

# Laparoscopic cholecystectomy: ultrasonic energy versus monopolar electrosurgical energy

A. ZANGHÌ, A. CAVALLARO, P. DI MATTIA, M. DI VITA, F. CARDÌ, G. PICCOLO, G. BARBERA, R. FISICHELLA, D. SPARTÀ, A. CAPPELLANI

Department of Surgery, University of Catania A.O.U. "Policlinico – Vittorio Emanuele", Catania, Italy

**Abstract. – OBJECTIVE:** Nowadays, laparoscopic cholecystectomy (LC) is undoubtedly considered the "gold standard" in the surgical treatment of symptomatic gallstones, gallbladder adenomas and acute cholecystitis. Among the alternative energy sources proposed (monopolar, bipolar electric scalpel, radiofrequency sealers) with the aim to dissect and/or seal, the ultrasonic energy has been frequently adopted, however without a widespread acceptance among surgeons for routine or emergency laparoscopic cholecystectomy. This study investigates the possible beneficial aspects of ultrasonic dissection and its efficacy in the closure of the cystic artery and duct.

**PATIENTS AND METHODS:** Patients were retrospectively divided into 2 groups according to the instruments used for division of the cystic artery and duct as well as for dissection of the liver bed: 121 patients in whom dissection and coagulation were performed using monopolar coagulation and 43 patients who were all treated with the ultrasonically activated scalpel harmonic ACE (Ethicon Endo-Surgery) as the sole instrument used in the whole procedure.

**RESULTS:** The mean operative time, was significantly shorter in the harmonic group than in the traditional group (35.36 + 10.15 min vs. 55.6+12.10 vs. respectively;  $p < 0.0001$ ). The rate of gallbladder perforation was significantly higher in the traditional group than in the harmonic group 20.66% (25 patients) vs. 6.98% (3 patients), respectively;  $p < 0.05$ ).

Intraoperative volume blood loss was significantly more in the traditional group than in the HS group (29.32+14.21 vs. 12.41+8.22;  $p < 0.0001$ ).

The mean amount of postoperative drainage was not significantly different among the two groups (18.41+6.54 vs. 15.96+8.69 ml,  $p > 0.05$ ).

No considerable visceral injury has been recorded in either group.

The postoperative parameters observed included postoperative hospital stay and morbidity for each group.

The hospital stay was not significantly shorter in harmonic group (48.15+4.29 vs. 49.06+2.94 h,  $p > 0.05$ ). The overall morbidity rate was 14.02 % (not significant).

**CONCLUSIONS:** The use of the harmonic scalpel shows some statistically significant ad-

vantages limited to a few intraoperative parameters.

We conclude that a wider use of harmonic scalpel not offers such advantages to make it the reference technique.

*Key Words:*

Clipless laparoscopic cholecystectomy, Ultracision, Harmonic scalpel, Ultrasonic energy, Cholecystectomy complications.

## Introduction

Nowadays, laparoscopic cholecystectomy (LC) is undoubtedly considered the "gold standard" in the surgical treatment of symptomatic gallstones, gallbladder adenomas and acute cholecystitis.

Since 1987, LC has largely replaced conventional open cholecystectomy. Monopolar electrocautery remains the main energy form used during laparoscopic dissection, representing the preferred method in more than 85% of surgeons<sup>1,2</sup>.

Cystic duct and cystic artery are commonly occluded by clips and cut by scissors; linear staplers, endoloops or sutures have been proposed over time as alternative techniques for cystic duct ligation, however, without significant diffusion.

Even if laparoscopic cholecystectomy is considered a safe procedure, some risks are associated with the use of monopolar electric scalpel, such visceral injuries on thermal basis, thus, leading to the search for alternative forms of energy. Moreover visceral injuries could be caused by the frequent instrument exchange (scissors, dissectors), and bile leakage caused by the slippage of the clips.

The majority of electrosurgical injuries manifests late or goes unrecognized. The occurrence of accidental burns caused by unintentional energy transmission during a LC ranges between 0.06% and 0.3%. However, only one or two patients in 1,000 are recognized<sup>3,4</sup>.

Among the alternative energy sources proposed, the ultrasonic energy has been frequently adopted, however, without a widespread accep-

tance among surgeons for routine or emergency laparoscopic cholecystectomy.

The ultrasonically activated scalpel technology (Harmonic – Ethicon Endo Surgery INC – Johnson & Johnson Medical SPA, Somerville, NJ, USA) relies on the application of ultrasound to tissues to obtain three purposes synergistically: coagulation, cutting, and cavitation.

The temperature obtained and the lateral energy spread are lower than those detected when the monopolar hook is used, thus, reducing the risk of tissue damage.

The Harmonic scalpel appears to be also an effective instrument for obliteration of biliary ducts and vessels whose diameter is within 4 mm-5 mm<sup>1-5</sup>.

This review investigates the possible beneficial aspects of ultrasonic dissection and its efficacy in the closure of the cystic artery and duct with the aim to demonstrate that ultrasonically activated scalpel is a safe instrument that could decrease the risk of visceral and parenchymal organ injuries.

## Patients and Methods

This study was carried out from January 2009 to December 2011.

During a 3-year period, 261 consecutive laparoscopic cholecystectomies were performed in the Department of Surgery, Polyclinic of Catania, Italy in patients affected by gallbladder lithiasis with or without common bile duct stones, gallbladder adenomas and acute cholecystitis.

All the patients were classified according their BMI (Body Mass Index): average value = 21.2 (range, 12.7 to 33).

All patients were subjected to thorough history and clinical examination focused on manifestation of gallstone disease.

Informed consent was obtained from all patients after explaining the nature of the disease and operative steps (including the use of harmonic scalpel) and possible complications.

The preoperative assessment was performed by abdominal ultrasound in all patients along with MR-Cholangiography in 232, we rather choose a wide use MR-Cholangiography among patients with the aim to reduce post cholecistectomy syndrome related to cbd stones. Besides excluding the concomitant lithiasis of the common bile duct, MRCP imaging allows accurate visualization of the intra- and extrahepatic biliary tracts and can reveal a greater number of anatomical variations<sup>6</sup>.

Keeping in mind these variations before the surgical intervention, the laparoscopic surgeon may reduce possible iatrogenic injury during laparoscopic cholecystectomy.

The exclusion criteria included patients above 80 years old (19 patients), patients with history of previous laparotomy (43 patients), patients with common bile duct stones (31 patients), patients with BMI above 30 (4 patients) and patients with cirrhosis where the hemostasis is more difficult<sup>7</sup>.

Sixtyeight patients were males, and ninetysix were females with an average age of 50.9 years (range, 18 to 80).

The patients underwent laparoscopic cholecystectomy performed by 2 surgeons with similar experience and skill levels, who adopted the same approach and techniques.

Under general anesthesia and preoperative administration of antibiotic prophylaxis (generally 1 g Ceftriaxone was administered, except for patients with beta lactamine idiosyncrasy), surgery was performed using conventional four ports: umbilical port, port below xiphoid, port below right costal margin and port in right iliac fossa. Pneumoperitoneum at pressure 12 mmHg was used.

Patients were retrospectively divided into 2 groups according to the instruments used for division of the cystic artery and duct as well as for dissection of the liver bed.

The 2 groups were comparable for age, sex, indication for cholecystectomy. Patients were randomly treated either with the ultrasonically activated scalpel or with clips.

The group A comprised 121 patients in whom dissection and coagulation were performed using monopolar coagulation. LC was done using traditional method by dissection of Calot's triangle and clipping of both cystic duct and artery by metal clips. After that, dissecting the gallbladder from its bed by hook using electrocautery technique was performed. Finally, we insert abdominal drain in Morrison pouch.

The group B consisted of 43 patients who were all treated with the ultrasonically activated scalpel harmonic ACE (Ethicon Endo-Surgery) as the sole instrument used in the whole procedure. LC was done by dissection of Calot's triangle and then occlusion of both cystic duct and artery using harmonic ACE.

For closure and division of cystic pedicle, we set the instrument at level "1", (more coagulation, less cutting power): when both artery and duct are well visualized and isolated, their sec-

tion is performed with a single application of ultrasonically activated scissors on minimum position (unlike other surgeons whose choice is multiple application of the blades along the cystic duct)<sup>3</sup>. It is important to close the blades carefully and slowly and to avoid lateral traction on the structure<sup>8</sup>. In case of large cystic ducts (with an external diameter exceeding 4 mm), an additional ligature with clips is performed. To assess its diameter, the duct is positioned between the blades of the ultrasonically activated scalpel: if the compressed cystic duct cannot be entirely included between them, an extra ligature is necessary.

Six patients with a cystic duct wider than 5 mm required, according the surgeon opinion, an additional ligature with clips.

When dissecting the gallbladder from its bed we set it to level 5 (more cutting power, less coagulation), and control of any bleeding from the bed using the active blade of harmonic ACE. We were as possible cautious to preserve the integrity of gallbladder: the perforation is an undesirable event for the risk of spreading in case with incidental gallbladder cancer<sup>8-9</sup>. Finally, we insert abdominal drain in Morrison pouch.

### **Statistical Analysis**

The statistical analysis of the data in this study was preferred using the SPSS version 10 (SPSS Inc., Chicago, IL, USA). Analysis of data was by intension to treat. For continuous variables, descriptive statistics were calculated and reported as mean+SD. Categorical variables were described using frequency distributions. The Student's *t* test for paired samples was used to detect differences in the means of continuous variables, and chi-square test was used in cases with low expected frequencies ( $p < 0.05$  was considered to be statistically significant).

## **Results**

### **Intraoperative Parameters**

The intraoperative parameters observed including duration of the operation, rate of gallbladder perforation, bile escape or leaks, volume of blood loss, amount of drainage, occasional visceral injuries and conversion rates were all recorded.

The mean operative time, according our experience, was significantly shorter in the harmonic group than in the traditional group (35.36 + 10.15 min vs. 55.6+12.10 vs. respectively;  $p < 0.0001$ ).

The rate of gallbladder perforation was significantly higher in the traditional group than in the harmonic group 20.66% (25 patients) vs. 6.98% (3 patients), respectively;  $p < 0.05$ ).

Intraoperative volume blood loss was significantly more in the traditional group than in the HS group (29.32+14.21 vs. 12.41+8.22;  $p < 0.0001$ ).

The mean amount of postoperative drainage was not significantly different among the two group (18.41+6.54 vs. 15.96+8.69 ml,  $p > 0.05$ ).

Laparoscopic cholecystectomy was successfully completed in 161 patients (96.95%). In the traditional group, four cases (3.3%) were converted to open surgery. In the HS group (not significant) only one case required conversion. In either groups conversion was due to diffuse peritoneal adhesions. Additional cystic duct clipping was necessary in 6 patients (13.95%) in group B because of a large duct or tissues whose closure was judged unsafe by the surgeon (acute cholecystitis or cases of gallbladder empyema).

No considerable visceral injury has been recorded in either group. The rate of superficial injuries (mainly on the liver bed) was not significantly different in the traditional group than in the HS group: 5 cases (4.13%) vs 1 case (2.32%)  $p > 0.05$ .

### **Postoperative Parameters**

The postoperative parameters observed included postoperative hospital stay and morbidity for each group.

The hospital stay was not significantly shorter in harmonic group (48.15+4.29 vs. 49.06+2.94 h,  $p > 0.05$ ).

The overall morbidity rate was 14.02 % (22/164).

According to the Clavien classification, postoperative complications were further categorized as major and minor depending on whether they were potentially life threatening, whether a reoperation was needed to treat them with or without residual disability, and whether hospital stay was prolonged, as a result of them.

Major complications included: ileal perforation, bile leak requiring surgical treatment, abscess, pancreatitis, chest infection and CBD injury.

Minor complications included: bile leak (conservative management), bile leak (observation), abdominal fluid collection, subclinical increase in pancreatic enzymes, pleural effusion, respiratory impairment, jaundice, urinary retention and fever.

In our caseload no mortality was observed in the postoperative period. Differences in morbidity between groups were not significant (Table I).

Table I.

	Group A (121)	Group B (43)	<i>p</i>	Overall (164)
Major complications	2 (1.65 %)	1 (2.43 %)	NS (> 0.05)	3 (1.83 %)
Ileal perforation	-	-		-
Bile leaks (surgical treatment)	1 (0.83 %)	-		1 (0.61 %)
Abscess	1 (0.83 %)	-		1 (0.61 %)
Blood loss (surgical treatment)	-	1 (2.43 %)		1 (0.61 %)
Pancreatitis (mild)	-	-		-
Chest infection	-	-		-
CBD injury	-	-		-
Minor complications	14 (11.57 %)	5 (11.62 %)	NS (> 0.05)	19 (11.58%)
Bile leaks (conservative management)	-	-		-
Bile leaks (observation)	1 (0.83 %)	1 (2.43 %)		2 (1.22 %)
Abdominal fluid collection	2 (1.65 %)	1 (2.43 %)		3 (1.83 %)
Subclinical increase in pancreatic enzymes	3 (2.48 %)	1 (2.43 %)		4 (2.44 %)
Pleural effusion	1 (0.83 %)	-		1 (0.61 %)
Respiratory impairment	-	-		-
Jaundice	1 (0.83 %)	-		1 (0.61 %)
Urinary retention	1 (0.83 %)	-		1 (0.61 %)
Fever	5 (4.13 %)	2 (4.65 %)		7 (4.26 %)

No significant difference for bile leak rate was found between groups A and B: there was a case of bile leak requiring surgical approach in the traditional group, encountered in one patients, likely because of a misdiagnosed accessory bile duct. We recorded one case of hemoperitoneum in the HS group due to bleeding of the hepatic bed, which required laparotomy. One case developed an abscess in the Morrison pouch which was drained by percutaneous drainage. Six months after the procedure, all patients were in good health and the follow-up was uneventful. We, apparently, didn't experience any abscess related to clip loss in those groups of patients<sup>10</sup>.

## Discussion

Because data are conflicting regarding the potential benefits and risks of ultrasonic dissection in laparoscopic cholecystectomy, this paper attempts to further explore such outcomes.

Several studies have confirmed the effectiveness and safety of the use of the ultrasonically activated scalpel for dissection of the gallbladder. In 1999, the use of ultrasonically activated shears for both dissection and closure-division of the cystic duct and artery was first reported<sup>11</sup>.

Ultrasonic dissection technology works by generating a high-frequency ultrasound and applying such energy to the tissues producing 3 main "C" effects:

1. Cavitation/tissue fragmentation (and dissec-

tion) caused by cellular destruction secondary to intracellular fluid evaporation, and this occurs due to "low pressure at the blade". Cavitation is an important effect of ultrasonic energy, because it causes separation of tissue planes facilitating dissection. This is particularly useful when looking for the "correct" plane of dissection between the liver and the gallbladder.

2. Cooptation/coagulation: caused by conversion of ultrasonic energy into a localized heat, this has been reported to reach to 60°C to 100°C. Denaturation of collagen in the walls of hollow structures (such as cystic artery and duct) can result in the occlusion or sealing of the lumen. The mechanism occurs when ultrasonic energy is transferred to tissue. This breaks the tertiary hydrogen bonds between the collagen and the proteins of extracellular matrix. These proteins denature and change from colloidal proteins into an insoluble gel that is able to seal the vessel walls. This gel coagulation is specific to ultrasonic dissection and the airtight pressure of a sealed cystic duct was calculated to be "higher than 320 mm Hg".

3. Cutting which is achieved by the "sharp" blade mode of the harmonic scalpel.

Some authors affirm that laparoscopic cholecystectomy performed with an ultrasonically activated scalpel is feasible and effective. The method offers several considerable advantages, such as the utilization of a single instrument both for dissection of the gallbladder from the hepatic bed; moreover the used of

Ultrasonic energy involves a minimal lateral spread of vibration current in the surrounding tissues minimizing the risk of injury compared with monopolar electrocautery, which is associated with 90% of visceral injuries and 15% of biliary tract injuries during laparoscopic cholecystectomy. However, only a few authors have examined its efficacy in the closure of the cystic artery and duct<sup>1-4</sup>.

According to other authors, this study clearly demonstrates that harmonic scalpel is an effective and safe tool for the closure of both cystic duct and artery in patients who undergo laparoscopic cholecystectomy.

One obstacle hindering the applicability of the procedure is the cystic duct size: if it exceeds 4 mm to 5 mm in diameter, an additional ligature is necessary.

Nevertheless, the main disadvantage of ultrasonic dissection is instrument's cost even if compared with combined cost of using multiple disposable instruments (scissors, a clipper, an electrocautery hook, and a grasper): this is particularly true if the surgical unit is equipped with reusable instruments<sup>12-15</sup>.

The Harmonic scalpel may provide a cost-effective option only in high volume centers where reducing operative time may balance the number of daily procedures<sup>16-18</sup>.

## Conclusions

This work compares two groups of patients undergoing laparoscopic cholecystectomy, with the aim to identify, among techniques, the one that shows greater benefits for the patients. The use of the harmonic scalpel shows some statistically significant advantages limited to a few intraoperative parameters: duration of the operation, rate of gallbladder perforation, intraoperative bile leaks or escapes, volume of blood loss. In contrast, the remaining intraoperative parameters (amount of drainage, occasionally visceral injuries and conversion rates) showed no statistical difference. The postoperative parameters (postoperative hospital stay and morbidity for each group) as well as the occurrence of postoperative complications, also showed in our experience, no statistical difference. These observations, the high cost related to the ultrasonic scalpel, the possibility of using multipurpose tools, lead us to conclude, according to other authors<sup>16-18</sup>, that a wider use of harmonic scalpel

not offers such advantages to make it the reference technique. The harmonic scalpel already demonstrated his advantages in the surgical treatment of thyroid diseases<sup>19</sup>. Moreover this kind of approach could be interesting in cancer patients so called frail patients as elderly and HIV-positive patients<sup>20-36</sup>.

## Conflict of Interest

The Authors declare that they have no conflict of interests.

## References

- 1) GELMINI R, FRANZONI C, ZONA S, ANDREOTTI A, SAVIANO M. Laparoscopic cholecystectomy with Harmonic scalpel. *JLS* 2010; 14: 14-19.
- 2) THARWAT KANDIL, AYMAN EL NAKEEB, EMAD EL HEFNAWY. Comparative Study between Clipless Laparoscopic Cholecystectomy by Harmonic Scalpel Versus Conventional Method: A Prospective Randomized Study. *J Gastrointest Surg* 2010; 14: 323-328.
- 3) NDUKA CC, SUPER PA, MONSON JR, DARZI AW. Cause and prevention of electrosurgical injuries in laparoscopy. *J Am Coll Surg* 1994; 179: 161-170.
- 4) HÜSCHER CG, LIRICI MM, DI PAOLA M, CRAFA F, NAPOLITANO C, MEREU A, RECHER A, CORRADI A, AMINI M. Laparoscopic cholecystectomy by ultrasonic dissection without cystic duct and artery ligature. *Surg Endosc* 2003; 17: 442-451.
- 5) BESSA SS, AL-FAYOUMI TA, KATRI KM, AWAD AT. Clipless laparoscopic cholecystectomy by ultrasonic dissection. *J Laparoendosc Adv Surg Tech A* 2008; 18: 593-598.
- 6) PICCOLO G, DI VITA M, ZANGHI A, CAVALLARO A, CARDI F, CAPELLANI A. Symptomatic Gallbladder Agenesis: Never Again Unnecessary Cholecystectomy. *Am Surg* 2014; 80: E12-13.
- 7) CAPELLANI A, CACOPARDO B, ZANGHI A, CAVALLARO A, DI VITA M, ALFANO G, LO MENZO E. Retrospective survey on laparoscopic cholecystectomy in the cirrhotic patient. *Eur Rev Med Pharmacol Sci* 2008; 12: 257-260.
- 8) CAVALLARO A, PICCOLO G, PANEBIANCO V, LO MENZO E, BERRETTA M, ZANGHI A, DI VITA M, CAPELLANI A. Incidental gallbladder cancer during laparoscopic cholecystectomy: managing an unexpected finding. *World J Gastroenterol* 2012; 18: 4019-4027.
- 9) CAVALLARO A, PICCOLO G, DI VITA M, ZANGHI A, CARDI F, DI MATTIA P, BARBERA G, BORZI L, PANEBIANCO V, DI CARLO I, CAVALLARO M, CAPELLANI A. Managing the incidentally detected gallbladder cancer: Algorithms and controversies. *Int J Surg*. 2014 Oct;12 Suppl 2:S108-19.
- 10) CAVALLARO A, CAVALLARO V, TRAINITI M, LICCIARDELLO A, CAPELLANI A. Post cholecystectomy syndrome: an out of date topic? *Ann Ital Chir* 2009; 80: 403-406.
- 11) HUSCER CGS, LIRICI MM, ANASTASI A, SANSONETTI A, AMINI M. Laparoscopic cholecystectomy by har-

- monic dissection. *Surg Endosc* 1999; 13: 1256-1257.
- 12) SASI W. Dissection by ultrasonic energy versus monopolar electrosurgical energy in laparoscopic cholecystectomy. *JLS* 2010; 14: 23-34.
  - 13) BESSA SS, AL-FAYOUMI TA, KATRI KM, AWAD AT. Clipless laparoscopic cholecystectomy by ultrasonic dissection. *J Laparoendosc Adv Surg Tech A* 2008; 18: 593-598.
  - 14) SUO G, XU A. Clipless minilaparoscopic cholecystectomy: a study of 1,096 cases. *J Laparoendosc Adv Surg Tech A* 2013; 23: 849-854.
  - 15) CATENA F, ANSALONI L, DI SAVERIO S, GAZZOTTI F, COCCOLINI F, PINNA AD. Prospective analysis of 101 consecutive cases of laparoscopic cholecystectomy for acute cholecystitis operated with harmonic scalpel. *Surg Laparosc Endosc Percutan Tech* 2009; 19: 312-6.
  - 16) VU T, AGUILO R, MARSHALL NC. Clipless technique of laparoscopic cholecystectomy using the harmonic scalpel. *Ann R Coll Surg Engl* 2008; 90: 612.
  - 17) WILLS E, CRAWFORD G. Clipless versus conventional laparoscopic cholecystectomy. *J Laparoendosc Adv Surg Tech A* 2013; 23: 237-239.
  - 18) MINUTOLO V, GAGLIANO G, RINZIVILLO C, LI DESTRI G, CARNAZZA M, MINUTOLO O. Usefulness of the ultrasonically activated scalpel in laparoscopic cholecystectomy: our experience and review of literature. *G Chir* 2008; 29: 242-245.
  - 19) ZANGHÌ A, CAVALLARO A, DI VITA M, CARDÌ F, DI MATTIA P, PICCOLO G, BARBERA G, URSO M, CAPPELLANI A. The safety of the Harmonic® FOCUS in open thyroidectomy: A prospective, randomized study comparing the Harmonic® FOCUS and traditional suture ligation (knot and tie) technique. *Int J Surg* 2014; pii: S1743-9191(14)00127-7.
  - 20) BERRETTA M, NASTI G, DE VITIIS C, DI VITA M, FISICHELLA R, SPARTÀ D, BARESC T, RUFFO R, URBANI M, TIRELLI U. Safety and efficacy of Oxaliplatin-based chemotherapy in the first line treatment of elderly patients affected by metastatic colorectal cancer. *WCRJ* 2014; 1: e235.
  - 21) BERRETTA M, DI FRANCIA R, TIRELLI U. The new oncologic challenges in the 3RD millenium. *WCRJ* 2014; 1: e233.
  - 22) BERRETTA M, TIRELLI U. Elderly cancer patients in the 3rd millenium: between hope and reality. *Anti-cancer Agents Med Chem* 2013; 13: 1299.
  - 23) MALAGUARNERA M, FRAZZETTO PM, ERDOGAN O, CAPPELLANI A, CATAUDELLA E, BERRETTA M. Geriatric evaluation of oncological elderly patients. *Anticancer Agents Med Chem* 2013; 13: 1300-1309.
  - 24) BERRETTA M, APRILE G, NASTI G, URBANI M, BEARZ A, LUTRINO S, FOLTRAN L, FERRARI L, TALAMINI R, FIORICA F, LLESHI A, CANZONIERI V, LESTUZZI C, BORSATTI E, FISICHELLA R, TIRELLI U. Oxaliplatin and Capecitabine (XELOX) Based Chemotherapy in the Treatment of Metastatic Colorectal Cancer: The Right Choice in Elderly Patients. *Anticancer Agents Med Chem* 2013; 13: 1344-1353.
  - 25) MARTELLOTTA M, BERRETTA M, CACOPARDO B, FISICHELLA R, SCHIOPPA O, ZANGHÌ A, SPARTÀ D, CAPPELLANI A, TALAMINI R, IZZI I, RIDOLFO A, TORRESIN A, FIORICA F, TIRELLI U. Clinical presentation and outcome of squamous cell carcinoma of the anus in HIV-infected patients in the HAART-era: a GICAT experience. *Eur Rev Med Pharmacol Sci* 2012; 16: 1283-1291.
  - 26) ZANET E, BERRETTA M, DI BENEDETTO F, TALAMINI R, BALLARIN R, NUNNARI G, BERRETTA S, RIDOLFO A, LLESHI A, ZANGHÌ A, CAPPELLANI A, TIRELLI U. Pancreatic Cancer in HIV-positive patients: a clinical case-control study. *Pancreas* 2012; 41: 1331-1335.
  - 27) BERRETTA M, CAPPELLANI A, FIORICA F, NASTI G, FRUSTACI S, FISICHELLA R, BEARZ A, TALAMINI R, LLESHI A, TAMBARO R, COCCIOLLO A, RISTAGNO M, BOLOGNESE A, BASILE F, MENEGUZZO N, BERRETTA S, TIRELLI U. Folfox4 in the treatment of metastatic colorectal cancer in elderly patients: a prospective study. *Arch Gerontol Geriatr* 2011; 52: 89-93.
  - 28) ZANET E, BERRETTA M, MARTELLOTTA F, CACOPARDO B, FISICHELLA R, TAVIO M, BERRETTA S, TIRELLI U. Anal cancer: focus on HIV-positive patients in the HAART-era. *Curr HIV Res* 2011; 9: 70-81.
  - 29) SIMONELLI C, TEDESCHI R, GLOGHINI A, TALAMINI R, BORTOLIN MT, BERRETTA M, SPINA M, MORASSUT A, VACCHER E, DE PAOLI P, CARBONE A, TIRELLI U. Plasma HHV-8 viral load in HHV-8 related lymphoproliferative disorders associated with HIV infection. *J Med Virol* 2009; 81: 888-896.
  - 30) ZANGHÌ A, CAVALLARO A, PICCOLO G, FISICHELLA R, DI VITA M, SPARTÀ D, ZANGHÌ G, BERRETTA S, PALERMO F, CAPPELLANI A. Dissemination metastasis after laparoscopic colorectal surgery versus conventional open surgery for colorectal cancer: a metanalysis. *Eur Rev Med Pharmacol Sci* 2013; 17: 1174-1184.
  - 31) CAVALLARO A, CAVALLARO V, DI VITA M, CAPPELLANI A. Main bile duct carcinoma management. Our experience on 38 cases. *Ann Ital Chir* 2009; 80: 107-111.
  - 32) DI VITA M, ZANGHÌ A, LANZAFAME S, CAVALLARO A, PICCOLO G, BERRETTA M, GROSSO G, CAPPELLANI A. Gallbladder metastases of breast cancer: from clinical-pathological patterns to diagnostic and therapeutic strategy. *Clin Ter* 2011; 162: 451-456.
  - 33) TORO A, ARDIRI A, MANNINO M, POLITI A, DI STEFANO A, AFTAB Z, ABDELAAL A, ARCERITO MC, CAVALLARO A, CAVALLARO M, BERTINO G, DI CARLO I. Laparoscopic Reversal of Hartmann's Procedure: State of the Art 20 Years after the First Reported Case. *Gastroenterol Res Pract* 2014; 2014: 530140.
  - 34) CAVALLARO A, BERRETTA M, LO MENZO E, CAVALLARO V, ZANGHÌ A, DI VITA M, CAPPELLANI A. Cystic peritoneal mesothelioma: report of a case. *Surg Today* 2011; 41: 141-146.
  - 35) RAJAN M, DIP F, SZOMSTEIN S, ZANGHÌ A, CAVALLARO A, DI VITA M, CARDÌ F, DI MATTIA P, CAPPELLANI A, LO MENZO E, ROSENTHAL R. Staple line as a cause of unusual early internal hernia after appendectomy. *Int J Surg* 2014; 12(Suppl 1): S159-161.
  - 36) CAPPELLANI A, DI VITA M, LO MENZO E, ZANGHÌ A, LANZAFAME S, VEROUX P, ZANET E, CAVALLARO A, BERRETTA M. Muscular metastasis from mesocolic and duodenal leiomyosarcoma. A case report and

a review of the literature. *Ann Ital Chir* 2011; 82:  
383-387.