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# Rapid HTA report



# Ultrasonic energy devices for surgery

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# Declaration on the conflict of interest and privacy

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.

# INDEX

# 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 razionale 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).

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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 port-operatorio nll'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 colorettale (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:

- Colecistectomia 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 colorettale laparoscopica (in particolare resezione colorettale 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 nerves[20]. 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 1990s[3]. 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 protein[20]. 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.



| Manufacturer | Device name | Variants | Surgical setting |
|---|---|---|---|
| Covidien | Sonicision | - | Open and Endoscopic |
| Ethicon Endo-surgery | Harmonic | ACE + Shears<br>ACE Shears<br>FOCUS Curved Shears<br>FOCUS + Curved Shears<br>FOCUS Long Curved Shears<br>LCSC5<br>WAVE Open Shears | Open and Endoscopic<br>Open and Endoscopic<br>Open<br>Open<br>Open<br>Endoscopic<br>Open |
| Olympus Medical Systems | SonoSurgX | - | Open<br>Endoscopic |
| | Thunderbeat* | - | Open and Endoscopic |
| | Sonicbeat | - | Open and Endoscopic |
| SRA Developments | Lotus Series 4 | Dissecting Shears<br>Liver Resector<br>Vessel Welder | Open and Endoscopic<br>Open and Endoscopic<br>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 procedures[90]. 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 procedures[91].

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 procedures[92].

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 procedures[93].

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 procedures[94].

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 generator[59]. The SonoSurgX device can be used in bariatric procedures which include: laparoscopic and general (open) surgery in intra-abdominal, obstetric/gynaecologic, thoracic and urologic procedures[95].

*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 procedures[96].

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 procedures[97]. 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.*



**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.*

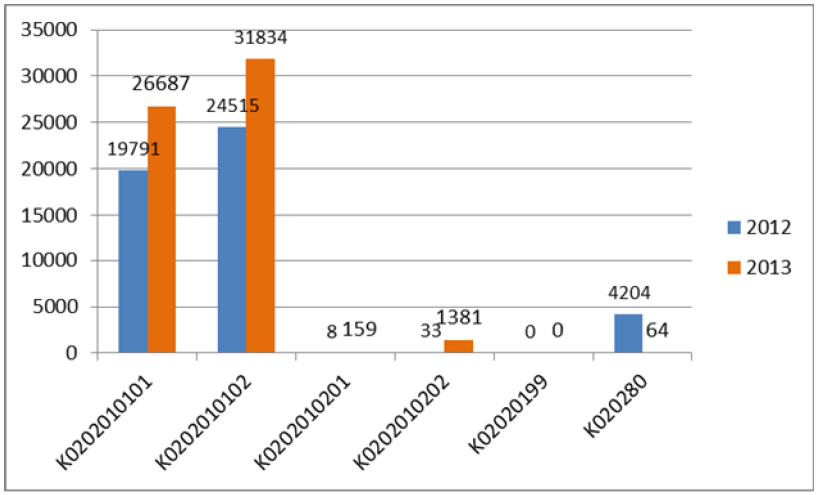
Figure 3.1 shows graphically the consumption in 2012 and 2013 of the ultrasonic devices belonging to K Class. Specifically, device consumption in 2013, compared to 2012, increased by 34.84% for "single-use ultrasonic scissors for open surgery", by 29.86% for "single-use ultrasonic scissors for endoscopic 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).

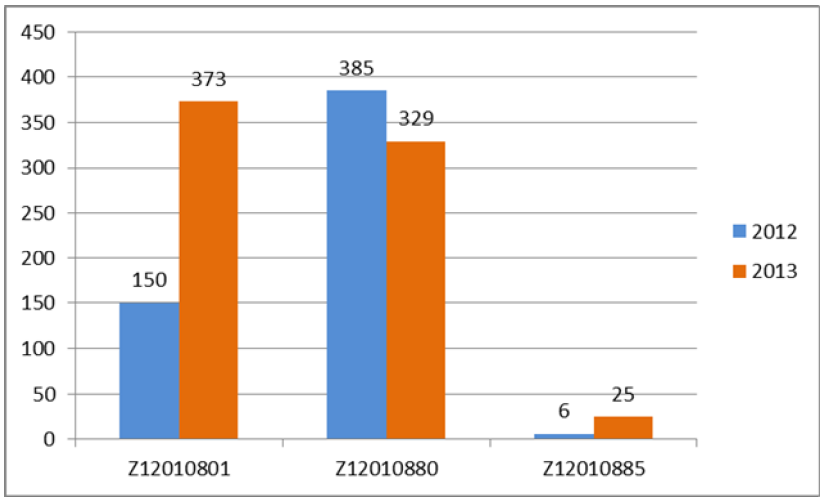
**Figure 3.1:** Consumption of K class devices in 2012 and 2013.





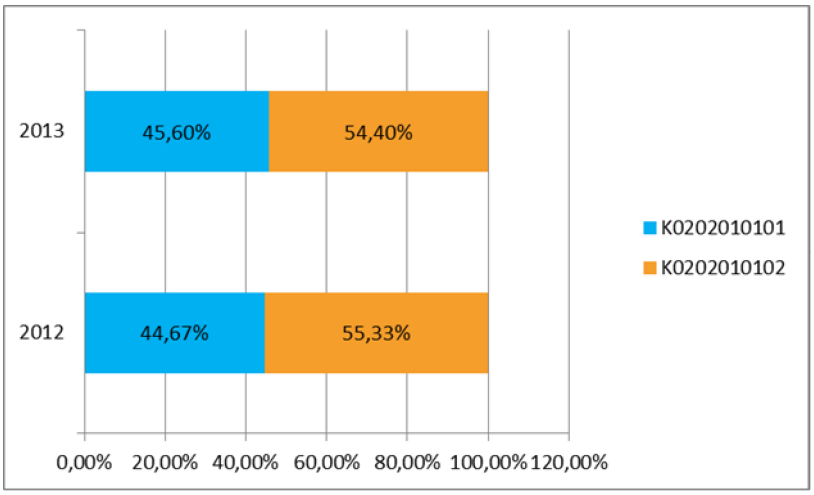

***Source:*** *Agenas analysis based on national database "Flusso consumi", years 2012 and 2013.*

**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.*



**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 tool[43]. Methodological quality of RCTs and CCTs was assessed using the criteria from the Cochrane Handbook for Systematic Reviews of Interventions[30].



## 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.*

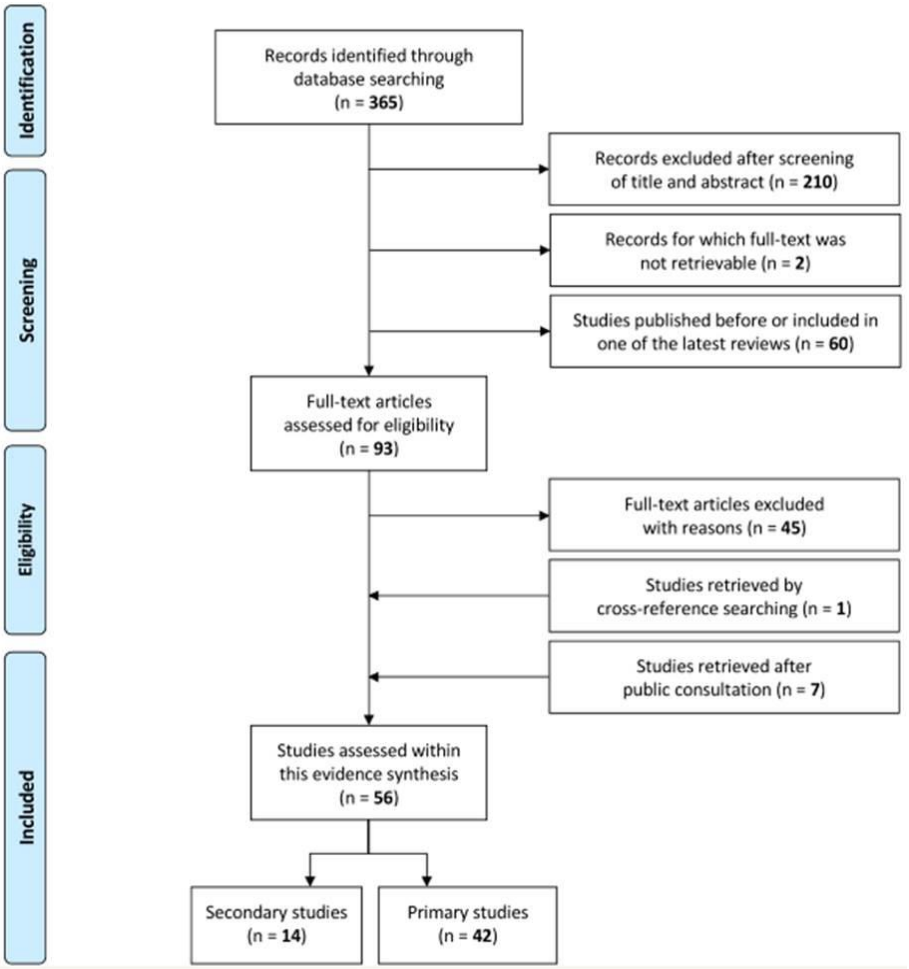


**Table 4.1:** Surgical procedures (or groups of procedures) identified for this evidence review (see Appendix 3).

| 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 mayor 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 procedures[37]. 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 dissection[17]. 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 CCT[11]; 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 techniques[63]. 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 CCT[7] 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 conduicts 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 RCT[54] and was then followed for 7 years[55] (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.



### *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 hemicolectomy[80], and two reporting on gastrectomy with lymph node dissection[34, 86].

In the study by Wilhelm at al.[80] 255 patients undergoing total gastrectomy for localised gastric cancer or hemi colectomy 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.



### *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 study[4]; 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 Kartsiounis 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 $CO_2$ 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.



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 cholecystectomy[81]. 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 cholecystectomy[51] 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 statistical significant lower incidence of gallbladder perforation, and duration of surgery. Moreover, the study by Mahabaleshwar 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 diseases[21]. 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 study[58] 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 study[53] 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 study[76] 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 7$^{th}$ 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 3$^{rd}$ day, $P<0.05$, and 26 mg/l vs. 54 mg/l at the 7$^{th}$ day, $P<0.01$; Creatine kinase blood levels: 2.4 ukat/l vs. 5.3 ukat/l at the 3$^{rd}$ day, $P<0.01$, and 1.1 ukat/l vs. 1.8 ukat/l at the 7$^{th}$ 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 study[78] 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 mayor myocutaneous flap dissection[19] and anterolateral thigh flap elevation[29].

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 tree-way comparison between energised vessel sealing systems and conventional "clamp-and-tie" or traditional electrosurgical methods to evaluate operation time and post-operative complications[15]. 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 RCT[67]; 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 study[13], while in the other 2 studies[70, 67] this was not clearly reported.



### *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 study[39] 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 |
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| Alexiou et al., 2011 | Total tonsillectomy | RCT | 33 RCTs;<br><br>3,139 patients. | Vessel sealing systems (VSS), Harmonic Scalpel (HS), Radiofrequency ablation (RFA)<br>VS<br>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).<br>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;<br><br>4,061 patients. | Ultrasonic systems (HS)<br>VS<br>Electrothermal bipolar vessel sealing systems (LS)<br>VS<br>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 laringeal 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. |

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| Currie et al., 2012 | Mastectomy for breast cancer | Comparative trials | 6 RCTs;<br><br>287 cases. | Ultrasonic dissection (UD)<br>VS<br>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).<br>Seroma development (5 studies): no statistically significant difference between the two groups (no significant statistical heterogeneity).<br>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).<br>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;<br>CCT | 2 RCTs;<br>2 CCTs;<br><br>408 procedures. | Electrothermal bipolar vessel sealing (EBVS)<br>VS<br>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.<br>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. |

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| Janssen et al., 2012 | Abdominal surgical procedures | RCT | 7 RCTs;<br><br>554 patients. | Vessel sealing device (VS)<br>VS<br>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.<br>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.<br>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.<br>None of the studies assessed quality of life or return to work.<br>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 at al., 2006 | Radial artery harvest | RCT;<br>CCT | 5 RCTs;<br>5 CCTs;<br><br>1,278 radial arteries. | Ultrasonic harvesting (US)<br>VS<br>Standard harvesting techniques (ST) | Of 5 studies reporting time to harvest, 3 report no difference and 2 report that US is quicker.<br>Six studies reported the marked reduction in the number of clips used with the US.<br>Two studies reported a small benefit in reducing spasm.<br>Two studies looked at the artery electron microscopically but no significant differences were seen.<br>Two studies reported less numbness and 2 studies no difference in numbness post-operatively.<br>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.<br>All studies were small and either used a single surgeon or a very small number of surgeons to harvest the radial artery.<br>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. |

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| Xiong et al., 2012 | Laparoscopic cholecystectomy | RCT | 11 RCTs;<br><br>1,434 patients. | Ultrasonic energy device (US)<br>VS<br>Monopolar electrosurgical energy device (MP) | 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).<br>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).<br>Mead 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).<br>Operation conversion (6 trials): No statistically significant difference was found between the two groups<br>Gallbladder perforation (6 trials): The pooled result favoured the US (OR, 0.31; 95% CI, 0.22–0.44; P < .00001).<br>Bile leakage (5 trials): US energy significantly reduced the incidence of bile leakage (OR, 0.31; 95% CI, 0.06–1.56; P = .16).<br>Intra-abdominal collections (2 trials): No difference.<br>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).<br>Postoperative nausea at 24 hours (2 trials): No difference. | |

**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 |
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| 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;<br><br>Group B (54 F): conventional surgery using scalpel and electrocautery | Harmonic Focus | There was no difference in operative time between groups.<br>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.<br>Breast drainage removed earlier in group A: 3.3 days (±1.1) vs. 2.1 (±1.1); p<0.001.<br>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.<br>Axillary drainage removed earlier in group A: 3.5 days (3.0-4.3) vs. 2.0 (1.8-3.0); p=0.001.<br>Median length of stay increased for group B: 4.5 days (4-6) vs. 4.0 days (3-5); p<0.001.<br>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.<br>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;<br><br>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).<br>Total drain volume lower in group A (323.65 ± 221.7 vs. 454 ± 315.7; P<0.005).<br>Drain removed earlier in group A (5.6 ± 0.8 vs. 7.1 ± 1.3 days; P<0.005).<br>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.<br>The use of Harmonic Focus during ALND is effective in reducing operating time, drain volume and complications. |

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| He et al.<br>2012<br>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<br><br>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).<br>The average number of postoperative length of stay was also significantly less in group A (11.5 vs. 14.7 days, P<0.001).<br>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.<br>2011<br>RCT | Patients with breast cancer | Breast surgery and axillary lymph-node dissection | Group A (30 F): traditional dissection;<br><br>Group B (30 F): ultrasonic dissection. | Harmonic Focus | No significant differences observed in terms of operative time.<br>A statistically significant benefit was observed in terms of:<br>Intraoperative blood loss (median: 60 vs. 40 ml);<br>Drainage volume (median for chest wall and axilla: 50 and 200 vs. 30 and 60 ml/day);<br>Axilla seroma formation (30% vs. 3.3%);<br>Hospital stay duration (median: 5 vs. 3 days).<br>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.<br>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. |

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| Lumachi et al. 2013<br>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;<br><br>Group B (71 F): conventional technique. | Harmonic | A statistically significant benefit was observed in terms of:<br>Operative time (95.7 ± 22.4 vs. 109.1 ± 25.7 minutes; P=0.001);<br>Intraoperative blood loss (56.1 ± 12.5 vs. 85.8 ± 15.5 ml; P<0.001);<br>Drainage output (412.6 ± 83.7 vs. 456.9 ± 69.0 ml; P<0.001);<br>Days of drain placement (5.2 ± 2.0 vs. 6.2 ± 1.2 days; P<0.001).<br>Hospital stay and postoperative office visits were also reduced, but the differences were not significant.<br>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<br>RCT | Breast cancer patients | Modified radical mastectomy | Group A (27): scalpel dissection;<br><br>Group B (26): electrocautery;<br><br>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).<br>Bleeding was significantly higher in group A (ml): 720.7±245 vs. 368±156 vs. 375±176 (p=0.001).<br>Seroma incidence was higher in group B (%): 37.0 vs. 53.8 vs. 34.4 (p=0.003).<br>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.<br>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.<br>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;<br><br>Group B (29): electrocautery and clips | Harmonic | Luminal volume after harvesting: 921 ± 80 vs. 559 ± 69 $mm^3$ (P=0.003).<br>Endothelial integrity measured by CD31 staining of random biopsy specimens did not show differences between harvesting techniques.<br>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).<br>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;<br><br>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).<br>Second and third phase flows were similar between the groups.<br>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).<br>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;<br><br>Group B (12): electrocoagulation;<br><br>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.<br>Six minor cases of lymphatic leakage occurred in group A; this resulted in no clinical problem.<br>There were no other significant differences between the three groups.<br>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. |

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| Mouton et al. 2011<br>Follow-up study | Patients with recurrent sapheno-femoral incompetence | Redo saphenous high ligation | Group A (12): ultrasonic dissection;<br><br>Group B (12): electrocoagulation;<br><br>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 (± 0.63) mm, 1.00 (± 0.45) mm and 0.50 (± 0.50) mm after 3 months and 4.29 (± 1.41) mm, 3.32 (± 0.90) mm and 3.00 (0.83) mm after 7 years (no significant difference between groups).<br>After 7 years no reflux was detected in 8/36 patients, no varicose veins were found in 14/36 patients.<br>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<br>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;<br><br>Group B (18): conventional + ultrasonic dissection<br><br>Group C (18): endoscopic + ultrasonic dissection | Harmonic | Harvest time was longer in Group C (45±19 min vs. 41±10 min vs. 61±24 min; P=0.0005).<br>Clinical outcomes were similar among the groups.<br>Radial artery harvest–related outcomes were also similar, with no incidence of hand ischemia, motor deficits, hematoma, or wound infection.<br>There was a significant difference with respect to sensory deficits (paresthesias and numbness), limited to the superficial radial nerve only in Group C.<br>Cosmetic results were superior in Group C.<br>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.<br>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;<br><br>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;<br><br>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).<br>Operative blood loss was significantly decreased in the ultrasonic group: 62.63 (12.46) vs. 136.05 (21.54) mL (P=0.006).<br>No significant change in haemoglobin concentration between the 2 groups: 19.53 (1.79) vs. -16.72 (2.5) g/L.<br>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).<br>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.<br>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;<br><br>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.<br>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.<br>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. |

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| Leblanc et al.<br>2011<br>CCT | Women with BRCA mutation, who were scheduled for bilateral salpingo-oophorectomy (BSO) | Ovarian transection | Group A (4): Scissors and bipolar coagulation;<br><br>Group B (3): stapler straight or roticulator with vascular tape;<br><br>Group C (4): bipolar scalpel;<br><br>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<br>Time (min) until complete haemostasis: A=2; B=1.3; C=4.4; D=1.6<br>Blood loss (ml): A<10; B<10; C<13; D<10<br>Rate of resected/total volume of ovary: A=19 (16–25); B=19 (4–36); C=36 (14–38); D=25 (21–32).<br>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).<br>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.<br>2009<br>RCT | Women with benign ovarian cysts | Laparoscopic excision of ovarian cysts | Group A (64): bipolar device;<br><br>Group B (57): ultrasonic device;<br><br>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.<br>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.<br>2010<br>RCT | Premenopausal women with symptomatic uterine leiomyoma | Laparoscopic myomectomy | Group A (80): electrosurgery devices with a vasoconstrictive solution;<br><br>Group B (80): ultrasonic device | Harmonic | Operative time: 88.8 ± 35.5 vs. 71.8 ± 26.7 minutes (P=0.000).<br>Intraoperative blood loss: 182.8 ± 116.8 vs. 135.2 ± 89.1 ml (P=0.004).<br>No differences were noted with respect to the degree of surgical difficulty.<br>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 |
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| Abo-hashem et al. 2010 RCT | Patients with Grade III and Grade IV haemorrhoidal disease | Haemorrhoidectomy | Group A (32): ultrasonic device<br><br>Group B (32): bipolar electrocautery | Harmonic | Postoperative pain was found to be significantly less in group A in all days of postoperative follow up.<br>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.<br>Incidence of postoperative bleeding was nearly comparable in both groups.<br>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).<br>No difference was found between both groups regarding wound infection, major short-term incontinence and swelling of the skin bridges.<br>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). | 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.<br>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. |

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| Boccasanta et al. 2006<br>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<br><br>Group B (20): ultrasonic device and circular stapler. | Harmonic | Short term:<br>The mean operating time and blood loss were significantly lower in group B (P<000.1).<br>There was no operative mortality or complications.<br>Mean hospital stay was 3.9 ± 0.8 in group A and 3 ± 0.5 days in group B (P<0.001).<br>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.<br><br>Long term:<br>No significant difference in mean time of inability to normal activity.<br>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<br>RCT | Patients with symptomatic Grade III and Grade IV hemorrhoids | Haemorrhoidectomy | Group A (80): ultrasonic device<br><br>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).<br>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).<br>Postoperative hospital stay was also lower for Group A (1.0±0.1 days vs. 1.2±0.4 days; p=0.001).<br>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).<br>Postoperative VAS pain scores (p=0.001):<br>Day 1: 5.4±0.7 vs. 6.8±1.3<br>Day 7: 4.0±0.8 vs. 5.2±1.2<br>Day 28: 0.01±0.1 vs. 1.4±0.2<br>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. |

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| Chung et al.<br>2005<br>RCT | Patients with Grade III haemorrhoidal disease | Haemorrhoidectomy | Group A (45): ultrasonic device<br><br>Group B (43): stapling device | Harmonic | No significant observable difference in operation time, blood loss, or postoperative day when the first bowel movement occurred.<br>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).<br>There was no difference in complication rate between the two groups.<br>At all follow-up visits there was no observable difference in incontinence scores between the two groups.<br>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.<br>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.<br>2007<br>RCT | Patients with Grade III and Grade IV haemorrhoidal disease | Haemorrhoidectomy | Group A (35): ultrasonic device<br><br>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.<br>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.<br>2005<br>RCT | Patients with Grade III and Grade IV haemorrhoidal disease | Haemorrhoidectomy | Group A (24): electrocautery device<br><br>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.<br>The operating time (median 11 vs. 18 minutes; P<0.001) was significantly less in group A.<br>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. |

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| Omar et al.<br>2011<br>RCT | Patients with symptomatic grade III & IV hemorrhoids | Haemorrhoidectomy | Group A (36): ultrasonic device<br><br>Group B (36): Conventional monopolar diathermy | Harmonic | Operative time, intraoperative blood loss and hospital stay were significantly less in Group A (p<0.001).<br>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.<br>Time off of work was significantly longer in Group B (p<0.001).<br>At 1 week: 18 (50%) vs. 3 (8.3%)<br>At 3 weeks: 4 (11.1%) vs. 11 (30.6%)<br>At 4 weeks: 4 (11.1%) vs. 9 (25%)<br>Severity of pain assessed with VAS was significantly lower in Group A during the first 28 days.<br>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.<br>2008<br>RCT | Patients with Grade III and Grade IV haemorrhoidal disease | Haemorrhoidectomy | Group A (22): open ultrasonic procedure<br><br>Group B (22): closed ultrasonic procedure<br><br>Group C (22): Milligan-Morgan procedure<br><br>Group D (21): Ferguson procedure | Harmonic | Bleeding volume was significantly lower in groups A and B (P<0.001).<br>Operation time was significantly shorter in group A (p<0.001).<br>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.<br>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. |

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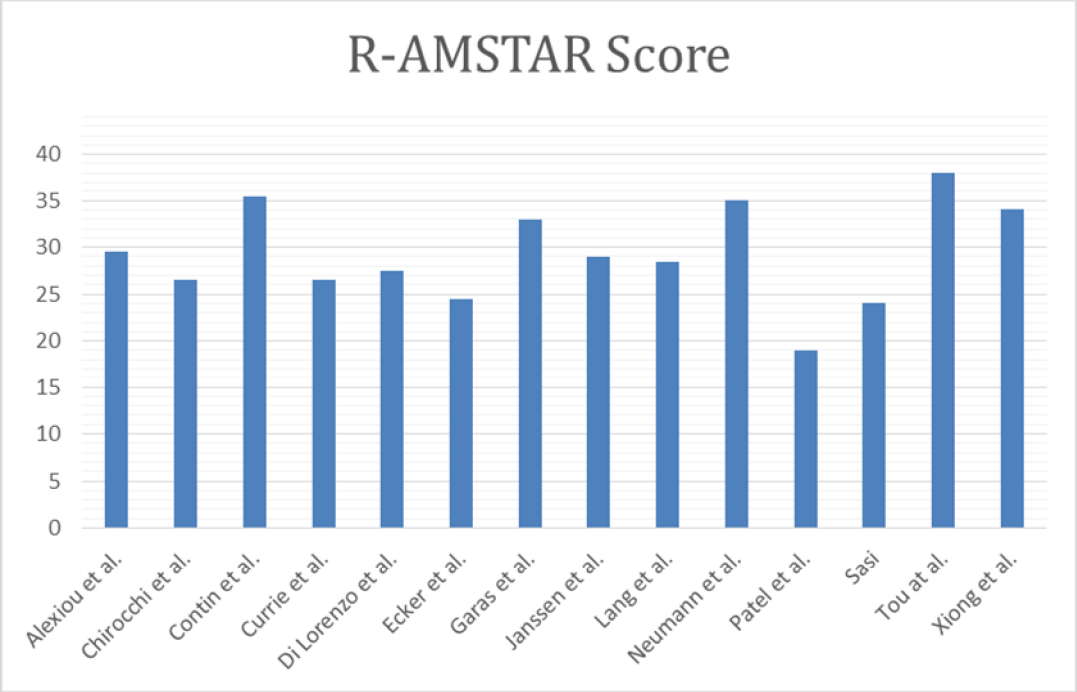
| Peker et al. 2013 RCT | Patients with Grade III and Grade IV haemorrhoidal disease | Haemorrhoidectomy | Group A (23): electrocautery device<br><br>Group A (23): ultrasonic device<br><br>Group C (23): conventional technique (Milligan-Morgan) | Harmonic | Mean operative time for group A and B was significantly 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. |

**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.

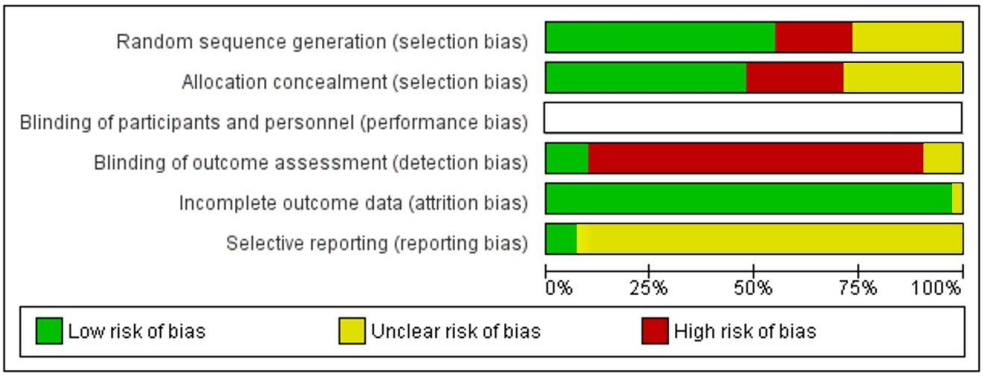





The summary of the methodological quality of the primary studies actually included in the present evidence review is reported in Figure 4.3. All the non-randomised studies or all the studies for which randomisation was not properly performed were considered at high risk of bias by default for what concern 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 used[57]. 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 transection[46], laparoscopic excision of ovarian cysts[48]), 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 surgery[73], the studies included did not report any significant difference in the occurrence of such complication[15].

## 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 adrenalectomy[37]. 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 mastectomy[17]. 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 harvest[63]. 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 conduicts[7], and graft preparation time[23]. 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 hemicolectomy[80], 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, post-operative 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 levatorplasty[6]. 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 associate 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 cholecystectomy[81]. 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 device[51].

### 4.5.9 Laparoscopic colorectal surgery

We identified evidence from secondary studies on laparoscopic colorectal resection[21]. 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 transplantation[58]. 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 biopsy[53]. 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 arthroplasty[76]. 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 surgery[78]. 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 mayor myocutaneous flap dissection[19] and anterolateral thigh flap elevation[29]. 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 surgery[15]. 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 tonsillectomy[2]. 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 study[39] in terms of post-operative pain, while equivalence was observed in terms of bleeding and wound healing.



## 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<br>Dec 2013 |
| NCT01717794 | Laparoscopic total hysterectomy with pelvic lymphadenectomy. | Randomised; Parallel ass. | Thunderbeat | Standard bipolar electrosurgery. | 36 | Oct 2012<br>Oct 2014 |
| NCT01717781 | Laparoscopic radical hysterectomy with pelvic lymphadenectomy. | Randomised; Parallel ass. | Thunderbeat | Standard bipolar electrosurgery | 26 | Oct 2012<br>Oct 2014 |
| NCT01999296 | Laparoscopic visceral or gynaecologic surgery (any). | Patient registry | Thunderbeat | NA | 250 | Oct 2013<br>Dec 2015 |
| NCT01812395 | Thyroidectomy. | Randomised; Parallel ass. | Harmonic FOCUS | Classic scalpel or scissors | 100 | Mar 2013<br>Apr 2014 |
| NCT01551914 | Total thyroidectomy. | Randomised; Parallel ass. | Harmonic FOCUS | Bi/monopolar electrosurgical instruments or clip coagulation techniques | 1,350 | Mar 2012<br>May 2014 |
| NCT02017834 | Neck dissection and tumour resection. | Randomised; Parallel ass. | Harmonic FOCUS | Standard technique | 36 | Feb 2012<br>Feb 2015 |
| **ONGOING BUT NOT RECRUITING** | | | | | | |
| NCT01565486 | Conventional thyroidectomy. | Randomised; Parallel ass. | Harmonic ACE | LigaSure Precise | 304 | Aug 2011<br>Aug 2017 |
| NCT01658085 | Total thyroidectomy. | Case control | Harmonic FOCUS | Harmonic ACE | 56 | Feb 2009<br>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 statement[33].

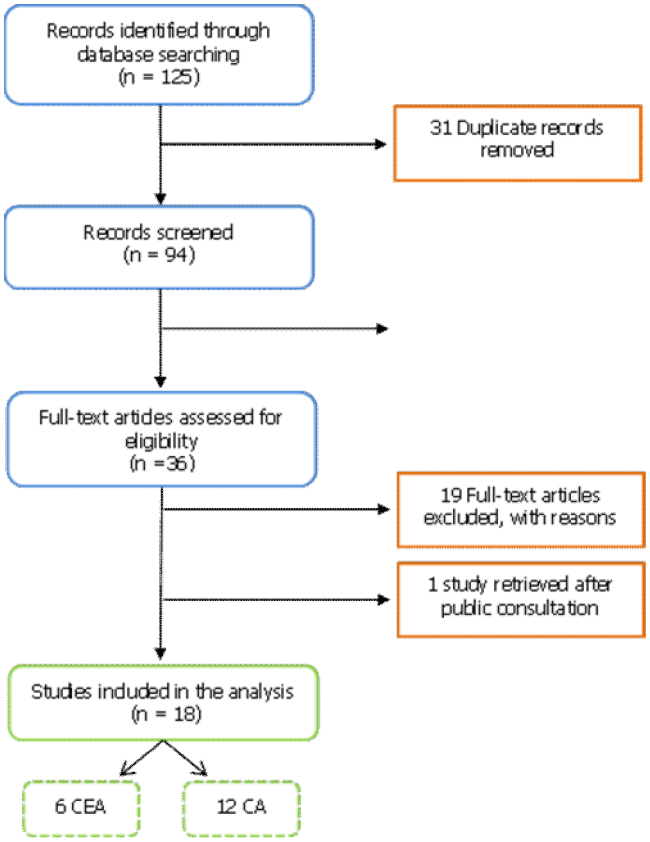


## 5.2 Results

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) | 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) | 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 hypocalcemias), 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<br>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 |

***Key:*** *US: ultrasound scalpel; MIVAT: minimally invasive video-assisted thyroidectomy; TEM: transanal endoscopic microsurgery; MES: monopolar electrosurgery 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 study[47] 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 statistically 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 laps 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 e 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.



### *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) thorugh their institution.

*Endoscopic thyroid surgery*

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

In particular, Barczyǹski 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 purchaising 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 | Effeciveness | | | | | 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 fatest 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<br>"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 | Comparation | Costs | | | | Economic results |
|---|---|---|---|---|---|---|
| | | Item | | | Source | |
| | | 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 € | - | "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 € | Company price lists | |
| | | | 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 | Effeciveness | | | | | Costs | | | | Economic results |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Outcome | | | Follow up | Source | Item | | | Source | |
| | | | | | Type | Device | Value | | | Type | 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 | 549 € | | |
| | | | | | | BVS | 105 | Phase A | Operation nurses | | UCS | 620 € | | |
| | | | | | | UCS | 90 | Phase A | Operation nurses | Theatre time cost | MES | 1.045 € | Institutional accounting department (value year 2007) | |
| | | | | | Intraoperative blood loss | MES | 125 ml | | Surgeon | | BVS | 812 € | | |
| | | | | | | BVS | 50 ml | | Surgeon | | UCS | 699 € | | |
| | | | | | | UCS | 50 ml | | Surgeon | Additional cost | MES | 102 € | Institutional accounting department (value year 2007) | |
| | | | | | Post-operative complications | MES | 10 pz | 30 days | Surgeon | | BVS | 0 € | | |
| | | | | | | BVS | 10 pz | 30 days | Surgeon | | UCS | 13 € | | |
| | | | | | | UCS | 6 pz | 30 days | Surgeon | Comprehensive sosts 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 | | | | Economic results |
|---|---|---|---|---|---|---|
| | | Item | | | Source | |
| | | Type | Device | Value | | |
| 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 | "Ultrasonic shears: $1747 ± $117 Fibula Free Laps ; Ultrasonic shears: $1606 ± $147 Anterolateral Thigh Free Flaps." |
| | | | LigaClip (average 5 clip) | 111 $/ pz | | "No Ultrasonic shears: $2239 ± $243 Fibula Free Laps; Ultrasonic shears: $2149 ± $192 Anterolateral Thigh Free Flaps." |
| | | Anesthesia | both | 6 $/ minute | | "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." |
| | | 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 | - | "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." |
| | | | 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 | Effeciveness | | | | | 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 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 | | |
| | | | | | | | | | | Materials | HS | €101.83 | - | |
| | | | | | | | | | | | EC | NR | | |
| | | | | | | | | | | Device | HS | 78.80 | - | |
| | | | | | | | | | | | EC | NR | | |
| | | | | | Total blood loss (ml) | HS | 1106±985 | - | | Total | HS | €729.98 | - | |
| | | | | | | EC | 2176±1764 | - | | | 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 | | | | Economic results |
|---|---|---|---|---|---|---|
| | | Item | | | Source | |
| | | 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) | - | | | CT | €1,148.40±153.25 | | |
| | | | | | intraoperative complications (n) | UHS | 0 | - | | | | | | |
| | | | | | | C | 0 | - | | | | | | |
| | | | | | lenght of hospitalization (days) | UHS | 1.07 | - | | | | | | |
| | | | | | | C | 1.15 | - | | | | | | |
| | | | | | transient postoperative complications (n) | UHS | 3 | - | | | | | | |
| | | | | | | C | 2 | - | | | | | | |
| | | | | | sequalae (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 | HS | 0.83 | discharge | | Total follow up (3 months) | HS | €107.82 | national pharmaceutical list; diagnostic and services list of Lazio region | |
| | | | | | | C | 0.78 | | | | C | €129.03 | | |
| | | | | | | HS | 0.90 | 1 month | | Total direct medical | HS | €2,400.34 | All the above sources | |
| | | | | | | C | 0.83 | | | | C | €2,540.52 | | |
| | | | | | | HS | 0.91 | 3 month | | Total direct non medical | HS | €342.77 | - | |
| | | | | | | C | 0.84 | | | | C | €535.51 | | |
| | | | | | | | | | | Total indirect | HS | €464.49 | Bank of Italy data | |
| | | | | | | | | | | | C | €456.93 | | |
| | | | | | | | | | | Total | HS | €3,207.60 | All the above sources | |
| | | | | | | | | | | | 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 | "The cost-effectiveness analysis showed that an additional 280 euros spent for a single-use ultrasonic shears was almost balanced by the 16.1-min gain in operative time and no need to use clips, ligatures, or bipolar coagulation; the combined cost of the latter elements was equal to 270.80 euros. However, if we include the depreciation costs of the ultrasonic HS impulse generator, the gap between these two values will increase to 20-30 euros per single operation." |
| | | | | | | 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 | | | Ligaure | 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 | | | | | | | |
| | | | | | Postoperative stay (days) | US | 1.3±0.5 | | | | | | | |
| | | | | | | CL | 1.4±0.6 | | | | CL | 100 €/single use | | |
| | | | | | Patients' cosmetic satisfaction | US | 88.9±9.7<br>96.7±3.2 | 1 month<br>6 months | | | | | | |
| | | | | | | CL | 81.9±5.4<br>95.4±3.9 | 1 month<br>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 | | | | Economic results |
|---|---|---|---|---|---|---|
| | | Item | | | Source | |
| | | 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 resulted 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 | | | | Economic results |
|---|---|---|---|---|---|---|
| | | Item | | | Source | |
| | | 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." |
| | | | 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 ISPOR[33]. 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 evaluation[67] has a higher level of quality (18/24) while the last one[5] 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).



## 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 one[67] 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, 1[61] added the hospitalization costs and the last one[67] 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 one[8] took into account only the device system cost. About the cost-effectiveness evaluations only one study[67] 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, 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-analised 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.



***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 mayor 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 thyreoidectomy (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, Roviaro 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 ligature 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.; Aguilella, 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. Kartsiounis 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.; Dedivitis, 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 electrosurgery 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. Mahabaleshwar 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 electrosurgical 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. JSLS 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 Haupert, 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, Nachtnebl 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, Kubitza 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

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# 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.