Lymph Node Dissection Versus No Lymph Node Dissection for Parathyroid Cancer

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Abstract

Surgery is the primary treatment for parathyroid carcinoma, but no consensus statement exists regarding the optimal extent of the initial resection. Given the rare nature of the disease, the literature is almost entirely limited to retrospective reviews, but was used in an attempt to determine the impact a routine central neck dissection has on recurrence, survival, and complications in patients being treated for parathyroid carcinoma. Nodal metastases do seem to predict recurrence but not worse survival. However, no clear difference was observed in recurrence or survival based on whether or not a lymph node dissection was performed indicating that there is minimal value in a nodal dissection as a routine procedure in all patients. While the addition of a central neck dissection does not increase rates of vocal cord palsies or hematomas, it does carry a significant risk of permanent hypoparathyroidism. Therefore, because there is no definitive benefit in patients with parathyroid carcinoma, the added risk of a routine central node dissection is not justified for all patients.

Keywords

Parathyroid cancer · Central compartment lymph node dissection · Lymph node metastases · Parathyroidectomy · Neck exploration

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Introduction

Parathyroid carcinoma is rare affecting less than one person per million people, and accounting for merely 0.005% of all malignancies diagnosed in the United States each year [1, 2]. However, the incidence is increasing, and for patients undergoing parathyroidectomy for primary hyperparathyroidism the reported incidence of parathyroid cancer has ranged from 0.5 to 5.3% [1, 3–17]. The treatment for parathyroid carcinoma is primarily surgical, but the optimal extent of resection is controversial. Retrospective reviews have failed to demonstrate a consistent link between lymph node metastases and survival, and as a result, some investigators question whether central neck dissection is necessary in the treatment of patients with parathyroid cancer and clinically negative nodes. A PICO format question, designed to address this controversy, is the focus of the current chapter [18] (Table 17.1). In other words, this chapter aims to review the impact routine central lymph node dissection has on disease recurrence, long-term survival, and complication rates for patients with parathyroid carcinoma.

Current Recommendations

In order to more fully understand the controversy at hand, a general knowledge of the current treatment strategies for parathyroid carcinoma is necessary. Surgery is the mainstay of treatment for patients with parathyroid carcinoma. Chemotherapy has added little to no benefit in terms of disease control, biochemical response, or survival [15, 19–23]. Radiotherapy has also been employed without a clear improvement in outcomes [1, 24–28]. This leaves surgery as the best and only hope for cure in patients with parathyroid cancer. No consensus exists, however, as to the ideal extent of surgery. Certainly, en bloc resection of the tumor keeps with sound oncologic principles and avoids tumor rupture. Furthermore, local excision is more likely to result in positive margins [26]. Unfortunately, many parathyroid cancers are locally excised when the surgeon believes it to be an adenoma and only realizes the tumor was malignant upon receiving the final pathology report. Some retrospective studies have demonstrated a link between the extent of the initial surgery and survival [23, 29], yet others have failed to identify a survival difference based on the initial surgery [1, 3, 5, 20, 24, 26]. Without a clear answer in the literature, prevailing opinions and institutional preferences are considered to be among the main influences determining the extent of the initial surgery [20]. In general, en bloc resection of the tumor with the ipsilateral thyroid, isthmus, involved strap muscles,

Table 17.1 PICO table

Population	Patients with parathyroid carcinoma
Intervention	Routine central lymph node dissection
Comparator	No lymph node dissection
Outcome	Recurrence, survival, and complications

and central lymph node compartment is recommended [2, 14, 28, 30–32]. A modified radical lymph node dissection is not merited as a routine [9, 32, 33]. However, the value of routine central compartment node dissection in patients with clinically negative nodes remains unclear.

Furthermore, the reported prognostic importance of lymph node metastases has varied [1–3, 24–26, 31]. Due at least in part to the paucity of clear prognosticators, the American Joint Committee on Cancer nor the National Comprehensive Cancer Network have developed a staging system for parathyroid cancer. At least two proposed TNM staging systems include lymph node status as a component, but their correlation with recurrence and survival has varied [3, 26, 31, 34]. Neither has been universally adopted. Thus recommendations for the optimal surgical treatment of parathyroid carcinoma remain ambiguous especially concerning the central lymph nodes.

Difficulty in Diagnosis

Regardless of the recommended surgical treatment, proper handling of parathyroid carcinoma requires pre- and intra-operative recognition. An accurate and timely diagnosis may prevent a simple excision as would be the preferred treatment for the majority of benign parathyroid pathology. Imaging is not consistently reliable, and no specific tumor marker exists. Markedly elevated parathyroid hormone and calcium levels may suggest a diagnosis preoperatively. Tumor adherence to surrounding tissue is a helpful sign and may allow proper recognition [28]. Also, parathyroid cancers may be gray and hard. While vocal cord paralysis and a palpable cervical mass in a patient with presumed primary hyperparathyroidism are concerning signs that make a diagnosis of cancer highly likely, the rate of patients presenting with a neck mass is decreasing [6, 8, 20, 23, 27, 33, 35, 36]. Large tumor size is another concerning feature. In one study, carcinomas were 3.8 cm on average compared with 1.7 cm for adenomas or hyperplastic glands ($P = 0.03$) [37]. However, tumor size is also decreasing [1, 37]. Earlier detection of parathyroid cancer with calcium screening and parathyroid hormone assays may be responsible for these trends [8, 35]. There is no question that timely recognition of parathyroid cancer affects the procedure that is ultimately undertaken [2, 20, 25, 28, 29]. Therefore, a high index of suspicion is key in treating patients with hyperparathyroidism so that the appropriate operation is performed.

Current Practice

The very low incidence of parathyroid cancer, the ambiguity of current recommendations, and the difficulty in obtaining a timely diagnosis are reflected in the great variability with which patients are currently being treated. The proportion of patients receiving an en bloc resection as their initial operation has ranged from 5 to 78%, however, population based data indicates this number is actually closer to the lower

end (5–11%) [1, 3, 22, 25, 26, 29, 31, 38]. Although institutional rates of central node dissection vary greatly (Table 17.2), only about a third of patients receive a lymph node evaluation as a part of their initial surgery [1–3, 5, 6, 8, 10, 25, 26, 28, 31, 32, 36]. The rate of node positivity is also quite variable, yet overall, lymph node metastases are an uncommon feature of parathyroid carcinoma. Taken as a whole, lymph node involvement is identified in less than one-sixth of patients with a node dissection. When considering the fact that most patients being treated for parathyroid cancer do not get a nodal evaluation, the rate of known lymph node metastases in all patients is less than 5%, although this value does not capture patients with lymph node metastases who did not get a lymph node dissection at their initial operation (Table 17.2).

Another important consideration involves the trouble in defining parathyroid carcinoma. The definition of parathyroid cancer has not only been difficult to develop but also has changed over time [17, 34, 39]. The validity of findings derived from population-based datasets depends on the accuracy of coding "parathyroid cancer." For example, inclusion of atypical adenomas or parathyromatosis could falsely decrease the overall incidence of lymph node metastases. On the other hand, calculating rates of nodal metastases from a collection of case reports might potentially falsely increase the incidence given that surgeons may be less likely to report early, unremarkable cancers diagnosed and treated appropriately [31].

Overall Outcomes

Despite the discrepancies in what is recommended and what is actually being done, disease specific survival is relatively good at 91–94% at 5 years and 69–90% at 10 years [1, 3, 25]. Because many patients with parathyroid carcinoma do not actually die from tumor burden but from the metabolic effects of hypercalcemia, they may not always get properly coded as having died from parathyroid carcinoma. Overall survival may capture more cancer-specific deaths, but this obviously becomes difficult to distinguish in large datasets. Overall survival has ranged from 78 to 86% at 5 years and 49–70% at 10 years [2, 21, 24, 25, 29]. Recurrence is quite variable, ranging from 33 to 86%, although some of the institutions reporting the higher rates may be influenced by referral bias [15, 19, 21, 22, 24, 29, 31, 38]. Reoperations in the neck for recurrence are common as locoregional recurrence constitutes 58–92% of the overall recurrence rates in larger studies [3, 15, 29, 31, 32].

Complication rates for the treatment of parathyroid carcinoma are also considerable. Nearly 45–60% of patients will experience a complication during their treatment including vocal cord paralysis in 18–38%, temporary hypocalcemia in 22–34%, and permanent hypocalcemia in 5.4% [24, 32]. Perioperative mortality can be as high as 1.8% [24]. Less frequently observed but important perioperative complications include hematoma, jugular venous thrombosis, esophageal injury, fluid collection, and wound infections [24, 32].

Table 17.2 Incidence of lymph node dissections and lymph node metastases in patients with parathyroid carcinoma

Study	Patient population	Total No. of patients	No. (%) of patients with LN dissection	No. of patients with LN metastases	% of patients with LND that have LN metastases	% of all patients that have known LN metastases[a]
Hsu et al. [25]	SEER, 1988–2010	405	114 (28.1)	12	10.5	3.0
Sadler et al. [26]	NCDB, 1998–2011	1022	295 (28.9)	23	7.8	2.3
Villar del Moral et al. [3]	Spain- multicenter 1980–2013	62	20 (32.3)	8	40.0	12.9
Schulteet al. [38]	International- multicenter	82	64 (78.0)	8	12.5	9.8
Schulteet al. [32]	United Kingdom-single institution, 2005–2009	11	11 (100)	1	9.1	9.0
Talat and Schulte [31]	Collection of case reviews, 1961–2009	330	43 (13.0)	27	62.8	8.2
Fernandez-Ranvieret al. [36]	United States- single institution, 1966–2005	28	3 (10.7)	5	100.0	17.9
Iihara et al. [5]	Japan- single institution, 1981–2005	38	22 (57.9)	3	13.6	7.9
Ippolito et al. [8]	France- single institution, 1974–2005	11	7 (63.6)	0	0	0
Lee et al. [1]	SEER, 1988–2003	224	150 (67.0)	9	6.0	4.0
Pelizzo et al. [10]	Italy- single institution, 1980–2000	17	2 (11.8)	0	0	0
Hundahl et al. [2]	NCDB, 1985–1995	286	105 (36.7)	16	15.2	5.6
Cordeiroet al. [28]	Brazil- single institution, 1970–1995	9	2 (18.2)	1	50.0	11.1
Wang andGaz [6]	United States- single institution, 1948–1983	28	4 (14.3)	1	25.0	3.6
Totals[b]		2553	842 (33.0)	114	13.5	4.5

LN Lymph Node, *LND* Lymph Node Dissection, *SEER* Surveillance, Epidemiology and End Results Registry, *NCDB* National Cancer Database

[a]Does not capture patients with LN metastases that did not get a LND

[b]Some patient data may be duplicated in the totals

The impact a central lymph node dissection has on recurrence, survival, and complications becomes difficult to discern especially considering the variations in the treatment of patients with parathyroid cancer. Nevertheless, a careful appraisal of the literature within the context of its limitations is important in order to understand the value of a central compartment node dissection in this disease.

Outcomes with and Without Central Lymph Node Dissection

All available data regarding lymph node dissections in patients with parathyroid carcinoma is retrospective in nature. Given this fact, one might expect a selection bias to be a major determining factor in which patients did and did not get a central lymph node dissection as a component of their operation for parathyroid carcinoma. Perhaps more concerning disease may have alerted the surgeon pre- or intraoperatively to proceed with a more extensive initial operation. However, using population based data to compare patients that did and did not receive a lymph node dissection, Hsu et al. were unable to identify any differences between the two groups in terms of age, gender, diagnostic period, tumor size, the presence of local invasion, or the presence of metastases [25]. Similarly, Talat and Schulte did not observe any difference in pathologic features based on the type of procedure performed [31]. Even though patients receiving and not receiving a central lymph node dissection appear to be similar cohorts in terms of demographics and tumor characteristics, the presence of a significant selection bias cannot be entirely ruled out. Retrospective data does not capture the operating surgeon's thought process, degree of suspicion, or threshold to perform a lymph node dissection. Nor do retrospective databases have variables describing the extent of local invasion or dense adherence to surrounding tissue. Therefore, comparisons between these two groups must be made allowing the possibility that more extensive disease might be clustered in the lymph node dissection group.

Recurrence

Both locoregional and distant recurrence are independent predictors of worse survival in patients with parathyroid carcinoma [3]. Survival worsens as the number of cervical recurrences increases [24]. While it stands to reason that a more extensive initial resection would decrease recurrence, actual reports vary. Many studies show higher recurrence after parathyroidectomy alone compared with en bloc resection [5, 23, 31], but not all [24]. En bloc resection resulted in fewer reoperations (32% versus 65%) when compared with local excision according data from cases gathered by Talat and Schulte [31]. Few studies specifically evaluated the impact of nodal dissection on recurrence. Villar del Moral et al. [3] found that performing a nodal dissection had no discernable effect on disease recurrence in a multicenter review of 62 patients [3]. In their review of 330 case reports, Talat and Schulte [31] did observe higher recurrence at 5 years and overall in patients who did not receive a

systematic lymph node dissection, although this latter group included both patients that received an en bloc resection without a node dissection as well as patients who simply underwent local excision. They suggest that high locoregional recurrence rates in patients following a resection with negative margins may be explained by the presence of occult nodal disease. In comparing patients getting an en bloc resection with or without node dissection, however, the number of reoperations for recurrence appeared similar, possibly indicating that the addition of a lymph node dissection did not decrease recurrence relative to an en bloc resection alone [31]. Additionally, patterns of initial recurrence indicate that recurrence in the cervical lymph nodes occurs infrequently (Table 17.3). For example, in a review of 95 cases of parathyroid cancer, Sandelin et al. [29] observed a recurrence rate of 42% requiring a range of reoperations from 1 to 9 in 36 patients. Lymph node metastases only accounted for three of these initial recurrences with the majority occurring elsewhere in the neck (n = 30) or the lungs (n = 9) [29]. These data suggest that occult nodal disease is not a major contributor to the high recurrence rates experienced by patients with parathyroid carcinoma.

While it does seem that lymph node metastases do predict higher recurrence rates, the evidence is not overwhelming. Unfortunately, population-based data generally lacks reliable recurrence information. In a single institution review of 37 patients, Harari et al. [24] found that lymph node metastases were a significant predictor of recurrence as did Talat and Schulte in their collection of case reports [31]. In a multicenter retrospective review by Villar del Moral et al. [3] nodal metastases were associated with recurrence on univariate analysis but not after controlling for other significant predictors of recurrence [3]. Given that the later review included only eight patients with lymph node metastases compared with the 27 in the review by Talat and Schulte, it seems that Villar del Moral et al. may have lacked the numbers necessary to identify higher recurrence in patients with lymph node metastases [3, 31]. Several even smaller studies have implicated lymph node metastases as a marker for recurrence. Fernandez-Ranvier et al. [36] reported recurrence in 5 out of 5 patients that presented with lymph node metastases [36]. In a review by Iihara et al. [5] 3 of 3 patients with lymph node metastases recurred and eventually died of disease [5]. Schulte et al. [32] found that 1 of 11 patients who underwent lymph node dissections had positive lymph nodes, and this same patient recurred [32].

Overall, lymph node metastases do seem to predict recurrence, yet it remains unclear if nodal disease contributes to the mechanism of recurrence or if it simply serves as a marker for more aggressive biologic behavior. In a review of 11 patients, Schulte et al. [32] found two lymph nodes that contained metastatic parathyroid cancer but only one was distinct from the large inflammatory mass that contained the primary tumor. They also observed that surgeons harvest fewer nodes from the central compartment in lymph node dissections for parathyroid cancer compared to thyroid cancer, and they suggest it may be because the contents of the central compartment were replaced by the tumor itself [32]. Thus, nodal disease likely reflects locoregional spread of disease rather than true lymphatic metastases. Given that the majority of locoregional recurrence does not involve the lymph nodes

Table 17.3 Initial recurrence patterns in patients with parathyroid carcinoma

Study	No. ofpatients, n	Lymph nodedissection, n (%)	Positivenodes, n (%)	Overallrecurrence, n (%)	Locoregional recurrence			Distant recurrence			
					Overall	Cervical	Lymphnodes	Overall	Lung	Bone	Other
Villar del Moralet al. [3]	62	20	8	14 (18.6)	13	10	3	3	0	3	0
Lee et al. [16]	7	NR	NR	1 (14.3)	0	0	0	1	1	0	0
Schulte et al. [32]	11	11	1	1 (9.1)	1	1	0	0	0	0	0
Talat and Schulte[31, 32]	330	43	27	207[a] (62.7)	97	26	19	100	67	16	27
Agarwal et al. [7]	4	NR	NR	3 (75.0)	2	2	1	1	0	0	1
Cordeiro et al. [28]	9	2	1	5 (55.6)	5	5	0	3	3	1	0
Sandelin et al. [29]	95	2	NR	40 (42.1)	–	30	3	–	9	2	0
Wynne et al. [15]	43	NR	NR	29[b] (67.4)	19	–	–	9	2	0	7

NR not reported

[a]Sites of recurrence only known for 166 (80%)

[b]Sites of recurrence only known in 25

(Table 17.3), the role lymphatic dissemination plays in recurrence is questionable. Tumor rupture may result in dissemination throughout the operative field and is likely responsible for many local recurrences [2, 22, 29]. Direct or discontinuous extensions of the cancer may be another mechanism responsible for locoregional recurrence [32]. Vascular invasion is another independent predictor of recurrence and likely a predominant mechanism of cancer dissemination [31, 38]. Hematogenous spread from vascular invasion may explain reports of distant metastases in patients without documented nodal disease. These data, together with the fact that nodal recurrence is uncommon, suggest that lymphatic spread is not a major contributor in the dissemination of parathyroid carcinoma but simply an important marker for recurrence.

Survival

As with recurrence, the available literature is somewhat contradictory regarding the impact of a nodal dissection on survival in patients with parathyroid carcinoma. Villar del Moral et al. [3] found that a lymph node dissection did not affect survival. Similarly, Lee et al. [1] and Sadler et al. [26] using the Surveillance, Epidemiology, and End Results (SEER) registry and National Cancer Database (NCDB), respectively, found that unknown nodal disease did not predict worse survival when compared to patients with known negative nodes [1, 26]. In fact, survival was similar between patients with no nodal dissection and those with known negative nodes after adjusting for other significant predictors of survival [26]. Hsu et al. [25], who also used SEER data, did not find any difference in rates of metastases and death between patients who did and did not have lymph nodes examined [25]. In an earlier NCDB study, Hundhal et al. reported generally similar 5-year overall survival between patients with negative nodes (83.3%) and unknown nodal status (86.7%). In contrast, Talat and Schulte [31] identified the omission of a systematic lymph node dissection as a significant predictor of 5-year mortality but not overall mortality. The reason for the discrepancies between Talat and Schultes' systematic review and population-based data from the United States is not immediately apparent. Talat and Schulte [31] used data from previously published case reports to construct their cohort of 330 cases of parathyroid carcinoma. A lymph node dissection was performed in 13% of the entire cohort, and lymph node metastases were observed in 62% of those undergoing lymph node dissection [31]. This is in contrast to the studies using population based data by Sadler and Hsu which both reported lymph node dissections in about 28%, and rates of nodal metastases nearly one-sixth that reported by Talat and Schulte [25, 26, 31]. In light of their unique method of collecting data, Talat and Schulte [31] suggest that a reporting bias may have skewed their results [31]. While all of the studies may be biased by the nonrandom selection of those who received a central node dissection, similar tumor size and similar rates of local invasion and metastases in the groups with and without lymph node evaluations would argue against a significant selection bias [25].

Even if a lymph node dissection does not have a clear impact on survival, it is important to investigate if lymph node metastases predict worse survival in patients with parathyroid carcinoma. While some investigators found that positive lymph nodes confer worse survival [3, 23, 24, 26, 31] others found this not to be the case [1, 2, 25]. However, due to the infrequency of lymph node metastases, small numbers were an unavoidable limitation in all reports (Table 17.4). The reported hazard ratios comparing mortality in patients with positive lymph nodes to those with known negative nodes ranged from 2.8 to 16.3. In addition to the wide range in risk, the confidence intervals also were quite large indicating the wide variability and imprecision that exists within the literature for this disease [1, 3, 24–26, 31]. This makes it difficult to really indicate the magnitude of risk lymph node metastases have on disease-specific mortality. Taken as a whole, it seems that the presence of lymph node metastases is a marker of more advanced disease and recurrence, but there is not sufficient evidence to consider it a marker of worse survival in all patients presenting with parathyroid cancer. There may be a subset of patients, however, for whom lymph node metastases may confer worse survival. Hsu et al. [25] reported a 7.5 times greater incidence in lymph node metastases in patients with tumors measuring over 3 cm (21% versus 2.8%, $p = 0.02$) [25]. Their findings indicate that it may be possible to identify patients who would be more likely to benefit from the prognostic value of a central neck lymphadenectomy as a component of their initial resection. Besides size, there may be other variables that would aid in the risk stratification of patients who would benefit from a more aggressive resection and allow surgeons to tailor a patient specific approach to the optimal extent of surgery.

Due to the conflicting data regarding the prognostic importance of nodal metastases, attempts to incorporate lymph node status into a staging system are not widely accepted. Lee et al. [1] compared survival based on SEER historic stage and found that unstaged patients (presumably for lack of lymph node or other metastatic data) experienced similar survival to patients with localized disease [1]. Both Shaha and Shah [34] and Talat and Schulte [31] proposed TNM staging systems. In Shaha and Shah's system lymph node metastases equated to stage IIIc [34]. In an attempt to validate Shaha and Shah's system, Talat and Schulte found that higher stages (III and IV) did not reliably correlate with worse survival than lower stages (I and II) where lymph nodes were uninvolved. In light of this, they introduced their own TNM staging system where both lymph node metastases and invasion of vital organs were considered stage III disease [31, 38]. They reported that unstagable patients, often due to lack of a lymph node evaluation, experienced survival worse those assigned stage III but better than stage IV, and suggested that unstaged patients are likely being under treated. In a more simplified risk classification system also developed by Talat and Schulte [31], patients are categorized into low or high risk categories with the presence of lymph node metastases placing patients in the high risk category even in the absence of other prognostic features [31]. In contrast to the findings by Talat and Schulte, Sadler et al. [26], reported that patients with unknown lymph node status experienced survival that was more akin to that seen in Shulte's low risk category. They

Table 17.4 Impact of lymph node metastases on survival in patients with parathyroid carcinoma

Study	Patient population	No. of patients with node dissection	No. of patients with negative nodes	No. of patients with positive nodes	Hazard ratio (95% confidence interval) Positive nodes versus Negative nodes	P
Hsu et al. [25]	SEER, 1988–2010	114	102	12	3.72[a] (0.5–26.4)	0.19
Sadler et al. [26]	NCDB, 1998–2011	295	272	23	6.47[b] (1.8–23.1)	0.004
Villar del Moral et al. [3]	Spain- multicenter1980–2013	20	12	8	16.3[a] (1.7–87.4)	0.01
Harari et al. [24]	United States- single institution, 1966–2009	NR	NR	NR	4.27[b] (1.2–15.3)	<0.05
Talat and Schulte [31]	Collection of case reviews, 1961–2009	43	16	27	6.16[b,c] (0.9–42.9)	<0.01
Lee et al. [1]	SEER, 1988–2003	150	141	9	2.84[b] (NR)	0.23
Koea and Shaw [23]	Collection of case reviews, 1933–1999	NR	NR	10	NR	<0.001

SEER Surveillance Epidemiology and End Results Registry, *NCDB* National Cancer Database, *NR* Not Reported

[a]Risk of disease specific mortality

[b]Risk of overall mortality

[c]Derived from a univariate analysis

suggest that there is insufficient evidence to recommend a prophylactic central node dissection for patients with clinically negative nodes [26]. Because lymph node metastases are not a common feature in patients with parathyroid carcinoma, it is possible that the impact patients with retained occult nodal metastases have on prognosis is negligible within the large cohort of patients without a lymph node evaluation. This further emphasizes the importance of targeting a select high-risk cohort who may benefit from the added node dissection. Taken as a whole however, the population of patients with parathyroid carcinoma and clinically negative nodes stands to benefit very little from a central node dissection. Therefore, in the absence of a therapeutic benefit and with prognostic value limited to predicting recurrence, routine central compartment lymphadenectomy must be considered within the context of its risks.

Complications

Any potential benefit achieved with a central node dissection in patients with parathyroid carcinoma must be carefully weighed against the risk of en bloc resection of the mass alone. There is a general lack of data comparing complications in patients with parathyroid carcinoma receiving en bloc resection with or without central neck dissection, but a relative wealth of retrospective data concerning the risks of a central neck dissection exists in patients with thyroid cancer. Analyzing retrospective data, many investigators have failed to identify a significant difference in vocal cord palsies or hypoparathyroidism based on the addition or omission of a central node dissection in patients receiving thyroidectomies [40–42]. In a comparison of 113 patients receiving a total thyroidectomy to 119 patients receiving a total thyroidectomy with central lymph node dissection reported by So et al. [42], the addition of a node dissection did not significantly increase vocal cord palsies, hematoma, or chyle leaks. Even though their observed rate of permanent hypocalcemia was three times greater in the group that received a lymph node dissection, this difference was not statistically significant [42]. Palestini et al. [43] reported significantly higher rates of transient hypocalcemia in patients who had the addition of a node dissection to their total thyroidectomy, but long term complications were comparable between groups [43]. On the other hand, the first prospective randomized controlled trial comparing central node dissection to its omission in patients with clinically node negative papillary thyroid cancer reported a higher rate of permanent hypoparathyroidism in patients who had the central neck dissection (19.4% versus 8.0%, $p = 0.02$) indicating that routine central node dissections are not without added risk [44]. In patients with thyroid cancer getting a central compartment neck dissection, hypoparathyroidism presumably occurs from the inadvertent removal of one or more inferior parathyroid glands within the nodal tissue. In extrapolating these data to patients with parathyroid carcinoma, it is logical to expect that the risk of permanent hypoparathyroidism is equal or greater. For parathyroid cancer, one gland is already being removed. If another is removed with the nodal dissection, and the others are injured during exploration of the contralateral neck, permanent hypoparathyroidism becomes

a strong possibility. However, this scenario may not occur in all parathyroid cancer cases, depending on preoperative localization studies. Therefore, total thyroidectomy is not universally comparable to operations for parathyroid cancer. Nonetheless, the most abundant data on central neck dissection comes from the thyroid cancer literature.

The risk of a central compartment dissection at the initial surgery must also be weighed within the context of reoperating for nodal disease that might later become apparent either as a recurrence or as progression of occult disease. In a study looking at complications from a central nodal dissection in a reoperative field compared to those from a central node dissection at the initial surgery, Alvarado et al. reported similar rates of vocal cord palsies, hypoparathyroidism, and wound infections [45]. These data indicate that waiting until a patient recurs before removing their central nodes is safe and spares patients who will not recur the added risk at the first operation. Furthermore, because locoregional recurrence and reoperations for such are common in patients with nodal metastases, it is unlikely that removing occult nodal disease at the first operation will spare a cervical reoperation.

Summary

Due to the retrospective nature of all of the available data, there are substantial limitations to the strength of conclusions derived in this chapter. A prospective trial comparing lymph node dissection to no lymph node dissection in patients with parathyroid carcinoma is impractical given the rarity of the disease. Data collaboratives such as the Collaborative Endocrine Surgery Quality Improvement Program will provide more abundant and uniform data on this type of rare endocrine tumor and may help direct future recommendations.

Parathyroid cancer is difficult to recognize partly due to its rare nature and similarity to benign parathyroid pathology. Surgery is the mainstay of therapy and offers the only hope for cure. A timely diagnosis affects the operation performed requiring surgeons to have a high clinical suspicion. The historically recommended operative approach is en bloc resection with adjacent tissues and the ipsilateral thyroid along with the lymph nodes of the central neck. Nodal metastases seem to be an important marker of aggressive biologic behavior and recurrence. Yet even though lymph node metastases predict higher recurrence, positive lymph nodes in parathyroid carcinoma are uncommon occurring in only 13.5% of patients with a lymph node evaluation. Furthermore, the current literature fails to identify a substantial therapeutic benefit of the inclusion of a central node dissection to an en bloc resection for parathyroid carcinoma in terms of disease recurrence or survival. The risk of permanent hypoparathyroidism is increased when a central node dissection is performed, and that risk must be weighed against the anticipated benefit of more extensive surgery. Tumor size is one factor, although there are likely other factors, that may allow surgeons to risk stratify who might benefit from a central node dissection, facilitate patient-specific treatment, and spare low-risk patients an unnecessary procedure.

Recommendations

The following recommendations are rated according to the GRADE format which takes the quality of evidence into account and assigns a grade according to the strength of the recommendation [18].

- Lymph node metastases in parathyroid carcinoma likely predict recurrence but do not definitively predict survival. Given that most patients will be enrolled in surveillance, predicting recurrence is not a sufficient indication for routine central node dissection (evidence quality low; weak recommendation).
- There is not a clear therapeutic benefit to adding a central node dissection to an en bloc resection in patients with clinically node negative parathyroid cancer as a whole, therefore routine central node dissection should not be performed. Certain patient subsets may benefit from central neck dissection, but further study is required to help surgeons risk stratify patients. (evidence quality low; weak recommendation).
- Locoregional recurrence is common and dominated by soft tissue involvement rather than nodal involvement. A central neck dissection performed during a cervical reoperation for recurrence may be performed safely if indicated (evidence quality low; weak recommendation).
- Patients with parathyroid cancers greater than 3 cm are more likely to have lymph node metastases and may benefit from a central node dissection (evidence quality low; weak recommendation).

Conclusions

Parathyroid carcinoma is rare but its incidence is increasing. Although lymph node metastases predict recurrence, nodal involvement is rare and routine central node dissections are not without complications. Furthermore, patients who do not receive a central node dissection as a component of their initial resection seem to have similar recurrence and survival compared with those that do. Subjecting all patients with parathyroid carcinoma to the risks of a routine central node dissection when the available literature cannot identify a therapeutic benefit is not justified. Future investigations may however, identify a more targeted cohort of patients with parathyroid carcinoma for which a central node dissection is indicated.

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