The current status of lymph node dissection in the treatment of papillary thyroid cancer. A literature review

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Abstract

Aim. Cervical lymph node micrometastases are observed in up to 90% of papillary thyroid cancers (PTC), showing that lymph nodal involvement is very common. Nevertheless, during the last years, the role of lymph node dissection in the treatment of PTC has been controversial and, at present, the best indications to the routine or therapeutic neck dissection remain subject of research. In order to better analyze the current role of lymph node dissection in the surgical treatment of PTC, an analysis of the most recent literature data was performed.

Study Design. By using as keywords lymph node dissection, selective, lateral or central lymph node dissection, modified radical neck dissection, prophylactic or therapeutic lymph node dissection, papillary thyroid cancer, a Pub Med data base research was carried out. The most recent guidelines of different referral endocrine societies, inhering neck dissection for PTC, were also evaluated.

Results. The role of neck dissection in PTC management remains controversial regarding routine or therapeutic indications, surgical extension, and its impact on local recurrence and long term survival. Due to inhomogeneous literature data, the current status of node dissection is still subject of research.

Conclusions. There is agreement between endocrine and neck surgeons about the extension of therapeutic lymph node dissection in N+ PTC patients, and also in the prophylactic treatment of N0 “high risk” patients. Considering a recent trend toward routine central lymphadenectomy avoiding radioactive treatment, prospective randomized trials are needed to evaluate the benefits of different approaches. Clin Ter 2013; 164(4):e343-346. doi: 10.7417/CT.2013.1599

Key words: active iodine ablation, routine central lymph node dissection, lymph node neck dissection, papillary thyroid cancer, radio, total thyroidectomy

Introduction

Lymph nodal involvement in papillary thyroid cancer (PTC) is very common, and in up to 90% of cases lymph node micrometastases are observed (1, 2). Substantial agreement exists among endocrinologists, endocrine and neck surgeons regarding the role of total thyroidectomy (TT) and Thyroid Stimulating Hormone (TSH) suppression therapy, considering the multifocal nature of the disease, the effectiveness of postoperative radioactive iodine (RAI) treatment and the monitoring of serum thyroglobulin (Tg) levels during follow-up. On the contrary, the extension of lymph node dissection (LD), its routine or therapeutic indication, and adjuvant RAI treatment are still subject of controversies. A “low aggressive behavior” in most PTC patients, a low locoregional recurrence rate, often an irrelevant mortality, associated with a need of long-term follow-up (more than 20 years), make difficult the evaluation of surgical outcomes. According to different referral endocrine societies, the role and extension of therapeutic LD in PTC patients with node involvement are well defined, while the indication to routine central lymph node dissection (RCLD), in absence of enlarged lymph node, identified by preoperative ultrasound and intraoperative inspection, and to RAI ablation in PTC ranging between 1 and 2 cm of diameter, are matter of research. Some authors recommend RCLD in order to prevent a future recurrence, citing the high risk of positive lymph nodes, better outcomes and a lower morbidity rate associated with the first operation (3), whereas others suggest that RCLD increases the risk of injury to parathyroid glands (4, 5) and recurrent laryngeal nerves, without any demonstrable benefits in terms of long-term survival (6). Central neck dissection may reduce loco-regional recurrence rate and postoperative serum Tg levels (athyroglobulinemia is very useful during follow-up), but is often associated with an higher risk of morbidity. In an attempt to better clarify the current role of LD in treating PTC, we analyzed the most recent literature data. Selective central and lateral neck dissection is indicated in case of metastatic lymph node, but, until conclusive evidence of RCLD benefit, we believe that prophylactic LD is still controversial, and needs to be more intensively investigated.

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Study Design

By using as keywords lymph node dissection, selective, lateral or central lymph node dissection, modified radical neck dissection, prophylactic or therapeutic lymph node dissection, papillary thyroid cancer, a PubMed database research was carried out. Prospective, retrospective and meta-analysis studies were analyzed. The most recent guidelines regarding neck dissection for papillary thyroid cancer, according to American Thyroid Association (ATA), European Thyroid Association (ETA), Unità Operative di Endocrinochirurgia (UEC), American Head and Neck Society and the American Academy of Otolaryngology-Head and Neck Surgery, were also reported. Regarding terminology of cervical lymphatic anatomy (neck levels) and classification of neck dissection, the most recent ATA guidelines were considered (7). LD benefits, complications and impact on locoregional recurrence rate and mortality were evaluated.

Discussion

Thyroid carcinoma, 2.5% of all malignancies, is increasing in frequency, representing the fifth most common cancer in women in the USA (1, 3). Papillary variants are by far the most frequent neoplasm (8), followed by follicular (10% to 20% of cases) and medullary thyroid cancer (5% to 8% of cases), often part of MEN-2 syndrome (9). Anaplastic Thyroid Carcinoma (ATC) represents a very rare and aggressive thyroid neoplasm that belongs to the group of killer tumors, with a mean survival period of 6.2 months, as reported for carcinosarcoma of other districts (10). The prognosis of DTC patients is favorable, with a 10-year mortality rate of about 7% (11, 12), while ATC patients have a very poor prognosis usually dying few months after the diagnosis.

Differently from the past, by identifying a higher number of small papillary cancer (<1 cm), by means elastography and US guided fine needle aspiration biopsy cytology (FNAB-C) allows a more precocious diagnosis (13-15). Long-term survival reflects the PTC indolent nature, and makes hard to define statistical significance of recurrence and mortality. However, about 20% of patients face the morbidity of loco regional recurrences, and PTc-related deaths (17-19). The trend to metastasizing to central or lateral cervical lymph nodes is very common in PTC, and micrometastases are observed in up to 90% of cases (13, 20, 21). Infiltration of thyroid capsule, patient age (pediatric or geriatric population), tumor size, several oncogenes (p53, BRAF) are associated with node involvement and are considered the main risk factors for recurrence (22-24). Lymphatic disease has been understated because of the excellent prognosis of differentiated thyroid cancers, and of the irrelevant impact of lymph node metastases on survival. Moreover, the discordance between the high rate of lymph node micrometastases, and the low incidence of clinical recurrence following TT without RCLD, may be correlated to postoperative RAI administration. Nevertheless, recently, it has been hypothesized that, especially in older patients, lymphatic metastases may affect recurrence and survival rates. There are no controversies about the role of TT and TSH suppression therapy, while LD is subject of research. In the treatment of low-risk DTC patients, without suspect lymph node, identified by preoperative ultrasound or intraoperative inspection, from hyoid bone to sternal notch, comprehending the carotid sheaths, TT is the operation of choice, as in most thyroid diseases (25-27). On the contrary, the role of LD remains controversial, and especially RCLD, proposed in the last decade, is to date under study. According to its proponents, a better chance of cure, reducing the recurrence risk, may be achieved with a low morbidity.

In case of central metastases, the so called “berry picking”, associated with an unacceptable recurrence rate, must not be performed, and a selective ipsi-or bilateral central dissection (level VI according to the American Academy of Otolaryngology-Head and Neck Surgery) is recommended. In high risk patients – male patient, age >45 years, T >3 cm, BRAF positive- or in presence of more than five metastatic lymph nodes, or of one lymph node greater than 3 cm - a selective lateral dissection may be associated (levels III-IV). In patients affected by lateral metastases, central and lateral neck dissection is required (levels II, III, IV, VI), reserving a bilateral modified radical neck dissection, in case of multiple lymphatic metastases, in high risk patients (28). Following selective neck dissection, a recurrence rate of 10% is reported. Regarding RCLD, endocrine and neck surgeons are divided between pro and cons. It is well known that in most cases routine LD does not affect patient’s prognosis, although some authors affirm that it can improve survival (29). Nevertheless, the high incidence of lymph node metastases, the observation that reoperation for central recurrence may have a greater morbidity, the insufficient diagnostic accuracy of intraoperative inspection and of ultrasonography, reported in 1/3 of DTC patients, and the failure of 131I ablation in about 30% of cases, are considered in favour of RCLD. ATA guidelines, published in 2006, state that RCLD should be considered in DTC, but this recommendation is not based on strong supporting data (30). Recently, according to ATA and UEC, prophylactic LD could be especially undertaken in high-risk patients with advanced primary tumors, so recognizing that this approach may be associated with increased morbidity, especially among low volume-surgeons (7, 31). Rates of permanent hypoparathyroidism and of unintentional permanent recurrent laryngeal nerve injury after TT were respectively 1-2 % and 0-5.5%, whereas, following TT associated with RCLD, they respectively increased to 0-14.3% and to 0-5.7%, according to White et al. (32). The authors, after an evidence-based medicine study, concluded that central nodal dissection reduces loco-regional recurrence, improves disease-free survival, and increases the number of patients with undetectable Tg levels, although is associated with a higher risk of injury to parathyroid glands. Pacini et al. observing that RCLD allows a better staging, believe that further benefits have not been demonstrated yet (33). In a recent paper (34) regarding the feasibility of a prospective randomized study of RCLD, the authors conclude that a trial is very expensive and not readily feasible. In the absence of sufficient statistical power to demonstrate significant differences in outcomes, the role of prophylactic surgery is still to be demonstrated. RCLD allows a better cancer staging, reduces postoperative serum Tg levels, but moreover Carling et al. concluded that to evaluate the benefits of RCLD,
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prospective randomized trials are needed (35). The careful reported literature analysis failed to demonstrate beneficial effects of RCLD. TT, followed by RAI administration and TSH suppression therapy, may guarantee optimal long-term results, with a low incidence of loco-regional lymph node recurrence (36). Regarding reoperation (lymph node dissection) outcomes, an higher morbidity is not reported, as confirmed by Shen et al. (4). After TT combined with RCLD, the authors do not observe significant advantages as regards to long-term results. RCLD seems to have a role in DTC staging and is useful to modify the treatment protocol, as demonstrated by Bonnet et al., that reported a 30% increase in the number of patients with T1 DTC (preoperatively considered to be N\textsubscript{3}), for whom \textsuperscript{131}I a blation was indicated following routine central and lateral nodal dissection, demonstrating unexpected nodal metastases (22). In absence of enlarged lymph node, and when RAI administration is advisable (tumour >2 cm in a patient >50-year-old) routine lymph node dissection is not indicated (37, 38). In low-risk patients with tumors ≤1 cm, lymph node dissection may discover metastases requiring RAI ablation, while in that cases already scheduled to undergo iodine treatment, the role of RCLD should be better defined. Nevertheless, in high-risk patients, RCLD may reduce loco-regional recurrence rate and postoperative serum T\textsubscript{g} levels. In absence of data supporting the beneficial effects of RCLD, we believe that, in the treatment of DTC without suspicious enlarged lymph node, it is not routinely indicated, as well as a lateral prophylactic node dissection is never indicated. Given the literature trend supporting prophylactic LD, the avoidance of RAI treatment, more prospective randomized studies are needed in the attempt to better define the role of RCLD and of postoperative radioiodine ablation.

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