

JCEM

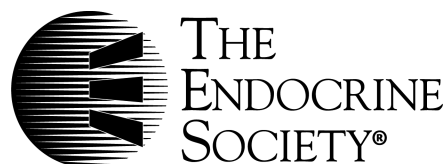
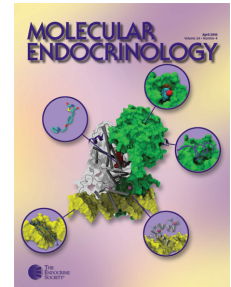
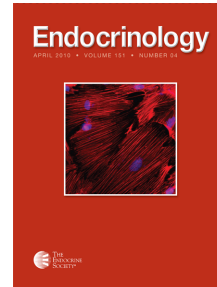
THE JOURNAL
OF CLINICAL
ENDOCRINOLOGY
& METABOLISM

Surgical Treatment of Low- and Intermediate-Risk Papillary Thyroid Cancer with Minimally Invasive Video-Assisted Thyroidectomy

Paolo Miccoli, Aldo Pinchera, Gabriele Materazzi, Agnese Biagini, Piero Berti, Pinuccia Faviana, Eleonora Molinaro, David Viola and Rossella Elisei

J. Clin. Endocrinol. Metab. 2009 94:1618-1622 originally published online Feb 17, 2009; , doi: 10.1210/jc.2008-1418

To subscribe to *Journal of Clinical Endocrinology & Metabolism* or any of the other journals published by The Endocrine Society please go to: <http://jcem.endojournals.org/subscriptions/>



Surgical Treatment of Low- and Intermediate-Risk Papillary Thyroid Cancer with Minimally Invasive Video-Assisted Thyroidectomy

Paolo Miccoli, Aldo Pinchera, Gabriele Materazzi, Agnese Biagini, Piero Berti, Pinuccia Faviana, Eleonora Molinaro, David Viola, and Rossella Elisei

Departments of Surgery (P.M., G.M., P.B., P.F.) and Endocrinology and Metabolism (A.P., A.B., E.M., D.V., R.E.), University of Pisa, 56100 Pisa, Italy; and AMBISEN Center (A.P.), High Technology Center for the Study of the Environmental Damage of the Endocrine and Nervous Systems, University of Pisa, 56124 Pisa, Italy

Background: Minimally invasive video-assisted thyroidectomy (MIVAT) was introduced in the clinical practice to treat small benign thyroid nodules. This method has recently been demonstrated to produce the same completeness as a conventional thyroidectomy in patients with papillary thyroid cancer (PTC). The low number of treated cases and the limited follow-up of these patients represent the major limitations of these studies.

Objective: The aim of the study was to compare the outcome of two groups of PTC patients, one treated with MIVAT and the other with conventional thyroidectomy, after a median follow-up of 5 yr.

Study Group: A total of 221 PTC patients were enrolled in this study according to the following criteria: 171 were treated with MIVAT (group A), and 50 were treated with conventional thyroidectomy (group B).

Results: The outcome and the cumulative ^{131}I activity administered to achieve curative status were compared. After a mean follow-up of 3.6 ± 1.5 yr (range, 1–8 yr; median, 5 yr), no differences were found between group A and group B. A similar rate of permanent hypoparathyroidism and/or nerve cord palsy was found in both groups.

Conclusion: We demonstrated that PTC patients operated on with MIVAT had a good outcome after 5 yr. This was similar to the outcome of patients treated with conventional thyroidectomy and the same degree of exposure to ^{131}I . These results, together with the evidence of a similar degree of completeness and rate of complications between the two surgical techniques, show that MIVAT is a valid option to treat low- and intermediate-risk PTC patients. (*J Clin Endocrinol Metab* 94: 1618–1622, 2009)

Papillary thyroid cancer (PTC) has a good prognosis in 95% of cases (1). According to the clinical guidelines for the treatment of PTC (2, 3), the initial treatment is total or near-total thyroidectomy. A conventional thyroidectomy, however, may be considered an overly aggressive approach for small PTCs that, in the few last years, have become more frequently diagnosed (4–6). The question of whether a PTC of less than 1 cm should be treated with a total thyroidectomy or lobectomy is still a matter for discussion (2, 3, 7).

Minimally invasive video-assisted thyroidectomy (MIVAT) was introduced into clinical practice in the late 1990s for the treatment of small benign thyroid nodules (8–10). In the last few years, MIVAT has been demonstrated to have several advantages over conventional thyroidectomy (e.g. a shorter postoperative recovery and hospitalization and a better cosmetic result) (11). This method, however, has only recently become the favored method of a reasonable number of surgeons (12–15). One of the major limitations inhibiting its use is the lack of evidence that it

can produce comparable results to a conventional thyroidectomy in the treatment of malignant thyroid tumors (13–16). Although we and others (17, 18) have demonstrated that MIVAT is capable of obtaining the same completeness as conventional thyroidectomy in PTC patients, surgeons are still very hesitant to treat PTC patients using an endoscopic approach. In particular, one of the major criticisms of our previous study was the relatively low number of cases and the absence of an adequate follow-up (19).

The aim of the present study was to compare the outcome of two groups of PTC patients, one treated with MIVAT and the other with conventional thyroidectomy. All patients were operated upon in the Department of Surgery of the University Hospital of Pisa between 1999 and 2005 and were followed up at the Department of Endocrinology at the same University Hospital for a median period of 5 yr.

Patients and Methods

Enrolled patients

Between January 1999 and June 2005, a total of 3251 patients presenting with a thyroid nodule that was determined to be a PTC via a cytological examination were referred to our institution to undergo surgical treatment. Among them, 234 patients were selected to enter the present study according to the following criteria: 1) PTC not exceeding 30 mm on its largest axis, determined by a neck ultrasound; 2) thyroid volume lower than 30 ml as measured by ultrasonography; 3) absence of echographic evidence of enlarged lymph nodes both in the central and lateral neck compartment; and 4) absence of evidence of thyroiditis in biochemical and echographic examinations.

Clinical and epidemiological data from patients were collected at diagnosis and during follow-up. Both were performed at the Department of Endocrinology of the University Hospital of Pisa.

The 234 PTC patients [194 females (83%) and 40 males (17%); female/male ratio, 4.8:1] were informed of the possibility of undergoing the surgical treatment either with a conventional thyroidectomy or MIVAT. They were informed about the advantages and disadvantages of both techniques. Patients expressed their choice regarding the surgical procedure and signed an informed consent form. This study was previously approved by the institutional ethical committee.

Among the 234 PTC patients, 184 chose the MIVAT procedure, whereas 50 preferred the conventional thyroidectomy. Thirteen of 184 patients were excluded from the present study because it was necessary to change from MIVAT to traditional cervicotomy. This was due to unexpected intraoperative findings of esophageal infiltration in nine cases and difficult dissection for unexpected thyroiditis in four. The analysis was thus performed on 221 patients, 171 treated with MIVAT (group A) and 50 treated with conventional thyroidectomy (group B).

Patients' mean age at the time of inclusion in the study was 39.1 ± 12.6 yr (range, 8–77 yr). The mean follow-up time was 3.6 ± 1.5 yr (range, 1 to 8 yr; median, 5 yr). According to the pathological Tumor-Node-Metastases (TNM) classification (20), 97 patients (43.8%) were T > 1, whereas 124 patients (56.2%) were T = 1. A total of 197 patients (89%) were N = 0, and 24 (11%) were N = 1. One patient (0.4%) showed lung metastases at the post-¹³¹I ablation whole body scan (WBS). According to the De Groot classification (21), 197 (89%) patients were in class I (intrathyroid tumor without nodal metastases), 18 (8%) were in class II (intrathyroid tumor with nodal metastases), six (2.6%) were in class III (extrathyroid tumor with or without nodal metastases), and one (0.4%) was in class IV (distant metastases).

The 24 patients belonging to classes II and III underwent total thyroidectomy without any suspicions of node metastases or extrathyroidal infiltration (evidence of enlarged lymph nodes at neck ultrasound was,

in fact, an exclusion criterion). In all 24 cases, the lymph node metastases were microscopic and were found histologically when the perithyroidal tissue was examined. For this reason, minimal node involvement did not necessitate changing from MIVAT to traditional cervicotomy. These 24 cases were considered as “intermediate risk,” to be distinguished from the 197 “low risk” cases belonging to class I.

Surgical treatment

The MIVAT procedure was performed through a 1.5-cm central incision made two fingers above the sternal notch with the patient in the supine position and the neck in a relaxed position. The midline was opened approximately 3–4 cm under direct vision, and two small retractors (army-navy type) were inserted so the operative space could be maintained without gas insufflations. Under endoscopic magnification by means of a 5-mm diameter 30° endoscope, the external branch of the superior laryngeal nerve, recurrent laryngeal nerve, and parathyroid glands were visualized. After dividing the upper pedicle, the nerve and parathyroids were identified and dissected, and the lobe was extracted and resected. Hemostasis was achieved with a harmonic scalpel and titanium clips. Three surgeons were involved in the operation: the operator, the endoscope holder, and the holder of the retractors, who maintained the operative space. The average time to perform one MIVAT in our institution was 45 min. Patients treated with MIVAT did not require neck drainage, had reduced local pain, and had a faster postoperative recovery. For these reasons, they were discharged from the hospital after a median time of 24 h.

The conventional thyroidectomy was performed with the patient in the supine position with the neck hyperextended. A 6- to 8-cm transverse cervicotomy two fingers above the sternal notch was performed, and the midline was opened. After the laryngeal nerves and parathyroids were visualized, the thyroidectomy was achieved. Hemostasis was obtained by tying or titanium clips. Patients were discharged from the hospital after a median time of 48 h.

Other treatments and follow-up

After total thyroidectomy, all patients were treated with 30 or 100 mCi ¹³¹I to ablate postsurgical thyroid remnant. The mean period of time elapsed between the thyroidectomy and ¹³¹I administration for postsurgical remnant ablation was 3–4 months.

After 1 yr, all patients underwent a recombinant human TSH stimulation for serum thyroglobulin (Tg) measurement and, if requested, a diagnostic WBS to determine persistence, recurrence, or absence of the disease. Patients with detectable (>1 ng/ml) basal or stimulated serum Tg or with positive neck ultrasound repeated ¹³¹I treatment.

Serum Tg was measured with a solid phase chemiluminescent immunometric assay with a functional sensitivity of 0.9 ng/ml (Immulite 2000 Thyroglobulin; Diagnostic Products Corporation, Los Angeles, CA).

All patients received hormone therapy with levothyroxine at a TSH-suppressive dosage until clinical remission of the disease. They were then shifted to substitutive therapy.

Assessment of surgical complications

Vocal cord motility was evaluated by direct laryngoscopy in all patients immediately before and 3 months after thyroidectomy by a laryngologist specialist. Recurrent laryngeal nerve injury was considered permanent if persistent at 6 months. All patients with cord palsy at 3 months were sent to a voice therapist.

Serum calcium values were monitored on the first and second postoperative days and every week for 3 weeks. Hypoparathyroidism (hypopPTH) was considered permanent when hypocalcemia was persistently present 6 months after surgery, independent of serum PTH values. Total serum calcium and phosphate were measured using standard methods. Serum-ionized calcium was measured by an ion-selective electrode method as previously described (22). Serum PTH (normal range in our laboratory, 15–75 pg/ml) was measured with a commercial immunoradiometric assay kit (Liason; Diasorin, Saluggia, Italy).

Outcome definition

Patients were considered “disease free” when WBS, serum Tg after endogenous or exogenous TSH stimulation (*i.e.* after levothyroxine withdrawal or after recombinant human TSH administration), and circulating Tg antibodies were all negative (23).

Patients with detectable levels of serum Tg or elevated values of circulating Tg antibodies were not considered as disease free, even if both WBS and other imaging techniques were unable to detect any metastatic lesions. These patients were defined as patients with “persistent disease.”

Patients with a disease-free period of at least 12 months who presented with new evidence of disease (*i.e.* detectable levels of serum Tg, disease identified by neck ultrasound or other imaging techniques) were defined as patients with a “recurrence” of the disease.

Statistical analysis

Data were analyzed by χ^2 test, Mann-Whitney *U* test, and an unpaired *t* test with StatView 4.5 software (Abacus Concepts Inc., Berkeley, CA). A *P* value < 0.05 was considered statistically significant.

Results

The epidemiological and pathological data for the two groups of patients are reported in Table 1. No significant differences were found between the two groups of PTC patients for age (*P* = 0.07), sex (*P* = 0.11), or mean follow-up (*P* = 0.77). The other pathological features (tumor size, lymph node metastases, and De Groot's classes) were similar in groups A and B (Table 1). Although there was no preoperative plan to perform lymph node dissection, 24 cases with micro lymph node metastases were identified through histology of the perithyroid tissues that were removed during surgery: 17 of 171 (10%) in group A, and 7 of 50 (14%) in group B (*P* = 0.41).

TABLE 1. Epidemiological data of low-risk and intermediate-risk PTC patients treated with MIVAT (group A) and conventional thyroidectomy (group B)

	Group A (n = 171)	Group B (n = 50)	<i>P</i>
Age (yr)			
Mean	38.3 ± 12.5	41.9 ± 13.2	0.07
Range	8–77	18–71	
Median	37	41	
Sex			
Females	146 (85.3%)	38 (76%)	0.11
Males	25 (14.7%)	12 (24%)	
Follow-up (yr)			
Mean	3.6 ± 1.6	3.6 ± 1.06	0.77
Range	1–8	2–6	
Median	5	5	
Tumor size			
T = 1 (≤2 cm)	93 (54.3%)	31 (62%)	0.3
T > 1 (>2 cm)	78 (45.7%)	19 (38%)	
Lymph node metastases			
N = 0	154 (90%)	43 (86%)	0.41
N = 1	17 (10%)	7 (14%)	
De Groot's classes			
Class I	152 (88.9%)	45 (90%)	0.82
Class II	12 (7%)	5 (10%)	
Class III	6 (3.5%)	0	
Class IV	1 (0.6%)	0	

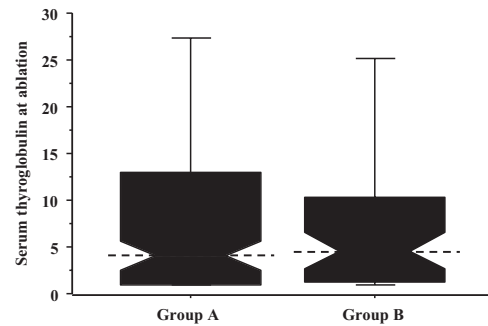


FIG. 1. Box plot of postsurgical serum Tg levels after thyroid remnant ^{131}I ablation in patients treated with MIVAT (group A) or conventional thyroidectomy (group B). Despite an abnormal distribution, the mean and median values of serum Tg were not different between the two groups.

At the time of thyroid remnant ablation, no differences in serum Tg (Fig. 1), TSH levels, or ^{131}I neck uptake were observed between the two groups (Table 2).

After a mean follow-up of 3.6 ± 1.5 yr (range, 1–8 yr; median, 5 yr), no thyroid cancer-related death was observed in either group. As far as the final outcome was concerned, the two groups of patients were similar (Fig. 2). Interestingly, the outcome was not different, even when the 13 group A patients, whose treatment was switched from MIVAT to conventional thyroidectomy, were included (data analyzed according to “intent to treat”). According to our definition of recurrence, none of our patients from either group experienced a recurrence during this follow-up period.

Although there was a small difference in the number of ^{131}I treatments (Table 2), no differences were found when the ^{131}I cumulative activity administered was compared between the two

TABLE 2. Postsurgical features related to the degree of surgical completeness in PTC patients treated with MIVAT (group A) and conventional thyroidectomy (group B) at the time of ^{131}I remnant ablation

	Group A (n = 171)	Group B (n = 50)	<i>P</i>
Serum Tg (ng/ml)			
Mean	25.3 ± 118.4	8.3 ± 9.5	0.8
Range	15–1322	1–38	
Median	4	4.9	
Serum TSH ($\mu\text{U/ml}$)			
Mean	56.1 ± 23.9	51.1 ± 17	0.3
Range	15–205	12.9–75	
Median	55.9	53	
Neck ^{131}I uptake (%)			
Mean	5.4 ± 5	5.5 ± 4.9	0.8
Range	0–31	0.3–21	
Median	3.9	3.6	
Initial ^{131}I activity administered			
30 mCi	167	49	0.5
100 mCi	4	2	
No. of ^{131}I treatments			
1	145	36	0.04
>1	26	14	
Cumulative ^{131}I activity (mCi)			
Mean	57.9 ± 82.1	81.5 ± 105.9	0.2
Range	30–560	30–460	
Median	30	30	

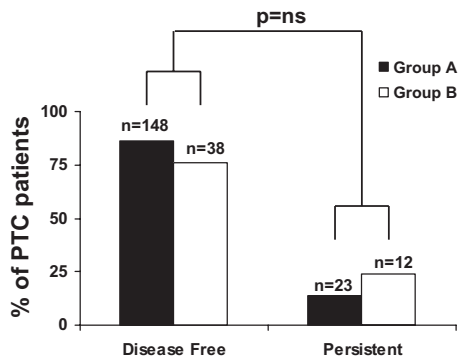


FIG. 2. The 5-yr follow-up failed to show differences in the prevalence of disease-free and persistent PTC patients in the two groups treated with MIVAT (A) or conventional thyroidectomy (B).

groups (Table 2). In particular, no difference in the ¹³¹I cumulative activity administered to reach the definitive cure was observed between patients treated with MIVAT and those treated with conventional thyroidectomy (Fig. 3).

Regarding postoperative morbidity, no bleeding was registered in any patient. As shown in Table 3, a similar rate of prevalence of permanent hypopTH and/or nerve cord palsy was found in both groups (*P* = 0.46).

Discussion

We previously demonstrated that the completeness of surgical resection obtained with MIVAT in the treatment of PTC was comparable to that obtained with conventional thyroidectomy by evaluating serum Tg levels and ¹³¹I neck uptake at the time of thyroid remnant ablation (17). Although this result has been confirmed in larger series (18, 24), to our knowledge, no studies that provide a follow-up of PTC patients treated with MIVAT have been published to date. In the present study, we compared two groups of PTC patients that were similar in epidemiological and pathological features and treated with MIVAT or conventional thyroidectomy. The mean and median follow-up times were also comparable, and, with the exception of the surgical treatment, all patients were treated and followed up with the same therapeutic and clinical protocol at the same institution. We found that the outcome of our two groups was similar after

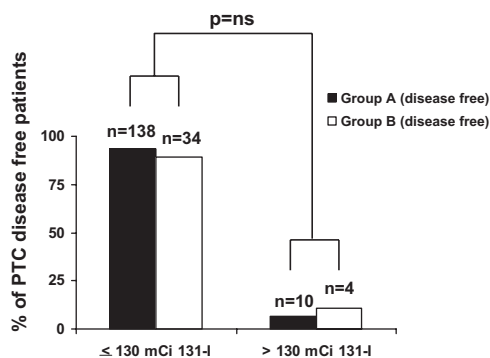


FIG. 3. No differences were found among disease-free PTC patients in the total amount of ¹³¹I needed to reach a definitive cure for patients treated with MIVAT (A) or conventional thyroidectomy (B).

TABLE 3. Pathological data of low-risk and intermediate-risk PTC patients treated with MIVAT (group A) and conventional thyroidectomy (group B)

	Group A (n = 170) ^a	Group B (n = 49) ^a	<i>P</i>
Complications, n (%)			
HypoPTH	6 (3.5)	3 (6.1)	0.4
Nerve cord palsy	5 (2.9)	1 (2.0)	0.7

^a Postsurgical complications were not assessed in two cases.

a median follow-up of 5 yr, regardless of surgical intervention. Moreover, the cumulative dose of ¹³¹I needed to definitively cure the PTC patients was the same between the groups. These results indirectly confirm that the two techniques are equivalent in terms of completeness. To our knowledge, this is the first demonstration that MIVAT can be safely employed in low- and intermediate-risk PTC patients without negative impact on patient outcome. We have confirmed this by demonstrating that the percentage of disease-free subjects and the amount of radioiodine needed to eliminate the cancer are equal between our groups.

It is well known that PTC can recur in the 10 yr after diagnosis and surgical resection. It is therefore necessary to have a longer follow-up period before drawing any final conclusions regarding MIVAT treatment. The first 5 yr after PTC diagnosis and the initial treatment, however, is when the highest risk of recurrence typically occurs (25). In our series, recurrence did not occur in either MIVAT or conventionally treated PTC patients within 5 yr. Taking into account that PTC patients in the present series are primarily low-risk patients (89% of the present series), the absence of recurrence in 5 yr led us to believe that recurrence will not occur in the future. On the basis of these considerations, we feel comfortable in considering the MIVAT technique as effective as conventional thyroidectomy, at least in the treatment of low- or intermediate-risk PTC patients.

We also confirmed that the completeness of MIVAT is similar to that obtained with conventional thyroidectomy, demonstrated by the comparable values of serum Tg and neck ¹³¹I uptake at the time of postsurgical thyroid remnant ablation between the two groups of patients. This observation is consistent with previous reports by us and others (17, 18, 24), and confirms the possibility of employing MIVAT in cases in which the completeness of the thyroidectomy is strongly requested (*i.e.* in PTC patients).

The safety of MIVAT has already been highlighted in several studies that have compared different endoscopic procedures with the standard open thyroidectomy (26–28). The modality of assessment of the morbidity and complication of thyroidectomy can greatly affect their rate, thus varying from 1–40% (29). In our hands, the rate of the two major complications brought about by total thyroidectomy (recurrent nerve palsy and hypopTH) was similar to that reported in other series (30). More interestingly, these occurrences did not differ between patients treated with MIVAT and those treated with conventional thyroidectomy. Although not statistically significant, it is worth noting that there was a slightly lower percentage of patients with

hypoPTH in the MIVAT group. It is conceivable that this result may be related to the optical magnification of the operative field obtained with the use of the endoscope as well as the decrease in stress on the parathyroid glands when using the harmonic scalpel (31, 32).

In conclusion, we have demonstrated that PTC patients operated on with MIVAT had a favorable outcome 5 yr after surgery, similar to the outcome of those patients treated with conventional thyroidectomy with the same degree of ¹³¹I exposure. These results, together with the evidence of a similar degree of completeness and rate of complications between the two surgical techniques, make MIVAT a valid option for the treatment of low- and intermediate-risk PTC patients when performed by a well-trained staff at a specialized center.

Acknowledgments

Address all correspondence and requests for reprints to: P. Miccoli, M.D., Department of Surgery, University of Pisa, Via Roma 64, 56100 Pisa, Italy. E-mail: p.miccoli@dc.med.unipi.it.

This study was supported in part by grants from Ministero della Istruzione Universitaria e Ricerca Scientifica (MIUR), Associazione Italiana per la Ricerca sul Cancro (AIRC), and Istituto Toscano Tumori (ITT).

The Department of Endocrinology and Metabolism of Pisa University is a World Health Organization Collaborating Center for the Diagnosis and Treatment of Thyroid Cancer and other Thyroid Diseases.

Disclosure Summary: The authors have nothing to disclose.

References

- Mazzaferri EL 2000 Long-term outcome of patients with differentiated thyroid carcinoma: effect of therapy. *Endocr Pract* 6:469–476
- Cooper DS, Doherty GM, Haugen BR, Kloos RT, Lee SL, Mandel SJ, Mazzaferri EL, McIver B, Sherman SI, Tuttle RM 2006 Management guidelines for patients with thyroid nodules and differentiated thyroid cancer. *Thyroid* 16:109–142
- Pacini F, Schlumberger M, Dralle H, Elisei R, Smit JW, Wiersinga W 2006 European consensus for the management of patients with differentiated thyroid carcinoma of the follicular epithelium. *Eur J Endocrinol* 154:787–803
- Mitchell I, Livingston EH, Chang AY, Holt S, Snyder 3rd WH, Lingvay I, Nwariaku FE 2007 Trends in thyroid cancer demographics and surgical therapy in the United States. *Surgery* 142:823–828; discussion, 828
- Kent WD, Hall SF, Isotalo PA, Houlden RL, George RL, Groome PA 2007 Increased incidence of differentiated thyroid carcinoma and detection of subclinical disease. *CMAJ* 177:1357–1361
- Davies L, Welch HG 2006 Increasing incidence of thyroid cancer in the United States, 1973–2002. *JAMA* 295:2164–2167
- Mazzaferri EL 2007 Management of low-risk differentiated thyroid cancer. *Endocr Pract* 13:498–512
- Miccoli P, Berti P, Conte M, Bendinelli C, Marcocci C 1999 Minimally invasive surgery for thyroid small nodules: preliminary report. *J Endocrinol Invest* 22:849–851
- Shimizu K, Akira S, Jasmi AY, Kitamura Y, Kitagawa W, Akasu H, Tanaka S 1999 Video-assisted neck surgery: endoscopic resection of thyroid tumors with a very minimal neck wound. *J Am Coll Surg* 188:697–703
- Bellantone R, Lombardi CP, Raffaelli M, Rubino F, Boscherini M, Perilli W 1999 Minimally invasive, totally gasless video-assisted thyroid lobectomy. *Am J Surg* 177:342–343
- Terris DJ 2008 Effect of video-assisted thyroidectomy on the risk of early postthyroidectomy voice and swallowing symptoms. *World J Surg* 32:701
- Miccoli P, Minuto MN, Ugolini C, Pisano R, Fosso A, Berti P 2008 Minimally invasive video-assisted thyroidectomy for benign thyroid disease: an evidence-based review. *World J Surg* 32:1333–1340
- Terris DJ, Angelos P, Steward DL, Simental AA 2008 Minimally invasive video-assisted thyroidectomy: a multi-institutional North American experience. *Arch Otolaryngol Head Neck Surg* 134:81–84
- Terris DJ 2007 Minimally invasive thyroidectomy: an emerging standard of care. *Minerva Chir* 62:327–333
- Lombardi CP, Raffaelli M, Princi P, De Crea C, Bellantone R 2006 Video-assisted thyroidectomy: report on the experience of a single center in more than four hundred cases. *World J Surg* 30:794–800; discussion, 801
- Duh QY 2003 Presidential address: minimally invasive endocrine surgery—standard of treatment or hype? *Surgery* 134:849–857
- Miccoli P, Elisei R, Materazzi G, Capezone M, Galleri D, Pacini F, Berti P, Pinchera A 2002 Minimally invasive video-assisted thyroidectomy for papillary carcinoma: a prospective study of its completeness. *Surgery* 132:1070–1073; discussion, 1073–1074
- Bellantone R, Lombardi CP, Raffaelli M, Alesina PF, De Crea C, Traini E, Salvatori M 2003 Video-assisted thyroidectomy for papillary thyroid carcinoma. *Surg Endosc* 17:1604–1608
- You YN, Wells Jr SA 2007 Role of surgeons in clinical trials for thyroid cancer. *World J Surg* 31:987–995
- Greene FL, Page DL, Fleming ID, Fritz AG, Balch CM, Haller DG, Morrow M 2002 AJCC cancer staging handbook. New York: Springer
- DeGroot LJ, Kaplan EL, McCormick M, Straus FH 1990 Natural history, treatment, and course of papillary thyroid carcinoma. *J Clin Endocrinol Metab* 71:414–424
- Cetani F, Pardi E, Borsari S, Tonacchera M, Morabito E, Pinchera A, Marcocci C, Dipollina G 2003 Two Italian kindreds with familial hypocalcemic hypercalcaemia caused by loss-of-function mutations in the calcium-sensing receptor (CaR) gene: functional characterization of a novel CaR missense mutation. *Clin Endocrinol (Oxf)* 58:199–206
- Pacini F, Capezone M, Elisei R, Ceccarelli C, Taddei D, Pinchera A 2002 Diagnostic ¹³¹I-iodine whole-body scan may be avoided in thyroid cancer patients who have undetectable stimulated serum Tg levels after initial treatment. *J Clin Endocrinol Metab* 87:1499–1501
- Lombardi CP, Raffaelli M, de Crea C, Princi P, Castaldi P, Spaventa A, Salvatori M, Bellantone R 2007 Report on 8 years of experience with video-assisted thyroidectomy for papillary thyroid carcinoma. *Surgery* 142:944–951
- Mazzaferri EL, Kloos RT 2001 Clinical review 128: current approaches to primary therapy for papillary and follicular thyroid cancer. *J Clin Endocrinol Metab* 86:1447–1463
- Lombardi CP, Raffaelli M, Princi P, Lulli P, Rossi ED, Fadda G, Bellantone R 2005 Safety of video-assisted thyroidectomy versus conventional surgery. *Head Neck* 27:58–64
- Miccoli P, Berti P, Raffaelli M, Materazzi G, Baldacci S, Rossi G 2001 Comparison between minimally invasive video-assisted thyroidectomy and conventional thyroidectomy: a prospective randomized study. *Surgery* 130:1039–1043
- Terris DJ, Gourin CG, Chin E 2006 Minimally invasive thyroidectomy: basic and advanced techniques. *Laryngoscope* 116:350–356
- Bhattacharyya N, Fried MP 2001 Benchmarks for mortality, morbidity, and length of stay for head and neck surgical procedures. *Arch Otolaryngol Head Neck Surg* 127:127–132
- Toniato A, Boschin IM, Piotto A, Pelizzo MR, Guolo A, Foletto M, Casalide E 2008 Complications in thyroid surgery for carcinoma: one institution's surgical experience. *World J Surg* 32:572–575
- Defechereux T, Rinken F, Maweja S, Hamoir E, Meurisse M 2003 Evaluation of the ultrasonic dissector in thyroid surgery. A prospective randomised study. *Acta Chir Belg* 103:274–277
- Miccoli P, Berti P, Dionigi G, D'Agostino J, Orlandini C, Donatini G 2006 Randomized controlled trial of harmonic scalpel use during thyroidectomy. *Arch Otolaryngol Head Neck Surg* 132:1069–1073