



Central compartment revision surgery for persistent or recurrent thyroid carcinoma: analysis of survival and complication rate

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Abstract

Purpose Locoregional recurrence of thyroid carcinoma is relatively common and reported rate are between 5 and 20%. Cervical nodes are usually involved, especially at the central compartment. The management of recurrent thyroid carcinoma at central compartment still remains challenging because of higher incidence of complication rate. The aim of the study is to evaluate the survival and complications rate after revision surgery.

Methods Retrospective cohort study on a group of patients that underwent revision surgery for persistent or recurrent thyroid carcinoma from January 1, 2003 to December 31, 2017. Survival outcomes were calculated using Kaplan–Meier method. Significant variables on univariate analysis were subjected to a Cox proportional hazards regression multivariate model.

Results Fifty-two patients involved, 22 male (40%) and 30 female (60%). Mean age was 54 years old (range 24–85). Mean follow-up was 79 months, median follow-up was 85 months, with a range between 8 and 153 months. The 5-year overall survival was 90.8% while at 10 years it was 69.8%. The 5-year disease-specific survival was 93.5%, while at 10 years it dropped to 77.9%. The rate of recurrent laryngeal nerve paralysis and persistent hypocalcemia in our series were 1.3% and 5.9%, respectively. No evidence of thoracic duct, esophageal or laryngeal and tracheal injury was found in this case series. Regarding prognostic factors, univariate and multivariate analysis highlighted as statistically significant: the aggressive histological variants, the presence extranodal extension or soft-tissue metastasis.

Conclusion The surgical option remains the gold standard in locoregional recurrences of thyroid carcinoma and should be performed by experienced surgeons to reduce postoperative complications.

Keywords Thyroid cancer · Nodal metastases · Neck dissection · Central compartment · Complications · Vocal fold palsy · Hypocalcemia

Introduction

Thyroid cancer, in particular well-differentiated thyroid types (WDTC), remains the most frequent endocrine tumor, with an annual incidence of 1–4 per 100,000 individuals. Female sex is prevalent and the median time of diagnosis is about 50 years [1].

Thyroid carcinoma have an excellent prognosis, but it is less favorable when the disease recurs after primary treatment [2, 3]. Local or regional recurrence occurs in 5–20% of patients and the most common localization of metastases is represented by the cervical nodes, even if in 10% of cases it might determine distant metastases, especially in the lungs and bones [4, 5]. The early diagnosis of recurrence, in particular the cervical ones, improves the survival rate, reduces the possible complications and allows to choose the best

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treatment, which can be revision surgery and/or radioactive iodine (^{131}I).

The management of the metastatic lymph nodes, in particular at the central compartment (CC) (VI and VII levels, Robbins' classification), still remains a therapeutic challenge because of the balance between complications and tumor eradication.

We present our experience of revision surgery for recurrent or persistent thyroid cancer, analyzing the survival and complication rate.

Materials and methods

Fifty-two patients with recurrent or persistent well-differentiated, medullary or poorly differentiated thyroid cancer were evaluated in a retrospective cohort study. They underwent primary or revision central compartment dissection with or without selective lateral neck compartment dissections and/or completion of the thyroidectomy between January 1, 2003, and December 31, 2017, at the Department of Oto-rhinolaryngology-Head and Neck Surgery of the University Hospital of Modena. The study was performed according to the declaration of Helsinki. Given the retrospective nature of this review, informed consent for this study was waived.

All patients underwent a complete oncological and endocrinological evaluation. Radiological exams with high-resolution ultrasound and computed tomography (CT) of the neck with contrast medium were performed. Other evaluations such as total body CT scan, magnetic resonance or bone scans were performed accordingly to the clinical presentation of every patient.

The indication for treatment was the suspicion of recurrence or persistence of thyroid cancers involving lymph nodes determined on the basis of: positive radiological imaging, fine-needle aspiration cytology, abnormal blood levels of calcitonin or thyroglobulin. The laryngeal function was checked with video laryngoscopy before and after the surgical treatment. All the surgical procedures were performed by an experienced head and neck surgeon.

The overall survival (OS) and the disease-specific survival (DSS) rates were analyzed. A univariate and multivariate analysis was performed to evaluate whether some parameters had an impact on the DSS.

The variables considered were: gender, age (cut-off 45 years old); aggressive variants of thyroid carcinoma (medullary, tall cell, undifferentiated), lymph nodes with extranodal extension (ENE) or soft-tissue metastasis (STM); recurrence after treatment; recurrence at less than 12 and 24 months from primary treatment, lymph node metastasis density (LND) higher than 50%. LND is the ratio between the number of positive lymph nodes excised and the total number of excised lymph nodes [6]. From the analysis of

survival rates, three patients were excluded because, on definitive histological examination, despite FNAC and radiology suggestive for recurrence, they did not present any pathologic evidence of recurrence of the disease. Regarding the complications, the rate of paralysis of the recurrent laryngeal nerves (RLN) and hypoparathyroidism were analyzed. At the moment, there is no consensus yet regarding the cutoff to distinguish between temporary and persistent RLN palsy [7]. We considered persist a vocal fold palsy lasting more than 6 months and not responsive to medical and physical therapies. Patients with preoperative paralysis of the nerve ($n=4$), patients treated with total laryngectomy because of laryngeal infiltration ($n=1$) and patients ($n=3$) with intraoperative finding of nerve infiltration by the tumor but without preoperative palsy were excluded from the analysis of the paralysis rate of RLN. Hypoparathyroidism occurs when a low intact parathyroid hormone level is accompanied by hypocalcemia. According to recent American Thyroid Association indications, we considered temporary hypoparathyroidism when occurring for less than 6 months after surgery, while permanent hypoparathyroidism continues beyond 6 months after surgery [8]. Patients who already had permanent hypocalcemia ($n=5$) were excluded from the analysis of the hypoparathyroidism rate.

Statistical analysis

All data were tabularized, and a chart review was performed with use of the Microsoft Excel, 15.33 version (Microsoft Corporation, Redmond, WA). OS was defined as the interval between the surgical treatment and the date of last follow-up or death. DSS was defined as the interval between the surgical treatment and the thyroid cancer death.

All data were analyzed with use of the "R" software, 3.4.1 version.

A log-rank test was used to compare OS and DSS calculated with Kaplan–Meier method. Factors with prognostic potential found at the univariate analyses were included in a multivariate analysis using the Cox proportional hazard regression model. Statistical significance was set to 0.05.

Results

The study population comprised 52 patients. Twenty-two patients were male (40%) and 30 were female (60%); the male/female ratio was 1:1.4. All patient characteristics concerning preoperative treatments are summarized in Table 1.

The mean age at the first reintervention was 54 years old (range from 24 to 85). A total of 67 surgical operations were performed: 38 patients (76%) required only 1 intervention, 13 patients (20%) underwent 2 surgical revisions and only 1

Table 1 Demographic characteristics and clinical data

Sex	
Male	22
Female	30
Age at time of surgery	
Mean	55
Median	56
Primary thyroid surgery	
Total	50
Lobectomy or subtotal	2
Initial or subsequent neck surgery	
Central neck dissection single side	8
Central neck dissection bilateral	11
Lateral neck dissection single side	16
Lateral neck dissection bilateral	6
Disease free time from primary surgery (months)	
Mean	54
Median	30

patient (4%) needed a third surgical operation. Every patient underwent VI–VII node level dissection. Moreover, one of the patients underwent total laryngectomy due to tumor infiltration of the laryngotracheal region, one underwent tracheotomy and two underwent posterior cordectomies for bilateral recurrent paralysis. All of these last three patients already had preoperative one-sided RLN paralysis and required sacrifice of the contralateral RLN during surgery because of its infiltration by the tumor. All surgical procedures are summarized in Table 2.

Focusing on postoperative adjuvant therapies, we observed that in 10/52 cases (19%) patients were subjected to radiotherapy, in 17/52 cases (33%) they performed radioactive iodine treatment therapy (RAI) and in 1/52 case (2%) the patient underwent both therapies; in 4/52 (8%) cases, data were not available and in the remaining 20/52 cases (38%) no adjuvant therapy was performed.

Survival rates

The mean follow-up was 79 months, median follow-up was 85 months, with a range between 8 and 153 months. The 5-year OS was 90.8% while at 10 years it was 69.8%. The 5-year DSS was 93.5%, while at 10 years it dropped to 77.9% (Fig. 1).

Univariate and multivariate analysis, on DSS, highlighted as statistically significant: the aggressive histological variants, the presence of ENE or STM. There were no statistically significant differences in sex, the lymph node density > 50%, subsequent recurrences after revision surgery or relapses before 12 or 24 months after first surgical treatment (Table 3).

Table 2 Surgical procedures

	No. of procedures
Central neck compartment surgery	
Single side	
RS total; 1st surgery; 2nd surgery; 3rd surgery	18; 14; 3; 1
LS total; 1st surgery; 2nd surgery; 3rd surgery	21; 16; 5; 0
Central neck dissection bilateral	
Total; 1st surgery; 2nd surgery; 3rd surgery	19; 18; 1; 0
Revision of central neck compartment	
Total; 1st surgery; 2nd surgery; 3rd surgery	23; 15; 7; 1
Lateral neck compartment surgery	
Single side	
RS total; 1st surgery; 2nd surgery; 3rd surgery	12; 11; 1; 0
LS total; 1st surgery; 2nd surgery; 3rd surgery	12; 8; 4; 0
Bilateral	
Total; 1st surgery; 2nd surgery; 3rd surgery	6; 6; 0; 0
Revision of LN	
Total; 1st surgery; 2nd surgery; 3rd surgery	8; 6; 2; 0
Completion thyroidectomy	4

RS right side, LS left side

Histological findings

The histological features of the 52 patients included in the study were analyzed. In 43/52 (82.7%) cases, the final diagnosis was papillary carcinoma, in 6/52 (11.5%) cases was a medullary carcinoma and in 3/52 (5.8%) cases was poorly differentiated thyroid cancer. Among the papillary carcinomas, the variants encountered were: classic in 39/43 (90.7%) patients, follicular in 3/43 (7%) patients, tall cells in one case (2.3%). In all the surgical revisions performed at our department that showed microscopic disease recurrence, histological diagnosis corresponded to the primitive one.

The number of microscopic recurrences found at the first reintervention was 49/52 (94%).

Some assessments were also made about the lymph nodes removed in all operations performed. The average number of metastatic nodes for lateral neck dissections (II–IV) was 2.75 (\pm 3.35 SD), while the percentage of positive lymph nodes was 12%. The CC neck dissection showed an average of 3 (\pm 2.99 SD) positive lymph nodes for metastasis, while the percentage of metastatic lymph nodes was 52% (Table 4).

The surgical procedures on the CC previously treated were also included in this statistical analysis, showing 44% of pathologic nodes with a mean of 1.5 (\pm 1.16 SD) nodes on the whole. In all the cases analyzed, we observed a total of 16 cases (30.8%) of positive extranodal extension or soft tissue metastasis.

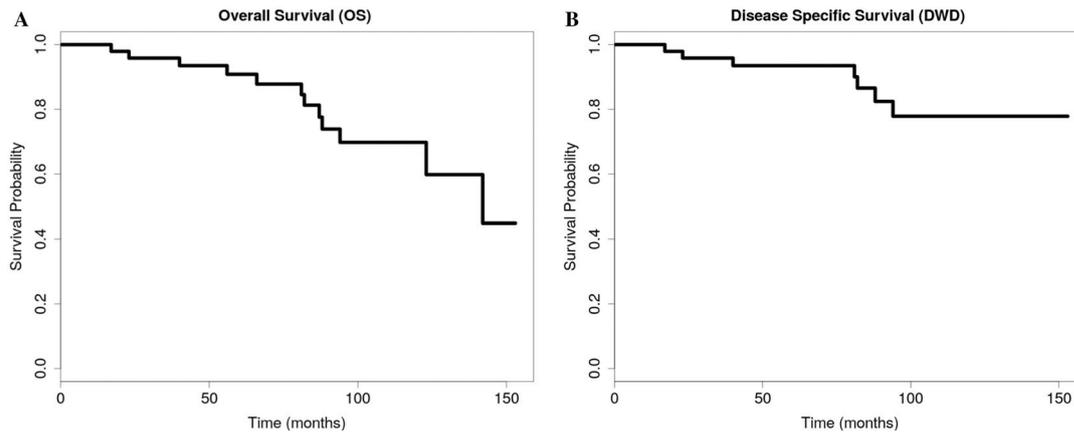


Fig. 1 **a** Kaplan–Meier overall survival curve; **b** Kaplan–Meier disease-specific survival curve

Table 3 Multivariate analysis of prognostic factors for disease-specific survival

	HR (95% CI for HR)	Wald test	<i>P</i> value
Sex	1.1 (0.24–4.9)	0.01	0.91
M=20			
F=29			
Age (>45 years old)	4.6 (0.55–38)	2	0.16
>45 years old=30			
≤45 years old=19			
Recurrence	2.8 (0.62–13)	1.8	0.18
Yes=13; no=36			
Recurrence <12 m	2.4 (0.54–11)	1.3	0.25
Yes=11; no=38			
Recurrence <24 m	2.4 (0.47–12)	1.1	0.29
Yes=24; no=25			
Aggressive histotype	7.9 (1.5–41)	6.1	0.014
Yes=10; no=39			
ENE or STM	16 (1.9–130)	6.5	0.011
Yes=16; no=33			
LND >50%	2.4 (0.29–20)	0.68	0.41
Yes=34; no=13			

Bold—statistical significance for *P* value < 0.05

Table 4 Pathologic findings on neck compartment

Neck treatment	Lymph nodes (no. and %)
Lateral neck dissection (II–IV)	
No. of nodes removed	708
pN+	86
Mean pN+ (SD)	2.75 (3.35)
LND (%N/pN+)	12%
Central compartment (VI–VII)	
No. of nodes removed	262
pN+	137
Mean pN+ (SD)	3 (2.99)
LND (%N/pN+)	52%
Revision of CC (VI–VII)	
No. of nodes removed	63
pN+	28
Mean pN+ (SD)	1.5 (1.16)
LND (%N/pN+)	44%
ENE or STM	16 (30.8%)

Complications

In our case series, according to the inclusion criteria previously described, the RLNs at risk, based on the description of the surgical procedures, were 74. In our case series, we reported three RLN palsies, of which just one did not recover after 6 months of specific rehabilitation provided by the speech therapist, while the other two cases totally recovered a normal vocal cord mobility. No RLN paralysis were encountered in the group of patients that underwent CC revision surgery. Therefore, the rate of paralysis in our series was 1.3%.

Analyzing a total of 68 procedures on the central compartment, following the inclusion criteria described above, we observed 7 transient cases of hypocalcemia (10.3%), of which two had undergone CC revision surgery, and 4 patients had persistent hypocalcemia (5.9%), of which one of them had undergone radicalization of thyroidectomy and unilateral CC dissection, two had undergone CC revision surgery and one had presented with CC metastasis and ENE. No evidence of thoracic duct, esophageal or laryngeal and tracheal injury was found in this case series.

Discussion

The treatment of lymph nodes of the central compartment of the neck is still controversial and many authors pointed out how challenging it is and its considerable rate of complications [9].

This study evaluates the OS and the DSS of a group of patients with locoregional recurrence or persistence of thyroid carcinoma located at CC and/or lateral neck compartment. The survival rate of these patients is coherent with the majority of data already present in the literature [10–12].

Our data point out that aggressive histologic variables, and the presence of ENE or STM are unfavorable prognostic factors, as previously described by various authors [10–12].

However, it is interesting to underline that patients with multiple relapses, more than 50% of metastatic lymph nodes, and early relapses (12/24 months) do not show significant prognostic differences. The analysis also reaffirms that surgical treatment should be preferred in case of multiple lymph node recurrences.

The most common neck localizations of node recurrence of WDTC are located at IV–VI and VII neck levels; the National Comprehensive Cancer Network guidelines for thyroid carcinoma recommend the surgical option for curative intent and to prevent the locoregional complications; especially tracheal, esophageal, vascular and nervous infiltration [13–16].

The re-operation of the central compartment is burdened by the higher rate of complications than primary surgery. This is related to the presence of scar tissue and consequent anatomical distortions, which prevents an optimal visualization and preservation of the main anatomical structures. The most frequent complications, described in the literature, are the RLNs injury, permanent hypoparathyroidism, lymphatic fluid leakage, Claude–Bernard–Horner Syndrome and vascular injuries. Despite this, some authors describe the revision surgery of CC as a safe and efficient oncological procedure with low rate complications and morbidity [12–14, 17, 18].

In our experience, the safest surgical strategy in these revision cases is as follows: the surgeon must use the magnifying loupes (2.5 to 3.5 ×) to better recognize the main anatomical landmarks, represented by the tracheoesophageal groove, the carotid artery and RLN entry point. Otherwise RLNs should be found and dissected not in the previous surgical field, but preferably far from the scar tissue in the space between common carotid artery, trachea and esophagus in the upper mediastinal region. As underlined by Coyune et al., the visualization of the RLNs remains the gold standard to ensure nerve preservation; moreover, the nerve monitoring system and the neurostimulator, when available, are useful aids [19–21].

Regarding preservation of parathyroid glands, their identification like in primary surgery is difficult. Their characteristic yellow–brown color is hardly noticeable during the dissection of the fibrocitrictorial tissue. If the surgeon finds a tissue, macroscopically compatible with a parathyroid, he can send a part to frozen section check. In the case of positivity if the tissue is completely devascularized, transplantation should be performed. In our series, we did not perform transplantation of parathyroid glands.

In the literature, the rate of RLN transient and permanent palsies is in a range between 0–21.2 and 0–6.4%, respectively. Temporary and permanent hypocalcemia ranges are between 6.1 and 46.3% and between 0 and 9.1%, respectively. Indeed, our results agree with what is stated in the literature and show a relatively low rate of complications [12, 22–27].

Concerning the management of vocal cord palsies, an optimal collaboration with speech therapist is crucial because, as described by Mattioli et al., an early rehabilitation strategy associated with possible injection laryngoplasty can lead to an optimal functional outcome [28, 29].

Regarding the analysis of lymph nodes, the average number of positive lymph nodes and their percentage compared to the total coincide with those of similar series. It is interesting to note that CC is positive in more than 50% of cases compared to 12% of compartment II–IV, pointing out the importance of a careful follow-up of this region. LND has already been shown to play a predictive role after surgery for papillary thyroid carcinoma [6, 13, 19–22].

However, it is essential to underline the high number of lymph nodes founded in the CC previously treated. This aspect can be likely explained by the undertreatment of central neck compartment during primary surgery, probably due to fear for surgical complication. Our series, similar to those reported in the literature, reinforces the evidence that these procedures should be performed by experienced head and neck surgeons and in centers with relevant case load, to reduce complications rates as much as possible and to provide a radical dissection of central compartment lymph nodes.

Limitations

This study has several limitations. First, the study is limited by its retrospective setting consisting of reviewing available medical records. A number of patients had limited follow-up (< 12 months) limiting the complete assessment of OS, DSS and certain complications, such as vocal cord palsy and hypoparathyroidism. The endocrine pathologic aspects analyzed are not uniform, as papillary, follicular, medullary and anaplastic thyroid carcinoma are all considered. In addition, our data were from a single referral center and might

have biased toward a surgical practice with relatively more advanced disease and treatment.

Conclusions

The study showed that some known prognostic factors, such as ENE/STM and the biological aggressiveness of the tumor, significantly impact on the survival rate. However, it was found that early relapses, age > or < 45 years, the percentage of positive lymph nodes higher than 50% or the further node recurrences, after the first one, did not significantly affect survival. These data confirm that the surgical option remains the gold standard in locoregional recurrences for this type of tumor.

The central compartment revision surgery is a very challenging surgical procedure which should be performed by experienced surgeons to reduce postoperative complications. Early identification of the main anatomical landmarks is crucial to avoid complications, especially in case of revision surgery.

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Compliance with ethical standards

Conflict of interest The authors declare no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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