OR Ultrasonic AND shears</p>	<p>AND</p>	<p>Surgery OR surgical</p>

Appendix 2 – Excluded studies (effectiveness and safety)

Table A2.1: Summary of the excluded records with reason for exclusion (from 366 records initially identified).

Reasons for exclusion	Number of records excluded
Study design – non comparative	14
Study design – retrospective	44
Study design – single-case report	2
Study design – ex vivo study	10
Study design – surgical technique	5
Study design – surgical management	6
Publication type – author reply	1
Study status – study protocol	2
Study type – narrative review	15
Study type – conference abstract	6
Irrelevant endpoint for this review	3
Other application of ultrasonic energy	69
Not on ultrasonic energy device	41
Device not specified or not of interest	18
Duplicate citations	4
Published before the timeframe of this review (i.e., 2004)	9
Language – not English	5
Inappropriate comparator	1
Not retrievable in full-text	2
Published before or included in one of the latest reviews	60
Total excluded	317

Table A2.2: Included studies.

Type of study	Number of included studies
Systematic reviews	14
Primary studies	35
Total included	49

List of the full references of the excluded records:

2. Adnan MT, Abdel-Fattah MM, Makhdoom NK, El-Khouly AA. Does the use of radiofrequency ultrasonic dissector in tonsillectomy have a beneficial effect over the use of laser? Saudi Med J 2008; 29(12):1775-8.

published before or included in one of the latest reviews

3. Agcaoglu O, Aliyev S, Mitchell J, Milas M, Siperstein A, Berber E. The use of the harmonic scalpel versus knot tying for modified radical neck dissection. Surg Innov 2013; 20(1):81-5.

study design (study design - retrospective)

4. Ahmed HU, Hindley RG, Dickinson L et al. Focal therapy for localised unifocal and multifocal prostate cancer: a prospective development study. *Lancet Oncol* 2012; 13(6):622-32.

other application of ultrasonic energy

5. Al-Mahfoudh R, Qattan E, Ellenbogen JR, Wilby M, Barrett C, Pigott T. Applications of the ultrasonic bone cutter in spinal surgery-our preliminary experience. *Br. J. Neurosurg.* 2014; 28(1):56-60.

other application of ultrasonic energy

6. Alam M. The future of noninvasive procedural dermatology. *Semin Cutan Med Surg* 2013; 32(1):59-61.

study type (study type – narrative review)

7. Aldrighetti L, Pulitano C, Arru M, Catena M, Finazzi R, Ferla G. "Technological" approach versus clamp crushing technique for hepatic parenchymal transection: a comparative study. *J Gastrointest Surg* 2006; 10(7):974-9.

study design (study design - retrospective)

8. Aldrighetti L, Pulitano C, Catena M et al. A prospective evaluation of laparoscopic versus open left lateral hepatic sectionectomy. *J Gastrointest Surg* 2008; 12(3):457-62.

study design (study design - retrospective)

10. Alfredson H. Ultrasound and Doppler-guided mini-surgery to treat midportion Achilles tendinosis: results of a large material and a randomised study comparing two scraping techniques. *Br J Sports Med* 2011; 45(5):407-10.

other application of ultrasonic energy

11. Ali E, Saso S, Ashrafian H, Athanasiou T. Does a skeletonized or pedicled right gastro-epiploic artery improve patency when used as a conduit in coronary artery bypass graft surgery? *Interact Cardiovasc Thorac Surg* 2010; 10(2):293-8.

study design (study design - non comparative)

12. Ali NS, Ikram M, Akhtar S, Moghira I, Nawaz A, Arain A. Harmonic scalpel versus electrocautery tonsillectomy: a comparative study in adult patients. *J Pak Med Assoc* 2011; 61(3):256-9.

not retrievable in full-text

13. Aloia TA, Zorzi D, Abdalla EK, Vauthey JN. Two-surgeon technique for hepatic parenchymal transection of the noncirrhotic liver using saline-linked cautery and ultrasonic dissection. *Ann Surg* 2005; 242(2):172-7.

study design (study design - retrospective)

14. Alongi F, Russo G, Spinelli A et al. Can magnetic resonance image-guided focused ultrasound surgery replace local oncology treatments? A review. *Tumori* 2011; 97(3):259-64.

other application of ultrasonic energy

15. Anitua E, Begona L, Orive G. Two-stage split-crest technique with ultrasonic bone surgery for controlled ridge expansion: a novel modified technique. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2011; 112(6):708-10.

other application of ultrasonic energy

16. Attwood SE, Lundell L, Ell C et al. Standardization of surgical technique in antireflux surgery: the LOTUS Trial experience. *World J Surg* 2008; 32(6):995-8.

study design (study design - non comparative)

17. Attwood SE, Lundell L, Hatlebakk JG et al. Medical or surgical management of GERD patients with Barrett's esophagus: the LOTUS trial 3-year experience. *J Gastrointest Surg* 2008; 12(10):1646-54; discussion 1654-5.

not on ultrasonic energy device

19. Aydogan F, Saribeyoglu K, Simsek O et al. Comparison of the electrothermal vessel-sealing system versus endoclip in laparoscopic appendectomy. *J Laparoendosc Adv Surg Tech A* 2009; 19(3):375-8.

not on ultrasonic energy device

20. Ayodeji ID, Hop WC, Tetteroo GW, Bonjer HJ, de Graaf EJ. Ultracision Harmonic Scalpel and multifunctional tem400 instrument complement in transanal endoscopic microsurgery: a prospective study. *Surg Endosc* 2004; 18(12):1730-7.

inappropriate comparator

21. Babademez MA, Yorubulut M, Yurekli MF et al. Comparison of minimally invasive techniques in tongue base surgery in patients with obstructive sleep apnea. *Otolaryngol Head Neck Surg* 2011; 145(5):858-64.

device not specified or not of interest

22. Bachmann G. Expanding treatment options for women with symptomatic uterine leiomyomas: timely medical breakthroughs. *Fertil Steril* 2006; 85(1):46-7; discussion 48-50.

study type (study type – narrative review)

23. Banerjee A, Singh S, Tempe DK. Intraoperative endocardial ablation of chronic atrial fibrillation along with mitral valve surgery using high frequency ultrasound with a ball-tipped harmonic scalpel probe. *Indian Heart J* 2004; 56(2):178-80.

other application of ultrasonic energy

24. Bang SL, Nalachandran S. Upper limb ischaemia - a single centre experience. *Ann Acad Med Singapore* 2009; 38(10):891-3.

study design (study design - retrospective)

25. Barczynski M, Konturek A, Cichon S. Minimally invasive video-assisted thyroidectomy (MIVAT) with and without use of harmonic scalpel--a randomized study. *Langenbecks Arch Surg* 2008; 393(5):647-54.

published before or included in one of the latest reviews

26. Basu S, Kamal SA, Basu S, Kamal SA. Harmonic scalpel tonsillectomy: a prospective and randomised study. XVIII IFOS World Congress 2005; Rome.

conference abstract (no full text-available)

27. Bessa SS, Abdel-Razek AH, Sharaan MA, Bassiouni AE, El-Khishen MA, El-Kayal el-SA. Laparoscopic cholecystectomy in cirrhotics: a prospective randomized study comparing the conventional diathermy and the harmonic scalpel for gallbladder dissection. *J Laparoendosc Adv Surg Tech A* 2011; 21(1):1-5.

published before or included in one of the latest reviews

28. Bessa SS, Al-Fayoumi TA, Katri KM, Awad AT. Clipless laparoscopic cholecystectomy by ultrasonic dissection. *J Laparoendosc Adv Surg Tech A* 2008; 18(4):593-8.

published before or included in one of the latest reviews

29. Bignell MB, Ramwell A, Evans JR, Dastur N, Simson JN. Complications of transanal endoscopic microsurgery (TEMS): a prospective audit. *Colorectal Dis* 2010; 12(7 Online):e99-103.

study design (study design - retrospective)

30. Blankenship DR, Gourin CG, Porubsky EA et al. Harmonic Scalpel versus cold knife dissection in superficial parotidectomy. *Otolaryngol Head Neck Surg* 2004; 131(4):397-400.

study design (study design - retrospective)

31. Blumberg D. Is operative conversion necessary for patients diagnosed with dense adhesions during an elective laparoscopic colectomy? *Surg. Innov.* 2008; 15(3):213-8.

study design (study design - non comparative)

33. Bouwsma EV, Gorny KR, Hesley GK, Jensen JR, Peterson LG, Stewart EA. Magnetic resonance-guided focused ultrasound surgery for leiomyoma-associated infertility. *Fertil Steril* 2011; 96(1):e9-e12.

other application of ultrasonic energy

34. Bove A, Bongarzoni G, Palone G et al. Comparative study of an electrothermal bipolar vessel sealing system (LigaSure(R)), a harmonic curved shears (Harmonic Focus), and traditional technique in total thyroidectomy. *Am Surg* 2010; 76(7):E94-6.

published before or included in one of the latest reviews

35. Brauer JA, Patel U, Hale EK. Laser skin resurfacing, chemical peels, and other cutaneous treatments of the brow and upper lid. *Clin Plast Surg* 2013; 40(1):91-9.

other application of ultrasonic energy

36. Braunewell S, Gunther M, Preusser T. Toward focused ultrasound liver surgery under free breathing. *Crit Rev Biomed Eng* 2012; 40(3):221-34.

other application of ultrasonic energy

38. Burdette TE, Kerrigan CL, Homa K. Harmonic scalpel versus electrocautery in breast reduction surgery: a randomized controlled trial. *Plast Reconstr Surg* 2011; 128(4):243e-9e.

device not specified or not of interest

39. Burton Martin J, Doree Carolyn. Harmonic scalpel versus other surgical procedures for tonsillectomy. *Cochrane Database of Systematic Reviews* .

study status (study status - study protocol)

40. Cakir B, Ulmar B, Schmidt R et al. Efficacy and cost effectiveness of harmonic scalpel compared with electrocautery in posterior instrumentation of the spine. *Eur Spine J* 2006; 15(1):48-54.

study design (study design - retrospective)

41. Calo PG, Pisano G, Medas F, Tatti A, Tuveri M, Nicolosi A. The use of the harmonic scalpel in thyroid surgery. Our experience. *Ann Ital Chir* 2012; 83(1):7-12.

study design (study design - retrospective)

42. Campagnacci R, De Sanctis A, Baldarelli M et al. Hepatic resections by means of electrothermal bipolar vessel device (EBVS) LigaSure V: early experience. *Surg Endosc* 2007; 21(12):2280-4.

published before or included in one of the latest reviews

43. Campagnacci R, de Sanctis A, Baldarelli M, Rimini M, Lezoche G, Guerrieri M. Electrothermal bipolar vessel sealing device vs. ultrasonic coagulating shears in laparoscopic colectomies: a comparative study. *Surg Endosc* 2007; 21(9):1526-31.

published before or included in one of the latest reviews

44. Caporossi A, Baiocchi S, Mazzotta C, Traversi C, Caporossi T. Parasurgical therapy for keratoconus by riboflavin-ultraviolet type A rays induced cross-linking of corneal collagen. Preliminary refractive results in an Italian study. *J. Cataract Refractive Surg.* 2006; 32(5):837-45.

other application of ultrasonic energy

45. Catena F, Ansaloni L, Di Saverio S, Gazzotti F, Coccolini F, Pinna AD. The HAC Trial (Harmonic for Acute Cholecystitis) Study. Randomized, double-blind, controlled trial of Harmonic(H) versus Monopolar Diathermy (M) for laparoscopic cholecystectomy (LC) for acute cholecystitis (AC) in adults. *Trials* 2009; 10:34.

published before or included in one of the latest reviews

46. Catena F, Ansaloni L, Di Saverio S, Gazzotti F, Coccolini F, Pinna AD. Prospective analysis of 101 consecutive cases of laparoscopic cholecystectomy for acute cholecystitis operated with harmonic scalpel. *Surg Laparosc Endosc Percutan Tech* 2009; 19(4):312-6.

published before or included in one of the latest reviews

48. Cengiz Y, Dalenback J, Edlund G et al. Improved outcome after laparoscopic cholecystectomy with ultrasonic dissection: a randomized multicenter trial. *Surg Endosc* 2010; 24(3):624-30.

published before or included in one of the latest reviews

49. Cengiz Y, Janes A, Grehn A, Israelsson LA. Randomized clinical trial of traditional dissection with electrocautery versus ultrasonic fundus-first dissection in laparoscopic cholecystectomy. *Br. J. Surg.* 2005; 92(7):810-3.

published before or included in one of the latest reviews

50. Chang HL, Lim HW, Su FH, Tsai ST, Wang YW. Win or lose? Percutaneous nephrostomy for a terminal-stage cervical-cancer patient featuring obstructive uropathy. *J Palliat Care* 2006; 22(1):57-60.

study design (single-case report)

51. Chaudhary A, Negi S, Bhojwani R. Frey's procedure using the harmonic scalpel. *Surg Today* 2005; 35(3):263-4.

study design (study design - non comparative)

52. Cheng LH, Hutchison IL. Thyroid surgery. *Br J Oral Maxillofac Surg* 2012; 50(7):585-91.

study type (study type – narrative review)

53. Choi J, Raghavan M. Diagnostic imaging and image-guided therapy of skeletal metastases. *Cancer Control* 2012; 19(2):102-12.

other application of ultrasonic energy

55. Chung CC, Ha JP, Tai YP, Tsang WW, Li MK. Double-blind, randomized trial comparing Harmonic Scalpel hemorrhoidectomy, bipolar scissors hemorrhoidectomy, and scissors excision: ligation technique. *Dis Colon Rectum* .

published before the timeframe (2002)

56. Cikirikçioğlu M, Yasa M, Kerry Z et al. The effects of the Harmonic Scalpel on the vasoreactivity and endothelial integrity of the radial artery: a comparison of two different techniques. *J Thorac Cardiovasc Surg* .

study design (study design - non comparative)

57. Cionni RJ, Crandall AS, Felsted D. Length and frequency of intraoperative occlusive events with new torsional phacoemulsification software. *J. Cataract Refractive Surg.* 2011; 37(10):1785-90.

other application of ultrasonic energy

59. Cirocchi R, D'Ajello F, Trastulli S et al. Meta-analysis of thyroidectomy with ultrasonic dissector versus conventional clamp and tie. *World J Surg Oncol* 2010; 8:112.

published before or included in one of the latest reviews

60. Colen RR, Jolesz FA. Future potential of MRI-guided focused ultrasound brain surgery. *Neuroimaging Clin N Am* 2010; 20(3):355-66.

other application of ultrasonic energy

61. Collison PJ, Weiner R. Harmonic scalpel versus conventional tonsillectomy: a double-blind clinical trial. *Ear Nose Throat J* 2004; 83(10):707-10.

published before or included in one of the latest reviews

62. Connor CW, Hynynen K. Patterns of thermal deposition in the skull during transcranial focused ultrasound surgery. *IEEE Trans Biomed Eng* 2004; 51(10):1693-706.

other application of ultrasonic energy

64. Cordon C, Fajardo R, Ramirez J, Herrera MF. A randomized, prospective, parallel group study comparing the Harmonic Scalpel to electrocautery in thyroidectomy. *Surgery* 2005; 137(3):337-41.

published before or included in one of the latest reviews

65. Cortadellas T, Cordoba O, Espinosa-Bravo M et al. Electrothermal bipolar vessel sealing system in axillary dissection: a prospective randomized clinical study. *Int J Surg* 2011; 9(8):636-40.

not on ultrasonic energy device

67. Cushing S, Chiodo A, El Masri W, Smith O. The painful truth: evaluating post-operative pain in monopolar cautery vs. harmonic scalpel tonsillectomy. 61st Annual Meeting of the Canadian Society of Otolaryngology - Head & Neck Surgery (CSOHNS) .

conference abstract (no full text-available)

68. Cushing SL, Smith O, Chiodo A, Elmasri W, Munro-Peck P. Evaluating postoperative pain in monopolar cautery versus harmonic scalpel tonsillectomy. *Otolaryngol Head Neck Surg* 2009; 141(6):710-5.e1.

published before or included in one of the latest reviews

69. D'Ajello F, Cirocchi R, Docimo G et al. Thyroidectomy with ultrasonic dissector: a multicentric experience. *G Chir* 2010; 31(6-7):289-92.

published before or included in one of the latest reviews

70. da Silva FB, Limoeiro AC, Del Bianco J et al. Impact of the use of vessel sealing or harmonic scalpel on intra-hospital outcomes and the cost of thyroidectomy procedures. *Einstein (Sao Paulo)* 2012; 10(3):354-9.

study design (study design - retrospective)

71. Dai LH, Xu B, Zhu GH. Hand-assisted laparoscopic surgery of abdominal large visceral organs. *World J Gastroenterol* 2006; 12(29):4736-40.

study design (study design - non comparative)

72. Danic D, Hadzibegovic AD, Stojadinovic T, Damjanovic D, Gudelj A, Mahovne I. Harmonic scalpel surgical treatment of the tongue angioleiomyoma--case report and review of the literature. *Coll Antropol* 2012; 36 Suppl 2:167-70.

study design (single-case report)

73. de la Fuente J, Miguel-Perez MI, Balius R, Guerrero V, Michaud J, Bong D. Minimally invasive ultrasound-guided carpal tunnel release: a cadaver study. *J Clin Ultrasound* 2013; 41(2):101-7.

study design (ex vivo study)

74. de la Pena JA, Soto-Miranda MA, Lopez-Salguero JF. Ultrasonically assisted face-lift. *Aesthetic Plast Surg* 2012; 36(4):780-7.

other application of ultrasonic energy

75. Del Valle-Fernandez R, Ruiz CE. Transcatheter heart valves for the treatment of aortic stenosis: state-of-the-art. *Minerva Cardioangiol* 2008; 56(5):543-56.

not on ultrasonic energy device

76. Demirturk F, Aytan H, Caliskan AC. Comparison of the use of electrothermal bipolar vessel sealer with harmonic scalpel in total laparoscopic hysterectomy. *J Obstet Gynaecol Res* 2007; 33(3):341-5.

study design (study design - retrospective)

78. Dhepnorrarat RC, Witterick IJ. New technologies in thyroid cancer surgery. *Oral Oncol* 2013; 49(7):659-64.

study type (study type - narrative review)

80. Di Luozzo G, Moussa F, Schor J, Traad E, Williams D, Carrillo R. Harmonic scalpel for pericardiectomy: novel approach to an old cardiac dilemma. *Heart Surg Forum* 2004; 7(5):E525-7.

study design (study design - retrospective)

81. Dibidino R, Ruggeri M, Marchetti M et al. Harmonic study: A cost-effectiveness evaluation of ultrasonically activated shears for total thyroidectomy. [Italian]. *PharmacoEconomics - Italian Research Articles* .

language – not English

82. Docimo G, Ruggiero R, Gubitosi A et al. Ultrasound scalpel in thyroidectomy. Prospective randomized study. *Ann Ital Chir* 2012; 83(6):491-6.

published before or included in one of the latest reviews

83. Dokleštic K, Karamarkovic A, Stefanovic B et al. The efficacy of three transection techniques of the liver resection: a randomized clinical trial. *Hepatogastroenterology* 2012; 59(117):1501-6.

device not specified or not of interest

84. Dong X, Yang Z. High-intensity focused ultrasound ablation of uterine localized adenomyosis. *Curr Opin Obstet Gynecol* 2010; 22(4):326-30.

other application of ultrasonic energy

85. Dotai T, Coker AM, Antozzi L et al. Transgastric large-organ extraction: the initial human experience. *Surg Endosc* 2013; 27(2):394-9.

not on ultrasonic energy device

86. Druzijanic N, Pogorelic Z, Perko Z, Mrklic I, Tomic S. Comparison of lateral thermal damage of the human peritoneum using monopolar diathermy, Harmonic scalpel and LigaSure. *Can J Surg* 2012; 55(5):317-21.

irrelevant endpoint

89. El Nakeeb A, Askar W, El Lithy R, Farid M. Clipless laparoscopic cholecystectomy using the Harmonic scalpel for cirrhotic patients: a prospective randomized study. *Surg Endosc* 2010; 24(10):2536-41.

published before or included in one of the latest reviews

90. Elias WJ, Huss D, Voss T et al. A pilot study of focused ultrasound thalamotomy for essential tremor. *N Engl J Med* 2013; 369(7):640-8.

other application of ultrasonic energy

91. Engh GA, Ammeen D. Is an intact anterior cruciate ligament needed in order to have a well-functioning unicondylar knee replacement? *Clin Orthop Relat Res* 2004; (428):170-3.

not on ultrasonic energy device

92. Entezari K, Hoffmann P, Goris M, Peltier A, Van Velthoven R. A review of currently available vessel sealing systems. *Minim Invasive Ther Allied Technol* 2007; 16(1):52-7.

study type (study type - narrative review)

93. Erkut B, Unlu Y, Karapolat S et al. Comparison of harmonic scalpel and high-frequency electrocautery in radial artery harvesting. *J Cardiovasc Surg (Torino)* 2008; 49(3):371-9.

device not specified or not of interest

94. Fabiani C, Franco V, Covello F, Brambilla E, Gagliani MM. Removal of surgical smear layer. *J Endod* 2011; 37(6):836-8.

other application of ultrasonic energy

95. Fan ST. Protection of the liver during partial hepatectomy. *Hepatobiliary Pancreat Dis Int* 2004; 3(4):490-4.

study design (surgical technique)

96. Fawzy HF. Harvesting of the radial artery for coronary artery bypass grafting: comparison of ultrasonic harmonic scalpel dissector with the conventional technique. *J Card Surg* 2009; 24(3):285-9.

study design (study design - retrospective)

97. Fennessy FM, Tempany CM. A review of magnetic resonance imaging-guided focused ultrasound surgery of uterine fibroids. *Top Magn Reson Imaging* 2006; 17(3):173-9.

other application of ultrasonic energy

98. Fennessy FM, Tempany CM, McDannold NJ et al. Uterine leiomyomas: MR imaging-guided focused ultrasound surgery--results of different treatment protocols. *Radiology* 2007; 243(3):885-93.

other application of ultrasonic energy

99. Ferns SP, Sprengers ME, van Rooij WJ et al. Late reopening of adequately coiled intracranial aneurysms: frequency and risk factors in 400 patients with 440 aneurysms. *Stroke* 2011; 42(5):1331-7.

not on ultrasonic energy device

100. Fiocca R, Mastracci L, Attwood SE et al. Gastric exocrine and endocrine cell morphology under prolonged acid inhibition therapy: results of a 5-year follow-up in the LOTUS trial. *Aliment Pharmacol Ther* 2012; 36(10):959-71.

not on ultrasonic energy device

101. Fiocca R, Mastracci L, Engstrom C et al. Long-term outcome of microscopic esophagitis in chronic GERD patients treated with esomeprazole or laparoscopic antireflux surgery in the LOTUS trial. *Am J Gastroenterol* 2010; 105(5):1015-23.

not on ultrasonic energy device

102. Fischer K, Gedroyc W, Jolesz FA. Focused ultrasound as a local therapy for liver cancer. *Cancer J* 2010; 16(2):118-24.

other application of ultrasonic energy

104. Fitzgerald JE, Malik M, Ahmed I. A single-blind controlled study of electrocautery and ultrasonic scalpel smoke plumes in laparoscopic surgery. *Surg Endosc* 2012; 26(2):337-42.

irrelevant endpoint

105. Fujimoto T, Lane GJ, Teramoto H, Kameoka S, Miyano T. Evaluation of ultrasonically activated scalpel performance in pediatric laparoscopic surgery. *Pediatric Endosurgery & Innovative Techniques* .

published before the timeframe (2000)

106. Funaki K, Sawada K, Maeda F, Nagai S. Subjective effect of magnetic resonance-guided focused ultrasound surgery for uterine fibroids. *J Obstet Gynaecol Res* 2007; 33(6):834-9.

other application of ultrasonic energy

107. Furusawa H, Namba K, Thomsen S et al. Magnetic resonance-guided focused ultrasound surgery of breast cancer: reliability and effectiveness. *J Am Coll Surg* 2006; 203(1):54-63.

other application of ultrasonic energy

108. Gaida JE, Cook J. Treatment options for patellar tendinopathy: critical review. *Curr Sports Med Rep* 2011; 10(5):255-70.

other application of ultrasonic energy

109. Galmiche JP, Hatlebakk J, Attwood S et al. Laparoscopic antireflux surgery vs esomeprazole treatment for chronic GERD: the LOTUS randomized clinical trial. *JAMA* 2011; 305(19):1969-77.

not on ultrasonic energy device

111. Garcia Segui A, Gascon Mir M. Comparative study between laparoscopic extraperitoneal and open adenectomy. [Spanish]. *Actas Urol Esp* .

language – not English

112. Georghiou GP, Stamler A, Berman M, Sharoni E, Vidne BA, Sahar G. Advantages of the ultrasonic harmonic scalpel for radial artery harvesting. *Asian Cardiovasc Thorac Ann* 2005; 13(1):58-60.

published before or included in one of the latest reviews

113. Gil-Moreno A, Puig O, Perez-Benavente MA et al. Total laparoscopic radical hysterectomy (type II-III) with pelvic lymphadenectomy in early invasive cervical cancer. *J Minim Invasive Gynecol* 2005; 12(2):113-20.

study design (study design - retrospective)

114. Gilbey P, Gadban H, Letichevsky V, Talmon Y. Harmonic scalpel tonsillectomy using the curved shears instrument versus cold dissection tonsillectomy: a retrospective study. *Ann Otol Rhinol Laryngol* 2008; 117(1):46-50.

study design (study design - retrospective)

115. Giraldo F, Esteva I, Bergero T et al. Corona glans clitoroplasty and urethroreputial vestibuloplasty in male-to-female transsexuals: the vulval aesthetic refinement by the Andalusia Gender Team. *Plast Reconstr Surg* 2004; 114(6):1543-50.

study design (surgical technique)

116. Goldberg DJ, Marmur ES, Hussain M. Treatment of terminal and vellus non-pigmented hairs with an optical/bipolar radiofrequency energy source-with and without pre-treatment using topical aminolevulinic acid. *J Cosmet Laser Ther* 2005; 7(1):25-8.

not on ultrasonic energy device

117. Gombos EC, Kacher DF, Furusawa H, Namba K. Breast focused ultrasound surgery with magnetic resonance guidance. *Top Magn Reson Imaging* 2006; 17(3):181-8.

other application of ultrasonic energy

118. Goretzki PE, Schwarz K, Lammers BJ. Implementing the general use of dissection devices in thyroid surgery from prospective randomized trial to daily use. *Surg Technol Int* 2009; 18:86-92.

published before or included in one of the latest reviews

119. Goretzki PE, Pohl P, Terorde N, Krause Paulus RM, Lammers BJ. [New methods in thyroid surgery - The ligation free preparation and dissection with LigaSure]. *Viszeralchirurgie* .

not on ultrasonic energy device

120. Gracia JA, Ramirez JM, Callejo D et al. Efficiency and outcomes of harmonic device in transanal endoscopic microsurgery compared with monopolar scalpel. *Surg Endosc* 2011; 25(10):3209-13.

study design (study design - retrospective)

121. Grauvogel J, Scheiwe C, Kaminsky J. Use of Piezosurgery for internal auditory canal drilling in acoustic neuroma surgery. *Acta Neurochir*. 2011; 153(10):1941-7.

other application of ultrasonic energy

122. Griffiths A, terHaar G, Rivens I, Giussani D, Lees C. High-intensity focused ultrasound in obstetrics and gynecology: the birth of a new era of noninvasive surgery? *Ultraschall Med* 2012; 33(7):E8-15.

other application of ultrasonic energy

123. Guerrieri M, Crosta F, De Sanctis A, Baldarelli M, Lezoche G, Campagnacci R. Use of the electrothermal bipolar vessel system (EBVS) in laparoscopic adrenalectomy: a prospective study. *Surg Endosc* 2008; 22(1):141-5.

published before or included in one of the latest reviews

124. Haji A, Ryan S, Bjarnason I, Papagrigroriadis S. High-frequency mini-probe ultrasound as a useful adjunct in the management of patients with malignant colorectal polyps. *Colorectal Dis* 2013; 15(3):304-8.

other application of ultrasonic energy

125. Hallgrimsson P, Loven L, Westerdahl J, Bergenfelz A. Use of the harmonic scalpel versus conventional haemostatic techniques in patients with Grave disease undergoing total

thyroidectomy: a prospective randomised controlled trial. *Langenbecks Arch Surg* 2008; 393(5):675-80.

published before or included in one of the latest reviews

127. Hanby DF, Gremillion G, Zieske AW et al. Harmonic scalpel versus flexible CO2 laser for tongue resection: a histopathological analysis of thermal damage in human cadavers. *World J Surg Oncol* 2011; 9:83.

study design (ex vivo study)

128. Hanssen A, Plotnikov S, Dubois R. Laparoscopic appendectomy using a polymeric clip to close the appendicular stump. *JLS* 2007; 11(1):59-62.

not on ultrasonic energy device

129. Heikkila J, Hynynen K. Investigation of optimal method for inducing harmonic motion in tissue using a linear ultrasound phased array--a simulation study. *Ultrason Imaging* 2006; 28(2):97-113.

not on ultrasonic energy device

130. Henteleff HJ, Kalavrouziotis D. Evidence-based review of the surgical management of hyperhidrosis. *Thorac Surg Clin* 2008; 18(2):209-16.

study design (surgical management)

131. Hermans MH. Preservation methods of allografts and their (lack of) influence on clinical results in partial thickness burns. *Burns* 2011; 37(5):873-81.

not on ultrasonic energy device

132. Hetzler D. In reference to histologic assessment of thermal injury to tonsillectomy specimens: a comparison of electrocautery, coblation, harmonic scalpel, and tonsillotome. *Laryngoscope* 2010; 120(5):1077.

study design (ex vivo study)

133. Heverhagen AE, Dietzel K, Waldmann J, Langer P, Fendrich V, Bartsch DK. Harmonic scalpel versus conventional dissection technique in pylorus-preserving partial duodenopancreatectomy. *Dig Surg* 2012; 29(5):420-5.

study design (study design - retrospective)

134. Holub Z, Voracek J, Jun LK, Lukac J. Laparoscopic hysterectomy: Randomized study of harmonic scalpel and electrosurgery. *J Gynecol Surg* .

published before the timeframe (2000)

135. Holub Z, Voracek J, Kliment L, Lukac J. Laparoscopic hysterectomy using harmonic scalpel versus electrosurgery: a randomized trial. 1st Congress on Controversies in Obstetrics, Gynecology & Infertility .

conference abstract (no full text-available)

136. Hsu TC. Abdominoperineal resection without an abdominal incision for rectal cancer has the advantage of no abdominal wound complication and easier stoma care. *Am Surg* 2012; 78(2):166-70.

not on ultrasonic energy device

137. Hsu TC. Feasibility of colectomy with mini-incision. *Am J Surg* 2005; 190(1):48-50.

not on ultrasonic energy device

138. Hu X, Ohnmeiss DD, Lieberman IH. Use of an ultrasonic osteotome device in spine surgery: Experience from the first 128 patients. *Eur. Spine J.* 2013; 22(12):2845-9.

other application of ultrasonic energy

139. Huang X, Zheng Y, Liu X et al. A comparison between endoscope-assisted partial parotidectomy and conventional partial parotidectomy. *Otolaryngol. Head Neck Surg.* 2009; 140(1):70-5.

not on ultrasonic energy device

140. Hubner M, Demartines N, Muller S, Dindo D, Clavien PA, Hahnloser D. Prospective randomized study of monopolar scissors, bipolar vessel sealer and ultrasonic shears in laparoscopic colorectal surgery. *Br J Surg* 2008; 95(9):1098-104.

published before or included in one of the latest reviews

141. Hudson SB, Stewart EA. Magnetic resonance-guided focused ultrasound surgery. *Clin Obstet Gynecol* 2008; 51(1):159-66.

other application of ultrasonic energy

142. Hung SH, Chu D, Chen FM, Chen T, Chen RC. Evaluation of the harmonic scalpel in breast conserving and axillary staging surgery. *J Chin Med Assoc* 2012; 75(10):519-23.

study design (study design - retrospective)

143. Ikeuchi H, Nakano H, Uchino M et al. Safety of one-stage restorative proctocolectomy for ulcerative colitis. *Dis Colon Rectum* 2005; 48(8):1550-5.

study design (study design - non comparative)

144. Inabnet WB, Shifrin A, Ahmed L, Sinha P. Safety of same day discharge in patients undergoing sutureless thyroidectomy: a comparison of local and general anesthesia. *Thyroid* 2008; 18(1):57-61.

not on ultrasonic energy device

146. Inoue K, Nakane Y, Michiura T et al. Ultrasonic Scalpel for Gastric Cancer Surgery: A Prospective Randomized Study. *J Gastrointest Surg* .

duplicate citation

148. Istre O. Management of symptomatic fibroids: conservative surgical treatment modalities other than abdominal or laparoscopic myomectomy. *Best Pract Res Clin Obstet Gynaecol* 2008; 22(4):735-47.

study type (study type - narrative review)

150. Jackson LL, Gourin CG, Thomas DS, Porubsky ES, Klippert FN, Terris DJ. Use of the harmonic scalpel in superficial and total parotidectomy for benign and malignant disease. *Laryngoscope* 2005; 115(6):1070-3.

study design (study design - retrospective)

151. Jacobs MA, Gultekin DH, Kim HS. Comparison between diffusion-weighted imaging, T2-weighted, and postcontrast T1-weighted imaging after MR-guided, high intensity, focused ultrasound treatment of uterine leiomyomata: preliminary results. *Med Phys* 2010; 37(9):4768-76.

other application of ultrasonic energy

152. Jagannathan J, Sanghvi NT, Crum LA et al. High-intensity focused ultrasound surgery of the brain: part 1--A historical perspective with modern applications. *Neurosurgery* 2009; 64(2):201-10; discussion 210-1.

other application of ultrasonic energy

153. Jain SK, Tanwar R, Kaza RC, Agarwal PN. A prospective, randomized study of comparison of clipless cholecystectomy with conventional laparoscopic cholecystectomy. *J Laparoendosc Adv Surg Tech A* 2011; 21(3):203-8.

published before or included in one of the latest reviews

155. Jedrzejczak P, Sokalska A, Spaczynski RZ, Duleba AJ, Pawelczyk L. Effects of presacral neurectomy on pelvic pain in women with and without endometriosis. *Ginekol Pol* 2009; 80(3):172-8.

study design (study design - non comparative)

156. Ji W, Ding K, Yang R, Liu XD, Li N, Li JS. Outpatient single-incision laparoscopic cholecystectomy in 22 patients with gallbladder disease. *Hepatobiliary Pancreat Dis Int* 2010; 9(6):629-33.

study design (study design - non comparative)

157. Jolesz FA, McDannold N. Current status and future potential of MRI-guided focused ultrasound surgery. *J Magn Reson Imaging* 2008; 27(2):391-9.

other application of ultrasonic energy

158. Kamal SA, Basu S, Kapoor L, Kulandaivelu G, Talpalikar S, Papasthatis D. Harmonic scalpel tonsillectomy: a prospective study. *Eur Arch Otorhinolaryngol* 2006; 263(5):449-54.

published before or included in one of the latest reviews

159. Kandil T, El Nakeeb A, El Hefnawy E. Comparative study between clipless laparoscopic cholecystectomy by harmonic scalpel versus conventional method: a prospective randomized study. *J Gastrointest Surg* 2010; 14(2):323-8.

published before or included in one of the latest reviews

160. Kang SK, Kunanandam T, Clark L. Prospective, case-control study of surgical efficiency of ultrasonic shear ('harmonic scalpel') thyroidectomy compared with conventional thyroidectomy. *J Laryngol Otol* 2008; 122(11):1194-6.

published before or included in one of the latest reviews

161. Kanter V, Weldon E, Nair U et al. A quantitative and qualitative analysis of ultrasonic versus sonic endodontic systems on canal cleanliness and obturation. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2011; 112(6):809-13.

other application of ultrasonic energy

162. Kaouk JH, Goel RK. Single-port laparoscopic and robotic partial nephrectomy. *Eur Urol* 2009; 55(5):1163-9.

study design (surgical technique)

164. Katz MH, Merchant NB, Brower S et al. Standardization of surgical and pathologic variables is needed in multicenter trials of adjuvant therapy for pancreatic cancer: results from the ACOSOG Z5031 trial. *Ann Surg Oncol* 2011; 18(2):337-44.

study design (surgical management)

165. Kaul SA, Menon M. Da Vinci assisted cystoprostatectomy and urinary diversion: a paradigm shift in surgical management of bladder cancer. *Minerva Urol Nefrol* 2007; 59(2):149-57.

study design (surgical management)

166. Kavlakoglu B, Pekcici R, Oral S. Clipless cholecystectomy: which sealer should be used? *World J Surg* 2011; 35(4):817-23.

published before or included in one of the latest reviews

167. Kavlakoglu B, Pekcici R, Oral S. Verification of clipless closure of cystic duct by harmonic scalpel. *J Laparoendosc Adv Surg Tech A* 2010; 20(7):591-5.

published before or included in one of the latest reviews

168. Kemal O. Harmonic scalpel versus bipolar tonsillectomy: a double-blind clinical trial. *Eur Arch Otorhinolaryngol* 2012; 269(5):1533-6.

device not specified or not of interest

169. Kendrisic M, Ivic G, Kendrisic ML, Kendrisic ML. Ultrasonic harmonic scalpel tonsillectomy. Proceedings of the 9th International Conference on Pediatric Otorhinolaryngology (ESPO), Paris, France, 18-21 June 2006 .

conference abstract (no full text-available)

171. Khan S, Pawlak SE, Eggenberger JC et al. Surgical treatment of hemorrhoids: prospective, randomized trial comparing closed excisional hemorrhoidectomy and the Harmonic Scalpel technique of excisional hemorrhoidectomy. *Dis Colon Rectum* .

published before the timeframe (2001)

172 Khan S, Khan S, Chawla T, Murtaza G. Harmonic Scalpel Versus Electrocautery Dissection in Modified Radical Mastectomy: A Randomized Controlled Trial.

Ann Surg Oncol. 2013 Nov 14.

device not specified or not of interest

173. Khoder WY, Sroka R, Siegert S, Stief CG, Becker AJ. Outcome of laser-assisted laparoscopic partial nephrectomy without ischaemia for peripheral renal tumours. *World J Urol* 2012; 30(5):633-8.

not on ultrasonic energy device

174. Kilic M, Keskek M, Ertan T, Yoldas O, Bilgin A, Koc M. A prospective randomized trial comparing the harmonic scalpel with conventional knot tying in thyroidectomy. *Adv Ther* 2007; 24(3):632-8.

published before or included in one of the latest reviews

175. Kim EC, Byun YS, Kim MS. Microincision versus small-incision coaxial cataract surgery using different power modes for hard nuclear cataract. *J. Cataract Refractive Surg.* 2011; 37(10):1799-805.

other application of ultrasonic energy

176. Kim JH, Lee YP. [Randomized trial comparing a Starion and a Harmonic Scalpel hemorrhoidectomy]. *Journal of the Korean Society of Coloproctology* .

language – not English

177. Kinami Y, Noda T, Ozaki T. Efficacy of low-intensity pulsed ultrasound treatment for surgically managed fresh diaphyseal fractures of the lower extremity: multi-center retrospective cohort study. *J Orthop Sci* 2013; 18(3):410-8.

other application of ultrasonic energy

178. Knight BC, Tait WF. Dacron Patch Infection Following Carotid Endarterectomy: A Systematic Review of the Literature. *Eur. J. Vasc. Endovasc. Surg.* 2009; 37(2):140-8.

not on ultrasonic energy device

179. Koch CA, Olsen SM, Martin EJ, Moore EJ. Ultrasonic shears in free-tissue transfer: Increased efficiency and cost savings. *Otolaryngol. Head Neck Surg.* 2011; 144(2):201-5.

study design (study design - retrospective)

180. Koh JS, Mohan PC, Howe TS et al. Fasciotomy and surgical tenotomy for recalcitrant lateral elbow tendinopathy: early clinical experience with a novel device for minimally invasive percutaneous microresection. *Am J Sports Med* 2013; 41(3):636-44.

other application of ultrasonic energy

181. Koh YW, Park JH, Kim JW, Lee SW, Choi EC. Clipless and sutureless endoscopic thyroidectomy using only the harmonic scalpel. *Surg Endosc* 2010; 24(5):1117-25.

study design (study design - non comparative)

182. Koh YW, Park JH, Lee SW, Choi EC. The harmonic scalpel technique without supplementary ligation in total thyroidectomy with central neck dissection: a prospective randomized study. *Ann Surg* 2008; 247(6):945-9.

published before or included in one of the latest reviews

183. Konopke R, Kersting S, Makowiec F et al. Resection of colorectal liver metastases: is a resection margin of 3 mm enough? : a multicenter analysis of the GAST Study Group. *World J Surg* 2008; 32(9):2047-56.

study design (surgical technique)

184. Kontos M, Kothari A, Hamed H. Effect of harmonic scalpel on seroma formation following surgery for breast cancer: a prospective randomized study. *J BUON* 2008; 13(2):223-30.

published before or included in one of the latest reviews

185. Kopelman D, Papa M. Magnetic resonance-guided focused ultrasound surgery for the noninvasive curative ablation of tumors and palliative treatments: a review. *Ann Surg Oncol* 2007; 14(5):1540-50.

other application of ultrasonic energy

186. Kos M, Engelke W. Advantages of a new technique of neck dissection using an ultrasonic scalpel. *J Craniomaxillofac Surg* 2007; 35(1):10-4.

device not specified or not of interest

187. Kowalski LP, Sanabria A, Vartanian JG et al. Total thyroidectomy with ultrasonic scalpel: a multicenter, randomized controlled trial. *Head Neck* 2012; 34(6):805-12.

published before or included in one of the latest reviews

188. Kozomara D, Galic G, Brekalo Z, Sutalo N, Kvesic A, Soljic M. A randomised two-way comparison of mastectomy performed using harmonic scalpel or monopolar diathermy. *Coll Antropol* 2010; 34 Suppl 1:105-12.

published before or included in one of the latest reviews

189. Kroon B, Johnson N, Chapman M, Yazdani A, Hart R. Fibroids in infertility--consensus statement from ACCEPT (Australasian CREI Consensus Expert Panel on Trial evidence). *Aust N Z J Obstet Gynaecol* 2011; 51(4):289-95.

study design (surgical management)

190. Kuroki T, Tajima Y, Kanematsu T. Surgical management for the prevention of pancreatic fistula following distal pancreatectomy. *J Hepatobiliary Pancreat Surg* 2005; 12(4):283-5.

study type (study type - narrative review)

192. Lachanas VA, Hajioannou JK, Karatzias GT, Filios D, Koutsias S, Mourgelas C. Comparison of LigaSure vessel sealing system, harmonic scalpel, and cold knife tonsillectomy. *Otolaryngol Head Neck Surg* 2007; 137(3):385-9.

published before or included in one of the latest reviews

194. Leaper M, Mahadevan M, Vokes D, Sandow D, Anderson BJ, West T. A prospective randomised single blinded study comparing harmonic scalpel tonsillectomy with bipolar tonsillectomy. *Int J Pediatr Otorhinolaryngol* 2006; 70(8):1389-96.

published before or included in one of the latest reviews

196. Leonard DS, Timon C. Prospective trial of the ultrasonic dissector in thyroid surgery. *Head Neck* 2008; 30(7):904-8.

published before or included in one of the latest reviews

197. Leventoglu S, Menten BB, Akin M, Oguz M. Haemorrhoidectomy with electrocautery or ultrashears and stapled haemorrhoidopexy. *ANZ J Surg* 2008; 78(5):389-93.

device not specified or not of interest

200. Litta P, Pluchino N, Freschi L, Borgato S, Angioni S. Evaluation of adhesions after laparoscopic myomectomy using the Harmonic Ace and the auto-crosslinked hyaluronan gel vs Ringer's lactate solution. *Clin Exp Obstet Gynecol* 2013; 40(2):210-4.

not on ultrasonic energy device

201. Liu HL, McDannold N, Hynynen K. Focal beam distortion and treatment planning in abdominal focused ultrasound surgery. *Med Phys* 2005; 32(5):1270-80.

other application of ultrasonic energy

202. Lombardi CP, Raffaelli M, Cicchetti A et al. The use of "harmonic scalpel" versus "knot tying" for conventional "open" thyroidectomy: results of a prospective randomized study. *Langenbecks Arch Surg* 2008; 393(5):627-31.

published before or included in one of the latest reviews

203. Lorenzo ND, Franceschilli L, Allaix ME, Asimakopoulos A, Sileri P, Gaspari AL. Radiofrequency versus ultrasonic energy in laparoscopic colorectal surgery: A metaanalysis of operative time and blood loss. *Surg. Endosc. Interv. Tech.* 2012; 26(10):2917-24.

duplicate citation

204. Lu X, Suo S, Liu H, Zhang S. Three-dimensional multimodal image non-rigid registration and fusion in a High Intensity Focused Ultrasound system. *Comput Aided Surg* 2012; 17(1):1-12.

other application of ultrasonic energy

205. Luciani N, Anselmi A, Gaudino M et al. Harmonic scalpel reduces bleeding and postoperative complications in redo cardiac surgery. *Ann Thorac Surg* 2005; 80(3):934-8.

study design (study design - retrospective)

206. Lukish J, Powell D, Morrow S, Cruess D, Guzzetta P. Laparoscopic appendectomy in children: use of the endoloop vs the endostapler. *Arch Surg* 2007; 142(1):58-61; discussion 62.

not on ultrasonic energy device

208. Lyons S, Morrison K, Tejiram S, Levering M, Polikandriotis JA, Bernasek T. Sensory neuropathy associated with aggressive cauterization using a bipolar radiofrequency device in primary TKA. *Orthopedics* 2013; 36(2):e147-50.

not on ultrasonic energy device

209. Macario A, Dexter F, Sypal J, Cosgriff N, Heniford BT. Operative time and other outcomes of the electrothermal bipolar vessel sealing system (LigaSure) versus other methods for surgical hemostasis: a meta-analysis. *Surg Innov* 2008; 15(4):284-91.

not on ultrasonic energy device

211. Mahomed AA, Hoare C, Welsh F, Driver CP. A two-center experience with the exclusive use of laparoscopic transperitoneal nephrectomy for benign renal disease in children. *Surg Endosc* 2007; 21(9):1532-6.

study design (study design - retrospective)

212. Malietzis G, Monzon L, Hand J et al. High-intensity focused ultrasound: advances in technology and experimental trials support enhanced utility of focused ultrasound surgery in oncology. *Br J Radiol* 2013; 86(1024):20130044.

other application of ultrasonic energy

213. Malinen M, Huttunen T, Hynynen K, Kaipio JP. Simulation study for thermal dose optimization in ultrasound surgery of the breast. *Med Phys* 2004; 31(5):1296-307.

study design (ex vivo study)

214. Manouras A, Lagoudianakis EE, Antonakis PT, Filippakis GM, Markogiannakis H, Kekis PB. Electrothermal bipolar vessel sealing system is a safe and time-saving alternative to classic suture ligation in total thyroidectomy. *Head Neck* 2005; 27(11):959-62.

not on ultrasonic energy device

215. Manouras A, Markogiannakis H, Genetzakis M et al. Modified radical mastectomy with axillary dissection using the electrothermal bipolar vessel sealing system. *Arch Surg* 2008; 143(6):575-80; discussion 581.

not on ultrasonic energy device

216. Manouras A, Markogiannakis H, Koutras AS et al. Thyroid surgery: comparison between the electrothermal bipolar vessel sealing system, harmonic scalpel, and classic suture ligation. *Am J Surg* 2008; 195(1):48-52.

study design (study design - retrospective)

217. Manouras A, Markogiannakis HE, Kekis PB, Lagoudianakis EE, Fleming B. Novel hemostatic devices in thyroid surgery: electrothermal bipolar vessel sealing system and harmonic scalpel. *Expert Rev Med Devices* 2008; 5(4):447-66.

study type (study type - narrative review)

218. Marcello PW, Roberts PL, Rusin LC, Holubkov R, Schoetz DJ. Vascular pedicle ligation techniques during laparoscopic colectomy. A prospective randomized trial. *Surg Endosc* 2006; 20(2):263-9.

not on ultrasonic energy device

219. Marda P, Prakash S, Devaraj CG, Vastardis S. A comparison of root surface instrumentation using manual, ultrasonic and rotary instruments: an in vitro study using scanning electron microscopy. *Indian J Dent Res* 2012; 23(2):164-70.

study design (ex vivo study)

220. Markogiannakis H, Kekis PB, Memos N et al. Thyroid surgery with the new harmonic scalpel: a prospective randomized study. *Surgery* 2011; 149(3):411-5.

published before or included in one of the latest reviews

221. Martel G, Boushey RP. Laparoscopic colon surgery: past, present and future. *Surg Clin North Am* 2006; 86(4):867-97.

study type (study type - narrative review)

222. Matsumoto K, Tsuneyoshi I, Iguro Y et al. Effects of ultrasonic skeletonization on internal thoracic and gastroepiploic arteries for coronary artery bypass grafting. *Eur J Cardiothorac Surg* 2006; 30(4):592-6.

study design (ex vivo study)

223. McDannold N, Clement GT, Black P, Jolesz F, Hynynen K. Transcranial magnetic resonance imaging- guided focused ultrasound surgery of brain tumors: initial findings in 3 patients. *Neurosurgery* 2010; 66(2):323-32; discussion 332.

other application of ultrasonic energy

224. McNally MM, Agle SC, Williams RF, Pofahl WE. A comparison of two methods of hemostasis in thyroidectomy. *Am Surg* 2009; 75(11):1073-6.

study design (study design - retrospective)

225. Medel R, Monteith SJ, Elias WJ et al. Magnetic resonance-guided focused ultrasound surgery: Part 2: A review of current and future applications. *Neurosurgery* 2012; 71(4):755-63.

other application of ultrasonic energy

226. Mendez-Gallart R, Bautista-Casasnovas A, Estevez-Martinez E, Rodriguez-Barca P. Bipolar electrothermal vessel sealing system and 5-mm 2 expandable trocar approach in pediatric laparoscopic varicocelectomy: a successful time-effective technical refinement. *Surg Laparosc Endosc Percutan Tech* 2011; 21(5):e256-9.

not on ultrasonic energy device

227. Miccoli P, Berti P, Dionigi G, D'Agostino J, Orlandini C, Donatini G. Randomized controlled trial of harmonic scalpel use during thyroidectomy. *Arch Otolaryngol Head Neck Surg* 2006; 132(10):1069-73.

published before or included in one of the latest reviews

228. Miccoli P, Materazzi G, Fregoli L, Panicucci E, Kunz-Martinez W, Berti P. Modified lateral neck lymphadenectomy: prospective randomized study comparing harmonic scalpel with clamp-and-tie technique. *Otolaryngol Head Neck Surg* 2009; 140(1):61-4.

published before or included in one of the latest reviews

229. Milito G, Cadeddu F, Muzi MG, Nigro C, Farinon AM. Haemorrhoidectomy with Ligasure vs conventional excisional techniques: meta-analysis of randomized controlled trials. *Colorectal Dis* 2010; 12(2):85-93.

not on ultrasonic energy device

230. Minutolo V, Gagliano G, Rinzi C, Li Destri G, Carnazza M, Minutolo O. Usefulness of the ultrasonically activated scalpel in laparoscopic cholecystectomy: our experience and review of literature. *G Chir* 2008; 29(5):242-5.

study type (study type - narrative review)

231. Mixson CM, Weinberger PM, Austin MB. Comparison of microdebrider subcapsular tonsillectomy to harmonic scalpel and electrocautery total tonsillectomy. *Am J Otolaryngol* 2007; 28(1):13-7.

study design (study design - retrospective)

232. Modi VK, Monforte H, Geller KA, Koempel JA. Histologic assessment of thermal injury to tonsillectomy specimens: a comparison of electrocautery, coblation, harmonic scalpel, and tonsillotome. *Laryngoscope* 2009; 119(11):2248-51.

study design (ex vivo study)

234. Molnar TF, Benko I, Szanto Z, Nagy A, Horvath OP. Complications after ultrasonic lung parenchyma biopsy: a strong note for caution. *Surg Endosc* 2008; 22(3):679-82.

study design (study design - retrospective)

235. Monclova JL, Targarona EM, Vidal P et al. Single incision versus reduced port splenectomy - Searching for the best alternative to conventional laparoscopic splenectomy. *Surg. Endosc. Interv. Tech.* 2013; 27(3):895-902.

study design (surgical management)

236. Monteith S, Sheehan J, Medel R et al. Potential intracranial applications of magnetic resonance-guided focused ultrasound surgery. *J Neurosurg* 2013; 118(2):215-21.

other application of ultrasonic energy

237. Monteith SJ, Kassell NF, Goren O, Harnof S. Transcranial MR-guided focused ultrasound sonothrombolysis in the treatment of intracerebral hemorrhage. *Neurosurg Focus* 2013; 34(5):E14.

other application of ultrasonic energy

238. Moon MR, Barner HB, Bailey MS et al. Long-term neurologic hand complications after radial artery harvesting using conventional cold and harmonic scalpel techniques. *Ann Thorac Surg* 2004; 78(2):535-8; discussion 535-8.

study design (study design - retrospective)

239. Mora R, Jankowska B, Crippa B et al. Effects of uvulopalatopharyngoplasty with Harmonic Scalpel on speech and voice. *Eur Arch Otorhinolaryngol* 2009; 266(12):1989-94.

device not specified or not of interest

240. Morino M, Rimonda R, Allaix ME, Giraudo G, Garrone C. Ultrasonic versus standard electric dissection in laparoscopic colorectal surgery: a prospective randomized clinical trial. *Ann Surg* 2005; 242(6):897-901, discussion 901.

published before or included in one of the latest reviews

241. Morita Y, Ito N, Hikida H, Takeuchi S, Nakamura K, Ohashi H. Non-invasive magnetic resonance imaging-guided focused ultrasound treatment for uterine fibroids - early experience. *Eur J Obstet Gynecol Reprod Biol* 2008; 139(2):199-203.

other application of ultrasonic energy

242. Mourad M, Rulli F, Robert A, Scholtes JL, De Meyer M, De Pauw L. Randomized clinical trial on harmonic focus shears versus clamp-and-tie technique for total thyroidectomy. *Am. J. Surg.* 2011; 202(2):168-74.

published before or included in one of the latest reviews

245. Msika S, Deroide G, Kianmanesh R et al. Harmonic scalpel in laparoscopic colorectal surgery. *Dis Colon Rectum* .

study design (study design - non comparative)

246. Mukhopadhaya N, De Silva C, Manyonda IT. Conventional myomectomy. *Best Pract Res Clin Obstet Gynaecol* 2008; 22(4):677-705.

other application of ultrasonic energy

248. Nieuwenhuis DH, Draaisma WA, Verberne GH, van Overbeeke AJ, Consten EC. Transanal endoscopic operation for rectal lesions using two-dimensional visualization and standard endoscopic instruments: a prospective cohort study and comparison with the literature. *Surg Endosc* 2009; 23(1):80-6.

not on ultrasonic energy device

249. Noble EJ, Smart NJ, Challand C, Sleight K, Oriolowo A, Hosie KB. Experimental comparison of mesenteric vessel sealing and thermal damage between one bipolar and two ultrasonic shears devices. *Br J Surg* 2011; 98(6):797-800.

study design (ex vivo study)

250. Nusrath MA, Postlethwaite KR. Use of piezosurgery in calvarial bone grafts and for release of the inferior alveolar nerve in sagittal split osteotomy: Technical note. *Br. J. Oral Maxillofac. Surg.* 2011; 49(8):668-9.

conference abstract (no full text-available)

251. Okada A, Morita Y, Fukunishi H, Takeichi K, Murakami T. Non-invasive magnetic resonance-guided focused ultrasound treatment of uterine fibroids in a large Japanese population: impact of the learning curve on patient outcome. *Ultrasound Obstet Gynecol* 2009; 34(5):579-83.

other application of ultrasonic energy

252. Oko MO, Ganly I, Loughran S, Clement WA, Young D, Geddes NK. A prospective randomized single-blind trial comparing ultrasonic scalpel tonsillectomy with tonsillectomy by blunt dissection in a pediatric age group. *Otolaryngology--Head and Neck Surgery : Official Journal of American Academy of Otolaryngology-Head and Neck Surgery . Otolaryngol Head Neck Surg.* 2005 Oct;133(4):579-84.

published before or included in one of the latest reviews

254. Onorati F, De Feo M, Cristodoro L et al. Can harvesting techniques modify postoperative results of the radial artery conduit? *Ital Heart J* 2005; 6(11):911-6.

not retrievable in full-text

255. Orsi F, Arnone P, Chen W, Zhang L. High intensity focused ultrasound ablation: a new therapeutic option for solid tumors. *J Cancer Res Ther* 2010; 6(4):414-20.

other application of ultrasonic energy

256. Ortega J, Sala C, Flor B, Lledo S. Efficacy and cost-effectiveness of the UltraCision harmonic scalpel in thyroid surgery: an analysis of 200 cases in a randomized trial. *J Laparoendosc Adv Surg Tech A* 2004; 14(1):9-12.

published before or included in one of the latest reviews

257. Ostapoff KT, Euhus D, Xie XJ, Rao M, Moldrem A, Rao R. Axillary lymph node dissection for breast cancer utilizing Harmonic Focus(R). *World J Surg Oncol* 2011; 9:90.

study design (study design - retrospective)

258. Oz BS, Mataraci I, Iyem H et al. Comparison of ultrasonically activated scalpel and traditional technique in radial artery harvesting: clinical research. *Thorac Cardiovasc Surg* 2007; 55(2):104-7.

device not specified or not of interest

260. Pampaloni E, Valeri A, Mattei R et al. Initial experience with laparoscopic adrenal surgery in children: is endoscopic surgery recommended and safe for the treatment of adrenocortical neoplasms? *Pediatr Med Chir* 2004; 26(6):450-9.

study design (surgical management)

261. Pampaloni F, Valeri A, Mattei R, Presenti L, Noccioli B. Experience with laparoscopic adrenalectomy in children. *Chir Ital* 2006; 58(1):45-54.

study type (study type - narrative review)

262. Papavramidis TS, Sapalidis K, Michalopoulos N et al. UltraCision harmonic scalpel versus clamp-and-tie total thyroidectomy: a clinical trial. *Head Neck* 2010; 32(6):723-7.

published before or included in one of the latest reviews

263. Parker DJ, Krupa K, Esler R, Vujovic P, Bennett IC. Use of the harmonic scalpel in thyroidectomy. *ANZ J Surg* 2009; 79(6):476-80.

study design (study design - non comparative)

264. Parsons SP, Cordes SR, Comer B. Comparison of posttonsillectomy pain using the ultrasonic scalpel, coblator, and electrocautery. *Otolaryngol Head Neck Surg* 2006; 134(1):106-13.

published before or included in one of the latest reviews

265. Pasic R, Abdelmonem A, Levine R. Comparison of cervical detachment using monopolar lap loop ligature and conventional methods in laparoscopic supracervical hysterectomy. *JLS* 2006; 10(2):226-30.

not on ultrasonic energy device

267. Pektok E, Cikirikcioglu M, Engin C, Daglkoz G, Ozcan Z, Posacioglu H. Does harvesting of an internal thoracic artery with an ultrasonic scalpel have an effect on sternal perfusion? *J Thorac Cardiovasc Surg* . *J Thorac Cardiovasc Surg*. 2007 Aug;134(2):442-7.

device not specified or not of interest

268. Pellegrino A, Fruscio R, Maneo A et al. Harmonic scalpel versus conventional electrosurgery in the treatment of vulvar cancer. *Int J Gynaecol Obstet* 2008; 103(2):185-8.

study design (study design - retrospective)

269. Peter B. Piezosurgery-assisted sliding genioplasty: A method for reduction of complications. Review and case report. *Eur. J. Plast. Surg.* 2010; 33(4):183-7.

other application of ultrasonic energy

270. Peterson JD, Goldman MP. Laser, light, and energy devices for cellulite and lipodystrophy. *Clin Plast Surg* 2011; 38(3):463-74, vii.

not on ultrasonic energy device

271. Phillips JM, Narula N, Deane LA et al. Histological evaluation of cold versus hot cutting: clinical impact on margin status for laparoscopic partial nephrectomy. *J Urol* 2008; 180(6):2348-52.

study design (ex vivo study)

272. Pons Y, Gauthier J, Ukkola-Pons E et al. Comparison of LigaSure vessel sealing system, harmonic scalpel, and conventional hemostasis in total thyroidectomy. *Otolaryngol Head Neck Surg* 2009; 141(4):496-501.

published before or included in one of the latest reviews

273. Potts KL, Augenstein A, Goldman JL. A parallel group analysis of tonsillectomy using the harmonic scalpel vs electrocautery. *Arch Otolaryngol Head Neck Surg* 2005; 131(1):49-51.

study design (study design - retrospective)

274. Prgomet D, Janjanin S, Bilic M et al. A prospective observational study of 363 cases operated with three different harmonic scalpels. *Eur Arch Otorhinolaryngol* 2009; 266(12):1965-70.

published before or included in one of the latest reviews

275. Rabinovici J, David M, Fukunishi H, Morita Y, Gostout BS, Stewart EA. Pregnancy outcome after magnetic resonance-guided focused ultrasound surgery (MRgFUS) for conservative treatment of uterine fibroids. *Fertil Steril* 2010; 93(1):199-209.

other application of ultrasonic energy

276. Rabinovici J, Stewart EA. New interventional techniques for adenomyosis. *Best Pract Res Clin Obstet Gynaecol* 2006; 20(4):617-36.

other application of ultrasonic energy

277. Rafii A, Camicas A, Ferron G et al. A comparative study of laparoscopic extraperitoneal lymphadenectomy. *Am J Obstet Gynecol* 2009; 201(4):370.e1-5.

study design (study design - retrospective)

278. Ragab SM. Six years of evidence-based adult dissection tonsillectomy with ultrasonic scalpel, bipolar electrocautery, bipolar radiofrequency or 'cold steel' dissection. *J Laryngol Otol* 2012; 126(10):1056-62.

device not specified or not of interest

279. Ramos FA, Ferreira RDP, Silva RHD, Prado EPd, Corso RJ, Pinto JA. Comparative study between two tonsillectomy techniques: Ultracision harmonic scalpel and traditional dissection with cold scalpel. *Revista Brasileira De Oto-Rino-Laringologia* .

language – not English

280. Rane A, Rao P, Rao P. Single-port-access nephrectomy and other laparoscopic urologic procedures using a novel laparoscopic port (R-port). *Urology* 2008; 72(2):260-3; discussion 263-4.

not on ultrasonic energy device

Rec #: 2500

281. Redwan AA. Single-working-instrument, double-trocar, clipless cholecystectomy using harmonic scalpel: a feasible, safe, and less invasive technique. *J Laparoendosc Adv Surg Tech A* 2010; 20(7):597-603.

published before or included in one of the latest reviews

282. Richter S, Kollmar O, Schuld J, Moussavian MR, Igna D, Schilling MK. Randomized clinical trial of efficacy and costs of three dissection devices in liver resection. *Br J Surg* 2009; 96(6):593-601.

device not specified or not of interest

283. Rimonda R, Arezzo A, Garrone C, Allaix ME, Giraud G, Morino M. Electrothermal bipolar vessel sealing system vs. harmonic scalpel in colorectal laparoscopic surgery: a prospective, randomized study. *Dis Colon Rectum* 2009; 52(4):657-61.

published before or included in one of the latest reviews

284. Roth JA, Pincock T, Sacks R et al. Harmonic scalpel tonsillectomy versus monopolar diathermy tonsillectomy: a prospective study. *Ear Nose Throat J* 2008; 87(6):346-9.

published before or included in one of the latest reviews

286. Rukosujew A, Reichelt R, Fabricius AM et al. Skeletonization versus pedicle preparation of the radial artery with and without the ultrasonic scalpel. *Ann Thorac Surg* 2004; 77(1):120-5.

published before or included in one of the latest reviews

287. Salami A, Bavazzano M, Mora R, Dellepiane M. Harmonic scalpel in pharyngolaryngectomy with radical neck dissection. *J Otolaryngol Head Neck Surg* 2008; 37(5):633-7.

device not specified or not of interest

288. Salami A, Dellepiane M, Bavazzano M, Crippa B, Guastini L, Mora R. Harmonic Scalpel vs "cold knife" dissection in uvulopalatopharyngoplasty. *Am J Otolaryngol* 2010; 31(6):442-7.

device not specified or not of interest

289. Salami A, Dellepiane M, Crippa B, Mora R. A new method for osteotomies in oncologic nasal surgery: Piezosurgery. *Am. J. Otolaryngol. Head Neck Med. Surg.* 2010; 31(3):150-3.

other application of ultrasonic energy

290. Salami A, Dellepiane M, Proto E, Mora R. Piezosurgery in otologic surgery: Four years of experience. *Otolaryngol. Head Neck Surg.* 2009; 140(3):412-8.

other application of ultrasonic energy

291. Salami A, Mora R, Dellepiane M, Crippa B, Santomauro V, Guastini L. Piezosurgery(registered trademark) versus microdrill in intact canal wall mastoidectomy. *Eur. Arch. Oto-Rhino-Laryngol.* 2010; 267(11):1705-11.

other application of ultrasonic energy

292. Salami A, Mora R, Dellepiane M, Guastini L. Piezosurgery for removal of symptomatic ear osteoma. *Eur Arch Otorhinolaryngol* 2010; 267(10):1527-30.

other application of ultrasonic energy

293. Salami A, Mora R, Mora F, Guastini L, Salzano FA, Dellepiane M. Learning curve for Piezosurgery in well-trained otological surgeons. *Otolaryngol Head Neck Surg* 2010; 142(1):120-5.

other application of ultrasonic energy

294. Salomir R, Delemazure AS, Palussiere J, Rouviere O, Cotton F, Chapelon JY. Image-based control of the magnetic resonance imaging-guided focused ultrasound thermotherapy. *Top Magn Reson Imaging* 2006; 17(3):139-51.

other application of ultrasonic energy

295. Sandonato L, Soresi M, Cipolla C et al. Minor hepatic resection for hepatocellular carcinoma in cirrhotic patients: Kelly clamp crushing resection versus heat coagulative necrosis with bipolar radiofrequency device. *Am Surg* 2011; 77(11):1490-5.

not on ultrasonic energy device

296. Sanguinetti A, Docimo G, Ragusa M et al. Ultrasound scissors versus electrocautery in axillary dissection: our experience. *G Chir* 2010; 31(4):151-3.

study design (study design - retrospective)

297. Sankaranarayanan G, Resapu RR, Jones DB, Schwaitzberg S, De S. Common uses and cited complications of energy in surgery. *Surg. Endosc. Interv. Tech.* 2013; 27(9):3056-72.

study type (study type - narrative review)

298. Sartori PV, De Fina S, Colombo G et al. Ligasure versus Ultracision in thyroid surgery: a prospective randomized study. *Langenbecks Arch Surg* 2008; 393(5):655-8.

published before or included in one of the latest reviews

299. Sartori PV, De Fina S, Colombo G et al. Ligasure versus Ultracision(registered trademark) in thyroid surgery: A prospective randomized study. *Langenbeck's Arch. Surg.* 2008; 393(5):655-8.

duplicate citation

300. Sartori PV, Romano F, Uggeri F et al. Energy-based hemostatic devices in laparoscopic adrenalectomy. *Langenbecks Arch Surg* 2010; 395(2):111-4.

study design (study design - retrospective)

302. Sasi W. The outcome of laparoscopic cholecystectomy by ultrasonic dissection. *Surg Technol Int* 2010; 19:70-8.

study duplication

303. Satoi S, Yanagimoto H, Toyokawa H. Use of the new ultrasonically curved shear in pancreaticoduodenectomy for periampullary cancer. *J Hepatobiliary Pancreat Sci* 2011; 18(4):609-14.

study design (study design - retrospective)

304. Savlid M, Strand AH, Jansson A et al. Transection of the liver parenchyma with an ultrasound dissector or a stapler device: results of a randomized clinical study. *World J Surg* 2013; 37(4):799-805.

device not specified or not of interest

305. Scarano A, Murmura G, Sinjiari B et al. Expansion of the alveolar bone crest with ultrasonic surgery device: clinical study in mandible. *Int J Immunopathol Pharmacol* 2011; 24(2 Suppl):71-5.

other application of ultrasonic energy

306. Schrey A, Pulkkinen J, Fremling C, Kinnunen I. Ultrasonically activated scalpel compared with electrocautery in tonsillectomy. *ORL J Otorhinolaryngol Relat Spec* 2004; 66(3):136-40.

study design (study design - retrospective)

307. Sciubba DM, Liang D, Kothbauer KF, Noggle JC, Jallo GI. The evolution of intramedullary spinal cord tumor surgery. *Neurosurgery* 2009; 65(6 Suppl):84-91; discussion 91-2.

not on ultrasonic energy device

309. Sharma A, Muna S, Fahmy FF. The ultrasonically activated scalpel versus bipolar diathermy for tonsillectomy: a prospective randomized trial. *Clin Otolaryngol* 2005; 30(3):284; author reply 284-5.

publication type (publication type - reply)

310. Shaw A, Hodnett M. Calibration and measurement issues for therapeutic ultrasound. *Ultrasonics* 2008; 48(4):234-52.

other application of ultrasonic energy

311. Sheahan P, Miller I, Colreavy M, Sheahan JN, McShane D, Curran A. The ultrasonically activated scalpel versus bipolar diathermy for tonsillectomy: a prospective, randomized trial. *Clin Otolaryngol Allied Sci* 2004; 29(5):530-4.

published before or included in one of the latest reviews

312. Shen HP, Gong JP, Zuo GQ. Role of high-intensity focused ultrasound in treatment of hepatocellular carcinoma. *Am Surg* 2011; 77(11):1496-501.

other application of ultrasonic energy

313. Shi J, Iesaki T, Kubota N et al. Skeletonization with an ultrasonic scalpel is as safe as a non-skeletonized dissection in preserving the endothelial function of the human gastroepiploic artery. *Interact Cardiovasc Thorac Surg* 2009; 8(2):216-20.

study design (study design - non comparative)

315. Shinhar S, Scotch BM, Belenky W, Madgy D, Hauptert M. Harmonic scalpel tonsillectomy versus hot electrocautery and cold dissection: an objective comparison. *Ear Nose Throat J* 2004; 83(10):712-5.

study design (study design - retrospective)

316. Simonato A, Varca V, Esposito M, Venzano F, Carmignani G. The Use of a Surgical Patch in the Prevention of Lymphoceles After Extraperitoneal Pelvic Lymphadenectomy for Prostate Cancer: A Randomized Prospective Pilot Study. *J. Urol.* 2009; 182(5):2285-90.

not on ultrasonic energy device

317. Sindwani R, Manz R. Technological innovations in tissue removal during rhinologic surgery. *Am J Rhinol Allergy* 2012; 26(1):65-9.

study type (study type - narrative review)

318. Sipos E, Stifter E, Menapace R. Patient satisfaction and postoperative pain with different postoperative therapy regimens after standardized cataract surgery: a randomized intraindividual comparison. *Int Ophthalmol* 2011; 31(6):453-60.

other application of ultrasonic energy

319. Sista F, Schietroma M, Ruscitti C et al. New ultrasonic dissector versus conventional hemostasis in thyroid surgery: a randomized prospective study. *J Laparoendosc Adv Surg Tech A* 2012; 22(3):220-4.

published before or included in one of the latest reviews

320. Skenazy J, Ercole B, Lee C, Best S, Fallon E, Monga M. Nephrolithiasis: "scope," shock or scalpel? *J Endourol* 2005; 19(1):45-9.

study type (study type - narrative review)

321. Smart OC, Hindley JT, Regan L, Gedroyc WM. Magnetic resonance guided focused ultrasound surgery of uterine fibroids--the tissue effects of GnRH agonist pre-treatment. Eur J Radiol 2006; 59(2):163-7.

other application of ultrasonic energy

322. So MJ, Fennessy FM, Zou KH et al. Does the phase of menstrual cycle affect MR-guided focused ultrasound surgery of uterine leiomyomas? Eur J Radiol 2006; 59(2):203-7.

other application of ultrasonic energy

323. Sohn VY, Martin MJ, Mullenix PS, Cuadrado DG, Place RJ, Steele SR. A comparison of open versus closed techniques using the Harmonic Scalpel in outpatient hemorrhoid surgery. Mil Med 2008; 173(7):689-92.

study design (surgical technique)

324. Song L, Chen Z, Liu T et al. The application of a patented system to minimally invasive percutaneous nephrolithotomy. J. Endourol. 2011; 25(8):1281-6.

not on ultrasonic energy device

325. Srimurthy KR, Ramesh S. Pediatric laparoscopic surgery--Indian scenario. Indian J Pediatr 2004; 71(12):1121-6.

study type (study type - narrative review)

326. Steventon N. Early postoperative pain reduction using harmonic scalpel for tonsillectomy compared with bipolar dissection in children: a prospective randomised trial. 8th International Congress of Paediatric Otorhinolaryngology .

conference abstract (no full text-available)

327. Stewart EA, Rabinovici J, Tempany CM et al. Clinical outcomes of focused ultrasound surgery for the treatment of uterine fibroids. Fertil Steril 2006; 85(1):22-9.

other application of ultrasonic energy

328. Stumpf M, Dreuw B, Tittel A, Schumpelick V. [The short gastric vessels by using the harmonic scalpel during the laparoscopic fundoplication.]. Minimal Invasive Chirurgie .

language – not English

329. Sugo H, Matsumoto K, Kojima K, Fukasawa M, Beppu T. Role of ultrasonically activated scalpel in hepatic resection: a comparison with conventional blunt dissection. Hepatogastroenterology 2005; 52(61):173-5.

study design (study design - retrospective)

330. Szynglarewicz B, Zietek M, Forgacz J et al. Urinary complications in rectal cancer patients are related to the dissection tool. Hepatogastroenterology 2012; 59(115):724-6.

study design (study design - retrospective)

331. Takada M, Ichihara T, Kuroda Y. Comparative study of electrothermal bipolar vessel sealer and ultrasonic coagulating shears in laparoscopic colectomy. *Surg Endosc* 2005; 19(2):226-8.

published before or included in one of the latest reviews

332. Takagi K, Hata Y, Sasamoto S et al. Late onset postoperative pulmonary fistula following a pulmonary segmentectomy using electrocautery or a harmonic scalpel. *Ann Thorac Cardiovasc Surg* 2010; 16(1):21-5.

study design (study design - retrospective)

333. Takeuchi S, Futamura N, Takubo S, Noda N, Minoura H, Toyoda N. Polycystic ovary syndrome treated with laparoscopic ovarian drilling with a harmonic scalpel. A prospective, randomized study. *J Reprod Med* .

published before the timeframe (2002)

334. Tam Ka Wai, Chan Edwin SY, Chen Chieh-feng. Ligasure vessel-sealing system or harmonic scalpel versus conventional vessel ligation for thyroidectomy. *Cochrane Database of Systematic Reviews* .

study status (study status - study protocol)

335. Tan JJ, Seow Choen F. Prospective, randomized trial comparing diathermy and Harmonic Scalpel hemorrhoidectomy. *Dis Colon Rectum* .

published before the timeframe (2002)

336. Targarona EM, Balague C, Marin J et al. Energy sources for laparoscopic colectomy: a prospective randomized comparison of conventional electrosurgery, bipolar computer-controlled electrosurgery and ultrasonic dissection. Operative outcome and costs analysis. *Surg Innov* 2005; 12(4):339-44.

published before or included in one of the latest reviews

337. Tepetes K, Symeonidis D, Christodoulidis G, Spyridakis M, Hatzitheofilou K. Pudendal nerve block versus local anesthesia for harmonic scalpel hemorrhoidectomy: a prospective randomized study. *Techniques in Coloproctology* .

duplicate citation

338. Tepetes K, Symeonidis D, Christodoulidis G, Spyridakis M, Hatzitheofilou K. Pudendal nerve block versus local anesthesia for harmonic scalpel hemorrhoidectomy: a prospective randomized study. *Tech Coloproctol* 2010; 14 Suppl 1:S1-3.

irrelevant endpoint

339. Thomas MS, Kundabala M. Pulp hyperthermia during tooth preparation: the effect of rotary--instruments, lasers, ultrasonic devices, and airborne particle abrasion. *J Calif Dent Assoc* 2012; 40(9):720-31.

other application of ultrasonic energy

340. Till H, Schaarschmidt K. Partial laparoscopic decapsulation of congenital splenic cysts. A medium-term evaluation proves the efficiency in children. *Surg Endosc* 2004; 18(4):626-8.

study design (study design - non comparative)

343. Tremp M, di Summa PG, Schaakxs D et al. Is ultracision knife safe and efficient for breast capsulectomy? A preliminary study. *Aesthetic Plast Surg* 2012; 36(4):888-93.

device not specified or not of interest

344. Truong LN, Patil S, Martin SS et al. Rapid detection of high-level oncogene amplifications in ultrasonic surgical aspirations of brain tumors. *Diagn Pathol* 2012; 7:66.

study design (ex vivo study)

345. Tsimoyiannis EC, Siakas P, Glantzounis G, Koulas S, Mavridou P, Gossios KI. Seroma in laparoscopic ventral hernioplasty. *Surgical Laparoscopy, Endoscopy & Percutaneous Techniques* .

not on ultrasonic energy device

346. Tsunozuka Y, Waseda R, Yachi T. Electrothermal bipolar vessel sealing device LigaSureV for pulmonary artery ligation--burst pressure and clinical experiences in complete video-assisted thoracoscopic major lung resection for lung cancer. *Interact Cardiovasc Thorac Surg* 2010; 11(3):229-33.

not on ultrasonic energy device

348. Wada K, Nawashiro H, Arimoto H, Ohkawa H, Ono K, Takahara T. Usefulness of an ultrasonic scalpel to harvest and skeletonize the superficial temporal artery for extracranial-intracranial bypass surgery. *Neurosurgery* 2009; 65(6 Suppl):141-7; discussion 147-8.

device not specified or not of interest

350. Walker RA, Syed ZA, Walker RA, Syed ZA. Harmonic scalpel tonsillectomy versus electrocautery tonsillectomy: a comparative pilot study. *Otolaryngol Head Neck Surg* .

published before the timeframe (2001)

351. Waraich N, Ahmed J, Rashid F, Mulvey D, Leeder P, Iftikhar SY. Is harmonic scalpel an effective tool for oesophagectomy? *Int J Surg* 2009; 7(4):330-3.

study design (study design - retrospective)

352. White I, Mills JK, Diggs B, Fortino Hima J, Ellis MC, Vetto JT. Sentinel lymph node biopsy for melanoma: comparison of lymphocele rates by surgical technique. *Am Surg* 2013; 79(4):388-92.

study design (study design - retrospective)

353. White PJ. Transcranial focused ultrasound surgery. *Top Magn Reson Imaging* 2006; 17(3):165-72.

other application of ultrasonic energy

355. Wille AH, Johannsen M, Miller K, Deger S. Laparoscopic partial nephrectomy using FloSeal for hemostasis: technique and experiences in 102 patients. *Surg Innov* 2009; 16(4):306-12.

not on ultrasonic energy device

356. Willging JP, Wiatrak BJ. Harmonic scalpel tonsillectomy in children: a randomized prospective study. *Otolaryngology--Head and Neck Surgery : Official Journal of American Academy of Otolaryngology-Head and Neck Surgery* .

published before the timeframe (2003)

357. Wills E, Crawford G. Clipless versus conventional laparoscopic cholecystectomy. *J Laparoendosc Adv Surg Tech A* 2013; 23(3):237-9.

study design (study design - retrospective)

358. Witzel K, Von Rahden BHA, Stein HJ. The effect of ultrasound dissection in thyroid surgery. *Eur. Surg. Res.* 2009; 43(2):241-4.

published before or included in one of the latest reviews

359. Wright CB, Barner HB, Gao A et al. The advantages of the Harmonic Scalpel for the harvesting of radial arteries for coronary artery bypass. *The Heart Surgery Forum* .

published before the timeframe (2001)

360. Wu Z, Chen Z, Peng L. Evaluation of the harmonic scalpel in open surgery for abdominal aortic aneurysm. *Front Med* 2012; 6(1):85-8.

study design (study design - retrospective)

362. Yildirim O, Umit T, Ebru M et al. Ultrasonic harmonic scalpel in total thyroidectomies. *Adv Ther* 2008; 25(3):260-5.

published before or included in one of the latest reviews

363. Yoon SW, Lee C, Cha SH et al. Patient selection guidelines in MR-guided focused ultrasound surgery of uterine fibroids: a pictorial guide to relevant findings in screening pelvic MRI. *Eur Radiol* 2008; 18(12):2997-3006.

other application of ultrasonic energy

364. Zarebczan B, Mohanty D, Chen H. A Comparison of the LigaSure and harmonic scalpel in thyroid surgery: a single institution review. *Ann Surg Oncol* 2011; 18(1):214-8.

study design (study design - retrospective)

365. Zowall H, Cairns JA, Brewer C, Lamping DL, Gedroyc WM, Regan L. Cost-effectiveness of magnetic resonance-guided focused ultrasound surgery for treatment of uterine fibroids. *BJOG* 2008; 115(5):653-62.

other application of ultrasonic energy

Studies suggested by reviewers from public consultation and excluded:

366. AbulNagah G, EL-Fayoumi T, Lotfy H, Shehab W, Tarek A. Comparative study between using harmonic scalpel and electrocautery in modified radical mastectomy. *Egyptian Journal of Surgery*, 2007; 26(4)176–180.

published before or included in one of the latest reviews

367. Khater A. Harmonic scalpel as a single instrument in modified radical mastectomy. Is it more cost effective than electrocautery and ligature? *Egyptian Journal of Surgery*, 2010; 29(2)59–63.

published before or included in one of the latest reviews

368. Hata M, Shiono M, Sezai A, Iida M, Saitoh A, Hattori T, Wakui S, Soeda M, Negishi N, Sezai Y. Determining the best procedure for radial artery harvest: prospective randomized trial for early postharvest complications. *J Thorac Cardiovasc Surg*. 2005; 129(4):885-9.

published before or included in one of the latest reviews

369. Di Vita G, Patti R, Petrone R, Arcara M, Sieli G. Milligan-Morgan hemorrhoidectomy with ultrasonic scalpel [L'emorroidectomia secondo Milligan-Morgan con bisturi ad ultrasuoni]. *Il Giornale di chirurgia*, 2003; 24(11-12)422–427.

published before the timeframe (2003)

Appendix 3 – Evidence tracking (effectiveness and safety)

Table A3.1: List of the 14 systematic reviews on the use of ultrasonic energy devices for surgery initially considered for analysis.

ID Study [ref.]	Timeframe of the Review		Intervention	Judgement for this review
	From	to		
Alexiou et al., 2011 []	Jan, 1990	Jul, 2010	Total tonsillectomy	Included
Chirocchi et al., 2010 []	No limit	Jan, 2010	Total thyroidectomy	Overlap
Contin et al., 2013 []	No limit	Dec, 2012	Open partial and/or total thyroidectomy	Included
Currie et al., 2012 []	1966	2011	Mastectomy for breast cancer	Included
Di Lorenzo et al., 2012 []	1990	Jun, 2011	Laparoscopic colorectal surgery	Included
Ecker et al., 2010 []	No limit	Nov, 2008	Different types of thyroid surgery	Overlap
Garas et al., 2013 []	Jan, 2000	Jun, 2012	Thyroid surgery	Overlap
Janssen et al., 2012 []	1998	Oct, 2011	Abdominal surgical procedures	Included
Lang et al., 2013 []	No limit	Jul, 2012	Total thyroidectomy	Overlap
Neumann et al., 2007 []	No limit	Sep, 2006	Bilateral tonsillectomy	Overlap
Patel et al., 2006 []	Jan 1990	Oct 2005	Radial artery harvest	Included
Sasi, 2010 []	No limit	2008 (unclear)	Laparoscopic cholecystectomy	Overlap
Tou et al., 2011 []	No limit	Mar, 2010	Laparoscopic or laparosc.-assisted colectomy	Overlap
Xiong et al., 2012 []	Jan, 1985	Feb, 2012	Laparoscopic cholecystectomy	Included

Key: *Included* = the review has been considered as the latest updated evidence on the topic; *Overlap* = the review presents overlaps with a more recent publication in terms of procedures and included studies.

Table A3.2: List of the 35 primary studies on the use of ultrasonic energy devices for surgery included in the evidence review.

Procedure (or group of procedures)	ID Study [ref.]	Procedure (or group of procedures)	ID Study [ref.]
Breast surgery	Cavallaro et al. 2011 []	Haemorrhoidectomy and ano-rectal surgery	Abo-hashem et al. 2010 []
Breast surgery	Iovino et al. 2011 []	Haemorrhoidectomy and ano-rectal surgery	Boccasanta et al. 2006 []
Breast surgery	Lumachi et al. 2013 []	Haemorrhoidectomy and ano-rectal surgery	Chung et al. 2005 []
Cardio-vascular surgery	Brazio et al. 2008 []	Haemorrhoidectomy and ano-rectal surgery	Ivanov et al. 2007 []
Cardio-vascular surgery	Dumantepe et al. 2011 []	Haemorrhoidectomy and ano-rectal surgery	Kwok et al. 2005 []
Cardio-vascular surgery	Mouton et al. 2005 []	Haemorrhoidectomy and ano-rectal surgery	Ozer et al. 2008 []
Cardio-vascular surgery	Mouton et al. 2011 []	Haemorrhoidectomy and ano-rectal surgery	Peker et al. 2013 []
ENT oncological surgery	Shin et al. 2013 []	Laparoscopic cholecystectomy	Mahabaleshwar et al. 2012 []
ENT oncological surgery	Walén et al. 2011 []	Liver transplant. Surgery	Olmez et al. 2012 []
Gastrointestinal surgery	Inoue et al. 2012 []	Lung biopsy	Molnar et al. 2005 []
Gastrointestinal surgery	Wilhelm et al. 2011 []	Orthopaedic surgery	Tomas et al. 2010 []
Gynaecological surgery	Awadzi et al. 2005 []	Pancreatic surgery	Uzunoglu et al. 2012 []
Gynaecological surgery	Fitz-Gerald et al. 2013 []	Plastic and reconstructive surgery	Deo et al. 2004 []
Gynaecological surgery	Kartsounis et al. 2011 []	Plastic and reconstructive surgery	Hamahata et al. 2012 []
Gynaecological surgery	Leblanc et al. 2011 []	Thyroid surgery	Cirocchi et al. 2012 []
Gynaecological surgery	Li et al. 2009 []	Thyroid surgery	Ruggeri et al. 2012 []
Gynaecological surgery	Litta et al. 2010 []	Thyroid surgery	Sebag et al. 2009 []
		Tonsillectomy	Khan et al. 2012 []

Key: ENT = ear, nose, and throat.

Appendix 4 – Quality assessment (effectiveness and safety)

Table A4.1. Average R-AMSTAR scores across two independent assessors of the review studies initially considered for inclusion in the present evidence review.

Authors [ref.]	Item 1	Item 2	Item 3	Item 4	Item 5	Item 6	Item 7	Item 8	Item 9	Item 10	Item 11	Score
Alexiou et al. []	3.5	1.0	4.0	1.5	2.0	4.0	3.0	1.5	3.5	3.0	2.5	29.5
Chirocchi et al. []	3.5	4.0	4.0	2.5	1.5	3.5	1.0	1.0	2.0	1.0	2.5	26.5
Contin et al. []	3.5	4.0	4.0	2.5	2.0	4.0	2.0	2.0	4.0	4.0	3.5	35.5
Currie et al. []	3.5	1.0	4.0	1.5	1.5	4.0	2.0	1.5	4.0	1.0	2.5	26.5
Di Lorenzo et al. []	3.5	4.0	4.0	1.0	2.5	3.5	1.0	1.0	3.5	1.0	2.5	27.5
Ecker et al. []	3.5	1.0	4.0	3.0	1.0	1.0	1.0	1.5	3.5	3.0	2.0	24.5
Garas et al. []	3.5	4.0	3.0	3.0	2.5	4.0	2.0	2.5	4.0	1.5	3.0	33
Janssen et al. []	3.5	4.0	4.0	3.0	1.5	3.5	2.0	2.0	1.0	1.5	3.0	29
Lang et al. []	3.5	3.5	4.0	2.0	3.5	3.5	1.0	1.0	2.0	3.5	1.0	28.5
Neumann et al. []	4.0	4.0	4.0	3.0	3.0	4.0	2.0	4.0	2.5	1.5	3.0	35
Patel et al. []	3.0	1.0	3.0	1.0	1.0	4.0	1.0	1.0	1.0	1.0	2.0	19
Sasi []	3.5	1.0	3.0	3.0	1.0	1.0	2.0	2.0	4.0	2.5	1.0	24
Tou at al. []	4.0	4.0	4.0	3.0	4.0	4.0	2.0	2.0	4.0	3.5	3.5	38
Xiong et al. []	3.5	4.0	4.0	2.0	2.0	3.5	3.0	2.0	4.0	3.5	2.5	34

Table A4.2. Quality assessment of included primary studies according to the criteria from the Cochrane Handbook for Systematic Reviews of Interventions (*adapted from: Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.0.2 [updated September 2009]. The Cochrane Collaboration. Available from www.cochrane-handbook.org 2009*). The studies are listed alphabetically according to the surgical procedure or group of procedures.

Author and study design	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
Breast surgery							
Boehm 2012	Low risk Random number table generated sequence	Low risk Random number table generated sequence	Not applicable	High risk No statement of blinding was given	Low risk Data about all patient included in the study was reported	Unclear risk Insufficient information on study protocol	-
RCT							

Cavallaro 2011 CCT	High risk The study was not randomised.	High risk The study was not randomised.	Not applicable	High risk No statement of blinding was given.	Low risk Data about all patients included in the study was reported.	Low risk Outcomes in the protocol were considered in the final publication.	-
Iovino 2011 RCT	Low risk Randomization was performed using a series of numbered envelopes containing cards.	Low risk The envelopes were opened in the operating room immediately before the operation by a member of the staff who was not involved in organizing the trial.	Not applicable	High risk No statement of blinding was given.	Low risk Data about all patients included in the study was reported.	Low risk Overall, we monitored and measured 13 variables, 4 of which were discarded (with reasons).	-
He 2012 RCT	Low risk Randomization by closed envelop	Low risk Randomization by closed envelop	Not applicable	High risk No statement of blinding was given	Low risk Data about all patient included in the study was reported	Unclear risk Insufficient information on study protocol	-
Lumachi 2013 RCT	High risk The study is not randomized (randomization was performed according to the availability of the ultrasonic device).	High risk The study was not randomised.	Not applicable	High risk No statement of blinding was given.	Low risk Data about all patients included in the study was reported.	Unclear risk Insufficient information on study protocol.	-
Yilmaz 2011 RCT	Unclear risk Randomization was achieved by consecutively enrolling pts to each group according to the pts admission time to the clinic.	Unclear risk Randomization was arranged sequentially	Not applicable	High risk No statement of blinding was given	Low risk Data about all patient included in the study was reported	Unclear risk Insufficient information on study protocol	-
Cardio-vascular surgical procedures							
Brazio 2008 CCT	High risk The study was not randomised (consecutive patients were assigned to the different treatment options).	High risk The study was not randomised.	Not applicable	Low risk Abnormalities on OCT were confirmed in each case by histologic findings performed by reviewers who were unaware of the harvesting method.	Low risk Data about all patients included in the study was reported.	Unclear risk Insufficient information on study protocol.	-
Dumantepe 2011 RCT	Unclear risk Consecutive patients were assigned to the different treatment options.	High risk The study was not randomised.	Not applicable	High risk No statement of blinding was given.	Low risk Data about all patients included in the study was reported.	Unclear risk Insufficient information on study protocol.	-

Mouton 2005 RCT	Unclear risk No details on randomisation.	Unclear risk No details on randomisation.	Not applicable	High risk No statement of blinding was given.	Unclear risk Data about all patients included in the study was reported. Follow up data available for 25 pts (69%).	Unclear risk Insufficient information on study protocol.	-
Mouton 2011 FUS	Low risk Consecutive patients were assigned to the different treatment options.	Low risk Patients were randomised by throwing dice.	Not applicable	High risk No statement of blinding was given.	Low risk Follow-up data collected for all patients.	Unclear risk Insufficient information on study protocol.	-
Shapira 2006 RCT	Low risk Randomization by a computer generated list	Low risk Computer generated random list	Not applicable	High risk No statement of blinding was given	Low risk Data about all patient included in the study was reported	Unclear risk Insufficient information on study protocol	This study was support by a research grant from CardioVations, a Johnson&Johnson company
ENT surgery							
Shin 2013 RCT	Unclear risk No details on randomisation.	Unclear risk No details on randomisation.	Not applicable	High risk No statement of blinding was given.	Low risk Data about all patients included in the study was reported.	Low risk. Protocol study is available and all data reported in the study.	-
alen 2011 RCT	Low risk Consecutive patients were assigned to the different treatment options.	Low risk Subjects were assigned to either the control or experimental groups via a predetermined 6x6 block randomization.	Not applicable	Low risk Personnel measuring the secondary outcomes were blinded to the surgical technique used.	Low risk Exclusions from analysis were motivated (two subjects were excluded from analysis and follow-up because of protocol violations).	Unclear risk Insufficient information on protocol study.	-
Gastrointestinal surgery							
Choi 2013 RCT	Low risk Randomization lists were generated from an independent randomization group using a permuted block design of size four within each stratum.	Low risk Randomization lists were generated from an independent randomization group using a permuted block design of size four within each stratum.	Not applicable	High risk No statement of blinding was given	Low risk Data about all patient included in the study was reported	Unclear risk Insufficient information on study protocol	No declaration about author's competing interests was found in the article
Inoue 2012 RCT	Unclear risk No details on randomisation.	Unclear risk No details on randomisation.	Not applicable	High risk No statement of blinding was given.	Low risk Data about all patients included in the study was reported.	Unclear risk Insufficient information on study protocol.	-

ilhelm 2011 RCT	Low risk A randomization list was generated separately for each participating institution in advance.	Low risk The randomization list was generated by block randomization. The block length was fixed before starting the investigation and was not known to the surgeons.	Not applicable	High risk No statement of blinding was given	Low risk Data about all patients included in the study was reported. Data on follow-up reported for all patients included.	Unclear risk Insufficient information on study protocol.	-
Gynaecological surgery							
Awadzi 2005 SPC	Unclear risk Patients were divided to one or other intervention by a randomization envelope.	Unclear risk No details on randomization.	Not applicable	Low risk The histopathologist was blinded.	Low risk Data about all patients included in the study was reported.	Unclear risk Insufficient information on study protocol.	-
Fitz-Gerald 2013 RCT	Low risk Randomisation by permuted blocks.	Low risk Opaque sealed envelopes.	Not applicable	Unclear risk When possible patients and data collectors were blinded until all data were collected.	Low risk Data about all patients included in the study was reported.	Unclear risk Insufficient information on study protocol.	-
Kartsiounis 2011 CCT	High risk The study was not randomised.	High risk The study was not randomised.	Not applicable	High risk No statement of blinding was given.	Low risk Data about all patients included in the study was reported.	Unclear risk Insufficient information on study protocol.	-
Leblanc 2011 CCT	High risk The study was not randomised.	High risk The study was not randomised.	Not applicable	High risk No statement of blinding was given.	Low risk Data about all patients included in the study was reported.	Unclear risk Insufficient information on study protocol.	-
Li 2009 RCT	Low risk Patients agreed to laparoscopy, were randomized into two groups.	Low risk Computer-generated randomized allocation schedule.	Not applicable	High risk No statement of blinding was given.	Low risk Follow-up data collected for all patients.	Unclear risk Insufficient information on study protocol.	-
Litta 2010 RCT	Low risk Randomisation by computer generated block randomization numbers.	Low risk Sealed opaque envelopes.	Not applicable	Unclear risk The ultrasonographer that evaluated patients before interventions was unaware of treatment assessment (not relevant for the post-operative outcomes).	Low risk Data about all patients included in the study was reported.	Unclear risk Insufficient information on study protocol.	-
Haemorrhoidectomy and ano-rectal surgery							
Abo-hashem 2010 RCT	Unclear risk No sufficient information about randomisation.	Unclear risk No sufficient information about randomisation.	Not applicable	Unclear risk No statement of blinding was given.	Low risk Data about all patients included in the study was reported	Unclear risk Insufficient information on study protocol.	-

Boccasanta 2006 RCT	Low risk Patients were randomly assigned to Group 1 or Group 2 by using a computer-generated randomization list, with block size varying from four to six.	Low risk Sealed envelopes with a random number table.	Not applicable	Unclear risk No statement of blinding was given.	Low risk No patients lost in follow-up and all data reported.	Unclear risk Insufficient information on study protocol.	-
Bulus 2012 RCT	Unclear risk No details on randomization	Unclear risk No details on randomization	Not applicable	High risk No statement of blinding was given	Low risk Data about all patient included in the study was reported	Unclear risk Insufficient information on study protocol	
Chung 2005 RCT	Low risk Randomisation performed by blocks.	Low risk Sealed envelope.	Not applicable	High risk No statement of blinding was given.	Low risk Data about all patients included in the study was reported.	Unclear risk Insufficient information on study protocol.	-
Ivanov 2007 RCT	Low risk Computer generated sequence.	Unclear risk No allocation concealment specified.	Not applicable	High risk No statement of blinding was given.	Low risk Data about all patients included in the study was reported.	Unclear risk Insufficient information on study protocol.	-
Kwok 2005 RCT	Low risk Randomization was performed at the time of anaesthesia	Low risk Computer-generated list.	Not applicable	Low risk Neither the patient nor the independent assessor were aware of the technique used at operation.	Low risk Data about all patients included in the study was reported.	Unclear risk Insufficient information on study protocol.	-
Omar 2011 RCT	Low risk Randomization by a closed envelope method	Low risk Randomization by a simple closed envelope method	Not applicable	High risk No statement of blinding was given	Low risk Data about all patient included in the study was reported	Unclear risk Insufficient information on study protocol	No declaration about author's competing interests was found in the article
Ozer 2008 RCT	Unclear risk Randomization was achieved by consecutively enrolling patients to each group according to their admission time to the clinic.	Unclear risk No allocation concealment specified.	Not applicable	High risk No statement of blinding was given.	Low risk Data about all patients included in the study was reported.	Unclear risk Insufficient information on study protocol.	-

Peker 2013 RCT	Low risk Patients enrolled for the study were randomized into three groups by a computer program.	Low risk Code enclosed in a numbered envelope corresponding to one of the three techniques was shown to the surgeon at the beginning of the operation.	Not applicable	High risk No statement of blinding was given.	Low risk Data about all patients included in the study was reported.	Unclear risk Insufficient information on study protocol.	-
Hepatic surgery							
Olmez 2012 RCT	Low risk Patients were randomised in 2 groups at the beginning of surgery.	Low risk Throwing dice at the beginning of surgery.	Not applicable	High risk No statement of blinding was given.	Low risk Data about all patients included in the study was reported.	Unclear risk Insufficient information on study protocol.	-
Laparoscopic cholecystectomy							
Mahabaleshwar 2012 RCT	Low risk Patients were randomly assigned to the 2 groups before the surgery.	Unclear risk Envelope method.	Not applicable	High risk No statement of blinding was given.	Low risk Data about all patients included in the study was reported.	Unclear risk Insufficient information on study protocol.	-
Lung biopsy							
Molnar 2005 RCT	Low risk Consecutive patients were assigned to the different treatment options.	Low risk Patients were randomised using the dice method in one of the two pronges.	Not applicable	High risk No statement of blinding was given.	Low risk Data about all patients included in the study was reported.	Unclear risk Insufficient information on study protocol.	-
Orthopaedic surgery							
Tomas 2010 RCT	Low risk Consecutive patients were randomly assigned to one of each groups.	Unclear risk No allocation concealment specified.	Not applicable	High risk No statement of blinding was given.	Low risk Data about all patients included in the study was reported.	Unclear risk Insufficient information on study protocol.	-
Pancreatic surgery							
Uzunoglu 2012 RCT	Low risk Patients were randomly assigned to the 2 groups the day before the surgery.	Low risk Sequence generated by an online randomisation tool.	Not applicable	High risk No statement of blinding was given.	Low risk Data about all patients included in the study was reported.	Unclear risk Insufficient information on study protocol.	-
Plastic and reconstructive surgery							
Deo 2005 RCT	Low risk Patients were randomised in two arms after obtaining informant consent.	Low risk Computer-generated sequence of numbers.	Not applicable	High risk No statement of blinding was given.	Low risk Data about all patients included in the study was reported.	Unclear risk Insufficient information on study protocol.	-
Hamahata 2012 RCT	Unclear risk Patients were randomised in two groups.	High risk No allocation concealment specified.	Not applicable	High risk No statement of blinding was given.	Low risk Data about all patients included in the study was reported.	Unclear risk Insufficient information on study protocol.	-
Thyroid surgery							

Cirocchi 2012 CCT	High risk The study was not randomised.	High risk The study was not randomised.	Not applicable	High risk No statement of blinding was given.	Low risk Data about all patients included in the study was reported.	Unclear risk Insufficient information on study protocol.	-
Ruggeri 2012 ES (from a RCT)	Unclear risk No mention about method of randomisation.	Unclear risk No mention about method of randomisation.	Not applicable	High risk No statement of blinding was given.	Low risk Data about all patients included in the study was reported.	Unclear risk Insufficient information on study protocol.	-
Sebag 2009 ES (from a CCT)	High risk The study was not randomised.	High risk The study was not randomised.	Not applicable	High risk No statement of blinding was given.	Low risk Data about all patients included in the study was reported.	Unclear risk Insufficient information on study protocol.	-
Tonsillectomy							
Khan 2012 CCT	High risk The study was not randomised.	High risk The study was not randomised.	Not applicable	High risk No statement of blinding was given.	Low risk Data about all patients, also regarding follow-up, was reported.	Unclear risk Insufficient information on study protocol.	-

Key: CCT = controlled clinical trial; ES = economic study; FUS = follow-up study; OCT = optical coherence tomography; RCT = randomised controlled trial; SPC = same-patient comparative study.

Appendix 5 – Search strategy – (Economic literature)

➤ MEDLINE (Pubmed)

DATE: 17 February 2014

LIMITS: Humans, Publication Date from 2004/01/01 to date, English and Italian

Health technology				Study design
Ultrasonic Surgical Procedures (MESH) OR Ultrasonic Surgical Procedures/economics (MESH) OR "ultrasonic surgical procedures" [Text Word] OR "ultrasound surgery" [Text Word] OR "Ultrasonic energy device" OR "surgical energy device" [Text Word] OR "Energy based devices" [Text Word]	AND	Scalpel [title/abstract] OR Shears [title/abstract] OR Coagulator* [title/abstract] OR Scissors [title/abstract]	AND	(Cost [title/abstract] AND analysis [title/abstract]) OR ("cost minimization" [title/abstract] OR CMA [title/abstract]) OR ("cost effectiveness" [title/abstract] OR CEA [title/abstract]) OR ("cost utility" [title/abstract] OR CUA [title/abstract]) OR ("health care" [Text Word] AND cost* [Text Word]) OR (economic [Text Word] AND (evaluation OR analysis OR aspect OR assessment) [Text Word]) OR "Budget Impact Analysis" [title/abstract]
OR				OR BIA [title/abstract]
Harmonic [title/abstract] OR Sonicision [title/abstract] OR SonoSurg [title/abstract] OR Thunderbeat [title/abstract] OR Ultracision [title/abstract] OR Lotus [title/abstract]				

Yield: 36

➤ EMBASE (Embase.com)

DATE: 17 February 2014

LIMITS: Humans, Publication Date from 2004 to date, English and Italian

Health technology				Study design
'ultrasound surgery'/exp OR 'ultrasound surgery'/exp AND 'health economics'/exp OR 'ultrasonic surgical procedures'/exp OR ('ultrasonic'/exp AND 'energy'/exp AND 'device'/exp) OR 'surgical energy device' OR 'energy based devices' OR 'energy based device'	AND	scalpel:ab,ti OR shears:ab,ti OR Coagulator*:ab,ti OR scissors:ab,ti OR dissector:ab,ti	AND	'cost analysis'/exp OR ('cost minimization':ab,ti OR cma:ab,ti) OR ('cost effectiveness':ab,ti OR cea:ab,ti) OR ('cost utility':ab,ti OR cua:ab,ti) OR 'health care'/exp AND cost* OR (economic AND ('evaluation'/exp OR 'analysis'/exp OR aspect OR assessment)) OR ('budget impact analysis':ab,ti OR bia:ab,ti)
OR				
harmonic:dn OR Sonicision:dn OR SonoSurg:dn OR Thunderbeat:dn OR Ultracision:dn OR Lotus:dn				

Yield: 48

➤ Cochrane Library

Date: 17 February 2014

Health technology				Study design
MeSH descriptor: [Ultrasonic Surgical Procedures] explode all trees OR 'ultrasonic surgical procedures' OR 'ultrasound surgery' OR 'ultrasonic surgical procedures' OR ultrasonic energy device OR surgical energy device OR 'energy based devices' OR 'energy based device'	AND	scalpel:ti,ab,kw OR shears: ti,ab,kw OR Coagulator*: ti,ab,kw OR scissors: ti,ab,kw OR dissector: ti,ab,kw	AND	'cost analysis':ti,ab,kw OR ('cost minimization': ti,ab,kw OR cma) OR ('cost effectiveness': ti,ab,kw OR cea) OR ('cost utility': ti,ab,kw OR cua) OR 'health care'/exp AND cost* OR (economic AND (evaluation OR analysis OR aspect OR assessment)) OR ('budget impact analysis': ti,ab,kw OR bia)
OR				

'Harmonic Scalpel': ti,ab,kw OR Sonicision: ti,ab,kw OR SonoSurg: ti,ab,kw OR Thunderbeat: ti,ab,kw OR Ultracision: ti,ab,kw OR Lotus: ti,ab,kw		
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Yield: 23

➤ **EcoLit**

Date: 21 February 2014

ultrasonic surgical procedure OR ultrasonic surgical procedures OR OR 'ultrasound surgery' OR 'ultrasonic surgical procedures' OR ultrasonic energy device OR surgical energy device OR 'energy based devices' OR 'energy based device' OR Harmonic or Sonicision or SonoSurg or Thunderbeat or Ultracision or Lotus).mp. [mp=heading words, abstract, title, country as subject]	AND	'cost analysis':ti,ab,kw OR ('cost minimization': ti,ab,kw OR cma) OR ('cost effectiveness': ti,ab,kw OR cea) OR ('cost utility': ti,ab,kw OR cua) OR 'health care'/exp AND cost* OR (economic AND (evaluation OR analysis OR aspect OR assessment)) OR ('budget impact analysis': ti,ab,kw OR bia)
(Scalpel* or Shear* or Coagulator* or Scissor*) mp. [mp=heading words, abstract, title, country as subject]		

Yield: 0

➤ **HEED**

Date: 21 February 2014

ultrasonic surgical procedure.all data OR ultrasonic surgical procedures.all data OR ultrasound surgery).all data OR ultrasonic surgical procedures.all data ' OR ultrasonic energy device.all data OR surgical energy device.all data OR energy based devices.all data OR	AND	cost OR costs OR economic OR budget
---	-----	--

energy based device.all data OR (Harmonic or Sonicision or SonoSurg or Thunderbeat or Ultracision or Lotus).all data		
(Scalpel* or Shear* or Coagulator* or Scissor*) all data		

Yield: 18

Table A5.1: Results of the search strategy

Database	Research date	Results
MedLine	17 February 2014	36
Embase	17 February2014	48
CL EED	18 February 2014	23
EcoLIT	21 February 2014	0
Health Economic Evaluations Databases (HEED)	21 February 2014	18

Appendix 6

Extraction sheets – Economic studies

- **Cost-effectiveness cost-utility and cost-benefit analysis**

General information	
Reviewer name:	
Date of extraction:	
Author/Year:	
Title:	
Journal:	
Source of funding:	
Study Characteristics	
Objective of study:	
Study population:	
Intervention:	
Comparator:	
Economic Study Type	Perspective
Cost-effectiveness Analysis <input type="checkbox"/>	NHS <input type="checkbox"/>
Cost-utility Analysis <input type="checkbox"/>	Societal <input type="checkbox"/>
Cost-benefit Analysis <input type="checkbox"/>	Hospital <input type="checkbox"/>
Cost-Consequence Analysis <input type="checkbox"/>	Not Stated <input type="checkbox"/>
Cost-Study <input type="checkbox"/>	Other <input type="checkbox"/>
Other (specify) <input type="checkbox"/>	
Not reported <input type="checkbox"/>	
Modelling	
Was a model used?	
Yes <input type="checkbox"/>	
No <input type="checkbox"/>	
If yes, state purpose and type:	
Source of Data	
<i>Source of effectiveness data</i>	<i>Source of Cost Data</i>
Single study <input type="checkbox"/>	Actual source (survey, direct contact, etc.) <input type="checkbox"/>
Synthesis of Previous Publication <input type="checkbox"/>	Literature source <input type="checkbox"/>

Source of effectiveness data

Effectiveness data from a single study

Study design

- RCT
- Non-RCT with concurrent controls
- Cohort study
- Historical control
- Before and after study
- Case series
- Other (specify)
- Not reported

Study population

- Number of patients in intervention group
- Number subject in control group
- Number excluded from study

Methods of sample selection:

Follow-up

- Duration of follow-up:
- Loss to follow-up:

Number of centres:

Any blinding for assessment of outcomes:

Analysis of clinical studies:

- Treatment completers
- Intention to treat

Study inclusion criteria:	Study exclusion criteria reported:
Effectiveness results: Study designs included: RCT <input type="checkbox"/> Non-RCT with concurrent controls <input type="checkbox"/> Cohort study <input type="checkbox"/> Historical control <input type="checkbox"/> Before and after study <input type="checkbox"/> Case seies <input type="checkbox"/> Other <input type="checkbox"/> Not reported	Number of primary studies included:
Sources searched reported:	Method of combination of primary study:
Criteria used to judge validity: Concealment of randomisation <input type="checkbox"/> Blind assessment <input type="checkbox"/> Low drop out rates <input type="checkbox"/> Other (specify) <input type="checkbox"/> Not reported <input type="checkbox"/>	Meta-analysis <input type="checkbox"/> Narrative methods <input type="checkbox"/> Other (specify) <input type="checkbox"/>
Results of the review (Effectiveness results):	
<i>Economic evaluation</i>	
Measures of Benefits used in the Economic Analysis	
yes <input type="checkbox"/>	
no <input type="checkbox"/>	
If yes, specify:	
Side effect considered	
yes <input type="checkbox"/>	
no <input type="checkbox"/>	
Direct costs: Health service	
Estimation based on:	
A guess <input type="checkbox"/>	
Actual data <input type="checkbox"/>	
Derived using Modelling <input type="checkbox"/>	
Other <input type="checkbox"/>	
Not reported <input type="checkbox"/>	

Direct costs: Patients	
Estimation based on:	
A guess	<input type="checkbox"/>
Actual data	<input type="checkbox"/>
Derived using Modelling	<input type="checkbox"/>
Other	<input type="checkbox"/>
Not reported	<input type="checkbox"/>
Source of Direct costs Data:	Discounting Undertaken
Price Year:	Yes <input type="checkbox"/>
Currency:	No <input type="checkbox"/>
	Discount rate:
Indirect costs:	
Estimation based on:	
A guess	<input type="checkbox"/>
Actual data	<input type="checkbox"/>
Derived using Modelling	<input type="checkbox"/>
Other	<input type="checkbox"/>
Not reported	<input type="checkbox"/>
Source of Indirect costs Data:	Discounting Undertaken
Price Year:	Yes <input type="checkbox"/>
Currency:	No <input type="checkbox"/>
Conversion rates used:	Discount rate:
<i>Statistical / sensitivity analyses</i>	
Statistical tests carried out?	Types of tests used in analysis of costs:
yes <input type="checkbox"/>	
no <input type="checkbox"/>	
Type of sensitivity analysis	Areas of uncertainty tested:
One-way analysis <input type="checkbox"/>	
Two-way analysis <input type="checkbox"/>	
Multi-way analysis <input type="checkbox"/>	
Threshold analysis <input type="checkbox"/>	
Analysis of Extremes <input type="checkbox"/>	
Probabilistic analysis <input type="checkbox"/>	
Not reported <input type="checkbox"/>	
Not carried out <input type="checkbox"/>	
Other:	

<i>Results of study</i>	
Clinical Outcome/Benefit:	
Duration of benefits	
Costs results:	
Cost of adverse events considered	
yes	<input type="checkbox"/>
No	<input type="checkbox"/>
Not relevant	<input type="checkbox"/>
How were the estimates of costs and benefits combined	
Cost-Life saved	<input type="checkbox"/>
Cost/Life gained	<input type="checkbox"/>
Cos/QALY	<input type="checkbox"/>
Not benefit	<input type="checkbox"/>
Incremental net benefit	<input type="checkbox"/>
Other	<input type="checkbox"/>
Not combined	<input type="checkbox"/>
Results of Synthesis of costs and benefits:	
Author s conclusion:	
Reviewer s conclusion:	
Overall assessment of study quality (CHEERS):	

Adapted from Bamford J, et al. Current practice, accuracy, effectiveness and cost-effectiveness of the school entry hearing screen. *Health Technol Assess* 2007;11(32).

▪ **Cost-analysis**

Study ID	Comparison	Costs				Source	Economic results
		Item					
		Type	Device	Value			

Appendix 7

Excluded studies

List of excluded studies with reasons for exclusion

No technology:

Savlid, M.; Strand, A. H.; Jansson, A.; Agustsson, T.; Soderdahl, G.; Lundell, L., and Isaksson, B. Transection of the liver parenchyma with an ultrasound dissector or a stapler device: results of a randomized clinical study (Provisional abstract). *World Journal of Surgery*. 2013; 37(4):799-805.

No comparator:

Chang, L. Y.; O'Neill, C.; Suliburk, J.; Sidhu, S.; Delbridge, L., and Sywak, M. Sutureless total thyroidectomy: a safe and cost-effective alternative. *ANZ J Surg*. 2011 Jul-2011 Aug 31; 81(7-8):510-4.

Suo, G. and Xu, A. Clipless minilaparoscopic cholecystectomy: A study of 1096 cases. *J. Laparoendosc. Adv. Surg. Techn*. 2013; 23(10):849-854.

Yung, E.; Gagner, M.; Pomp, A.; Dakin, G.; Milone, L., and Strain, G. Cost comparison of reusable and single-use ultrasonic shears for laparoscopic bariatric surgery. *Obes. Surg*. 2010; 20(4):512-518.

No study design:

Cirocchi, R.; D'Ajello, F.; Trastulli, S.; Santoro, A.; Di Rocco, G.; Vendettuoli, D.; Rondelli, F.; Giannotti, D.; Sanguinetti, A.; Minelli, L.; Redler, A.; Basoli, A., and Avenia, N. Meta-analysis of thyroidectomy with ultrasonic dissector versus conventional clamp and tie. *World J. Surg. Oncol*. 2010; 8.

Huang, Y.; Mu, G. C.; Qin, X. G.; Lin, J. L.; Liu, C.; Chen, Z. B., and Zeng, Y. J. The application of ultrasonic harmonic scalpel in the radical surgery of gastric cancer (Provisional abstract). *Clinical and Translational Oncology*. 2013; 15(11):932-937.

Sasi, W. Dissection by ultrasonic energy versus monopolar electro-surgical energy in laparoscopic cholecystectomy. *JLS*. 2010 Jan-2010 Mar 31; 14(1):23-34.

Sileshi, B.; Achneck, H.; Ma, L., and Lawson, J. H. Application of energy-based technologies and topical hemostatic agents in the management of surgical hemostasis. *Vascular*. 2010; 18(4):197-204.

Hartl, D.-M. The place of new haemostatic techniques in thyroid surgery. *Eur. Ann. Otorhinolaryngol. Head Neck Dis*. 2011; 128(4):200-202.

Neumann, C.; Street, I.; Lowe, D., and Sudhoff, H. Harmonic scalpel tonsillectomy: a systematic review of evidence for postoperative hemorrhage (Structured abstract). *Otolaryngology - Head and Neck Surgery*. 2007; 137(3):378-384.

Wright, C. Invited commentary. *Ann. Thorac. Surg.* 2007; 84(6):2080.

No date range:

Meurisse, M.; Defechereux, T.; Maweja, S.; Degauque, C.; Vandelaer, M., and Hamoir, E. [Evaluation of the Ultracision ultrasonic dissector in thyroid surgery. Prospective randomized study]. *Annales De Chirurgie.* 2000; 125(5):468-72.

Erian M, McLaren G R Buck R J Wright G. Reducing costs of laparoscopic hysterectomy. 1999; 6:471-475.

Lirici M M, Di Paola M Ponzano C Huscher C G S. Combining ultrasonic dissection and the Storz operation rectoscope. 2003; 17:1292-1297.

Ohtsuka T, Wolf R K Wurnig P Park S E. Thoracoscopic limited pericardial resection with an ultrasonic scalpel. 1998; 65:855-856.

Richards S R, Simpkins S. Comparison of the harmonic scissors and endostapler in laparoscopic supracervical hysterectomy. 1995; 3(1):87-90.

Underwood R A, Dunnegan D L Soper N J. Prospective, randomized trial of bipolar electrocoagulation vs ultrasonic coagulation for division of short gastric vessels during laparoscopic Nissen fundoplication. 1999; 13:763-768.

No preliminary results:

Lombardi, C. P.; Raffaelli, M.; Cicchetti, A.; Marchetti, M.; De Crea, C.; Di Bidino, R.; Oragano, L., and Bellantone, R. The use of "harmonic scalpel" versus "knot tying" for conventional "open" thyroidectomy: results of a prospective randomized study. *Langenbecks Arch Surg.* 2008 Sep; 393(5):627-31.

No duplicate:

Dibidino, R.; Ruggeri, M.; Marchetti, M.; Lombardi, N.; Raffaelli, M.; Attina, G., and Cicchetti, A. Harmonic study: A cost-effectiveness evaluation of ultrasonically activated shears for total thyroidectomy. [Italian]. *PharmacoEconomics - Italian Research Articles.* 2010; 12(3):143-155.