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Local resection versus radical surgery for parathyroid carcinoma: A National Cancer Database analysis

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ABSTRACT

Introduction: Parathyroid carcinoma (PC) is rare and often diagnosed incidentally after local resection (LR) for other indications. Although recommended treatment has traditionally been radical surgery (RS), more recent guidelines suggest that LR alone may be adequate. We sought to further investigate outcomes of RS versus LR for localized PC.

Materials and methods: PC patients from 2004 to 2015 with localized disease were identified from the National Cancer Database, then stratified by surgical therapy: LR or RS. Demographic and clinicopathologic data were compared. Cox proportional hazard models were constructed to estimate associations of variables with overall survival (OS). OS was estimated from time of diagnosis using Kaplan-Meier curves.

Results: A total of 555 patients were included (LR = 522, RS = 33). The groups were comparable aside from LR patients having higher rates of unknown nodal status (66.9% versus 39.4%; p = 0.003). By multivariable analysis, RS did not have a significant association with OS (hazard ratio (HR) = 0.43, 95% confidence interval (95%CI) = 0.10, 1.83; p = 0.255), nor did positive nodal status (HR = 0.66, 95% CI = 0.09, 5.03; p = 0.692) and unknown nodal status (HR = 1.30, 95%CI = 0.78, 2.17; p = 0.311). There was no difference in OS between the LR and RS groups, with median survival not reached by either group at 10 years (median follow-up = 60.4 months; p = 0.20).

Conclusions: There was no difference in OS between LR and RS for localized PC. RS and nodal status may not impact survival as previously identified, and LR should remain a valid initial surgical approach. Future higher-powered studies are necessary to assess the effects of surgical approaches on morbidity and oncologic outcomes.

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Introduction[1]

Parathyroid carcinoma (PC) is a rare malignancy, and its low incidence has resulted in a dearth of evidence-based guidelines for management [1–3]. In addition, it is difficult to diagnose preoperatively in the absence of overt symptoms [4–8]. This presents a unique clinical quagmire for surgeons when final histopathology reveals carcinoma after parathyroidectomy for a presumed benign indication.

Radical surgery (RS), in the form of en bloc resection of the tumor and ipsilateral thyroid, central neck dissection, and often lateral neck dissection, has long been considered the index operation of choice if PC is suspected, or as a second operation after final pathologic evaluation [8]. This recommendation was based on the aggressive nature of PC, lack of effective systemic chemotherapeutic agents, and poor response to radiation [1–3]. However, recent studies have suggested that RS, compared to local resection (LR), may not affect overall survival as much as previously

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postulated [9–12]. The American Association of Endocrine Surgeons guidelines for primary hyperparathyroidism management comment that if PC is encountered, en bloc resection should be performed if necessary to avoid capsular disruption, but prophylactic central or lateral neck dissection should be avoided [13]. Considering the lack of convincing data for or against RS, and the significant morbidity that may be associated with RS, especially in a re-operative setting, the role for RS warrants further evaluation [14,15]. We sought to compare outcomes of LR versus RS for localized PC using a large national database.

Materials and Methods

The National Cancer Database (NCDB) is a large national dataset maintained by the American College of Surgeons and the American Cancer Society. Due to the retrospective, deidentified nature of the data, this study was deemed exempt from review by our institutional review board.

NCDB data was queried for data between January 2004 and December 2015 for the primary site of the parathyroid glands (World Health Organization International Classification of Diseases 3.0.1 topography code 75.0). Patients with histologically confirmed carcinoma of the parathyroid glands (World Health Organization International Classification of Diseases 3.0.1 histology code 8010) treated with surgery were identified. The LR group included patients with surgical extent defined by the NCDB as "total surgical removal of primary site" (NCDB C75.0 site-specific surgery code 40), while RS was defined by the NCDB as "partial or total removal of the primary site WITH a resection in continuity (partial or total removal) with other organs" (NCDB C75.0 site-specific surgery code 60). Patients with distant metastatic disease at time of surgery were excluded (n = 42) as surgeries for these patients were likely palliative. Those with regional lymphatic metastatic disease were not excluded. Patients who received chemotherapy were excluded (n = 55) to avoid confounding due to a small sample size and lack of information regarding indications. Patients with missing follow-up information (n = 38) were excluded as well. The cohort was then stratified into two groups: those who underwent LR and those who underwent RS (Fig. 1).

Demographic and clinicopathologic data were compared between RS and LR groups using two-sample *t*-test, Wilcoxon rank-sum test, chi-square test, or Fisher's exact test where appropriate. Overall survival was estimated from time of diagnosis using Kaplan-Meier curves and compared using log-rank test. Associations of variables with overall survival were analyzed with univariate and multivariable cox proportional hazard models and reported as hazard ratios (HR) with 95% confidence intervals (95% CI). The multivariable model was constructed by purposeful selection using variables whose association with overall survival was measured to be $p < 0.10$ by univariate analysis. Significance was established at $p < 0.05$. Statistical analyses were performed using R version 3.5.1 (R Foundation, Vienna, Austria).

Results

A total of 555 patients were included in our analysis, with 522 in the LR cohort and 33 in the RS cohort. The LR and RS cohorts were comparable in terms of demographics, including age, sex, ethnicity, income, insurance, area of treatment, facility type, and Charlson/Deyo comorbidity index (Table 1). Patients were predominantly white (373 [67.2%]), male (286 [51.5%]), and younger (in years: 18–54 = 229 [41.3%], 55–64 = 156 [28.1%], 65–74 = 110 [19.8%], ≥75 = 60 [10.8%]). The RS cohort was more likely to have known lymph node status (LR = 173 [33.1%], RS = 20 (60.6%); p = 0.003). The proportion of patients receiving radiation therapy were not significantly different between the two groups (LR = 457 [87.5%], RS = 25 [75.8%]; p = 0.063).

Age, ethnicity, income, insurance, Charlson/Deyo score, and pathologic nodal status were identified by the univariate model as variables to be included in the multivariable model (Table 2). By multivariable analysis, age over 75 years (HR 2.87, 95% CI 1.42–5.77; p = 0.003), unknown ethnicity (HR 2.38, 95% CI 1.19–4.74; p = 0.014), government insurance (HR 2.11, 95% CI 1.10–4.06; p = 0.024), and Charlson/Deyo score of 1 (HR 2.12, 95% CI 1.25–3.60; p = 0.005), and Charlson/Deyo score of ≥2 (HR 2.73, 95% CI 1.32–5.67; p = 0.007) were associated with worse survival. RS (HR 0.43, 95% CI 0.10–1.83; p = 0.255), positive nodal status (HR 0.66, 95% CI 0.09–5.03; p = 0.692), and unknown nodal status (HR 1.30, 95% CI 0.78–2.17; p = 0.311) did not have significant associations with overall survival (Table 2). By the Kaplan-Meier method,

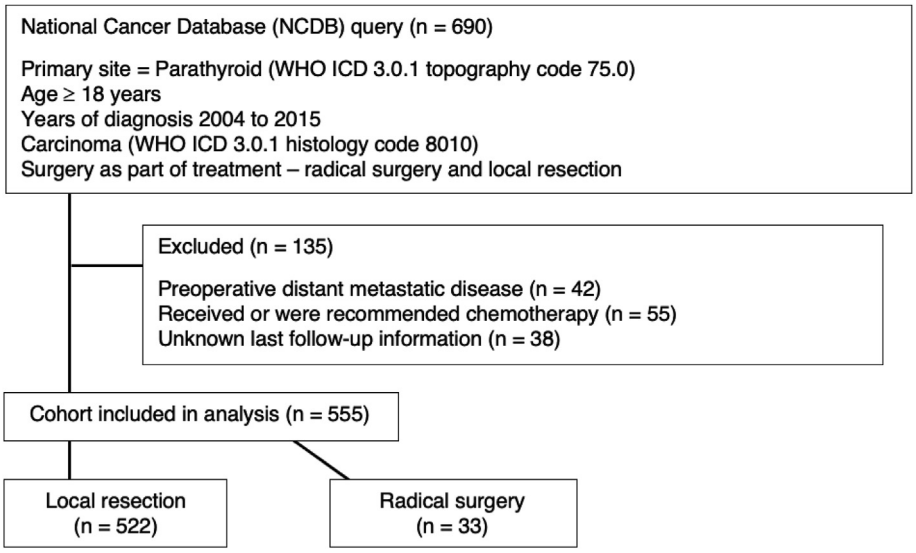

Fig. 1. Data sorting process from National Cancer Database query to final cohort selection. Abbreviations: ICD, International Classification of Diseases; WHO, World Health Organization.

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Table 1
Comparison of demographics and clinicopathologic characteristics between local resection and radical surgery groups.

Characteristic	Variable	Local Resection Total (%) n = 522	Radical Surgery Total (%) n = 33	p-Value
Age	18–54	211 (40.4)	18 (54.5)	0.999
	55–64	148 (28.4)	8 (24.2)	
	65–74	107 (20.5)	3 (9.1)	
	≥75	56 (10.7)	4 (12.1)	
Sex	Female	253 (48.5)	16 (48.5)	0.999
	Male	269 (51.5)	17 (51.5)	
Ethnicity	White	348 (66.7)	25 (75.8)	0.778
	Black	84 (16.1)	6 (18.2)	
	Hispanic	44 (8.4)	1 (3.0)	
	Other	17 (3.3)	0 (0.0)	
	Unknown	29 (5.6)	1 (3.0)	
Year of diagnosis	2004–2007	204 (39.1)	10 (30.3)	0.419
	2008–2011	180 (34.5)	15 (45.5)	
	2012–2015	138 (26.4)	8 (24.2)	
Income	Below median	211 (40.4)	14 (42.4)	0.873
	Above median	309 (59.2)	19 (57.6)	
	Unknown	2 (0.4)	0 (0.0)	
Insurance	Private	262 (50.2)	22 (66.7)	0.151
	Government	209 (40.0)	8 (24.2)	
	None	33 (6.3)	3 (9.1)	
	Unknown	18 (3.4)	0 (0.0)	
Area	Metropolitan	446 (85.4)	26 (78.8)	0.328
	Unknown	8 (1.5)	0 (0.0)	
	Urban/rural	68 (13.0)	7 (21.2)	
Treatment facility	Academic	234 (44.8)	14 (42.4)	0.720
	Community	191 (36.6)	11 (33.3)	
	Other/unknown	97 (18.6)	8 (24.2)	
Charlson/Deyo score	0 (none)	432 (82.8)	27 (81.8)	0.417
	1 (mild)	68 (13)	6 (18.2)	
	≥2 (moderate/severe)	22 (4.2)	0 (0.0)	
Surgical margins	Negative	308 (59.0)	21 (63.6)	0.790
	Positive	104 (19.9)	5 (15.2)	
	Unknown	110 (21.1)	7 (21.2)	
Pathologic nodal status	Negative	163 (31.2)	18 (54.5)	0.003
	Positive	10 (1.9)	2 (6.1)	
	Unknown	349 (66.9)	13 (39.4)	
Radiotherapy	No	65 (12.5)	8 (24.2)	0.063
	Yes	457 (87.5)	25 (75.8)	

there was no difference in overall survival between the LR and RS groups, with median survival not reached by either group at 10 years (median follow-up 60.4 months; p = 0.20) (Fig. 2).

Discussion

In our study, we found no significant difference in overall survival between patients with parathyroid carcinoma treated with LR when compared to RS. To our knowledge, this is the largest study examining the impact of the extent of surgical resection on survival for parathyroid carcinoma.

Current treatment guidelines for the management of PC recommend complete parathyroidectomy with en bloc resection of adherent structure to avoid capsular disruption [1–3,13]. Surgery is considered the cornerstone of treatment as radiotherapy and chemotherapy remain unproven with regards to disease control or survival [1–3,13]. However, RS can cause significant morbidity in the form of recurrent laryngeal nerve palsy and muscular dysfunction of the neck and shoulder [14,15]. Furthermore, the risk of morbidity is increased in a re-operative setting [15]. This is often the case for RS, as many PC patients undergo RS as a second procedure after LR for a presumed benign indication [4–7,15]. PC is associated with its own set of morbidities, namely hypercalcemia and morbidity associated with local invasion, such as dysphagia. However, these conditions are much more likely in patients with advanced disease [16]. Additionally, there is conflicting evidence regarding the role for surgery for the control of hypercalcemia in patients with PC [17,18]. Considering the morbidity associated with RS, and the lack of proven oncologic or disease-specific morbidity benefits, this radical approach is being challenged [19].

Arguments in favor of RS cite locoregional control as the main advantage over a less aggressive surgical approach in terms of extending survival, as locoregional control is intended to control local disease and prevent distant metastases [2,8]. However, there is a growing body of evidence that a less radical approach may be able to achieve locoregional control in certain situations [4,9–13]. Pathologic evidence of locoregional control with LR was shown in one study, where 7 patients were diagnosed with PC on final pathology after LR for benign indications. Of those patients, 6 underwent RS to achieve locoregional control, and none were found to have any residual disease on final pathological evaluation [4]. With regards to preventing distant metastases, this was demonstrated in a retrospective review of 11 patients with PC who were treated with LR. They found that only one out of 11 patients (9.1%) developed metastatic disease during a median follow-up period of 99.6 months [9]. Another study of 75 patients with PC demonstrated no association between extent of resection and rates of distant metastases with a median follow-up period of 77.0 months [11].

More recent research has focused on evaluating surgical approaches by overall survival [2,11]. In a previous NCDB analysis, it was demonstrated that overall survival was improved in patients with PC by any surgical approach, and not specifically by RS, among 733 patients with a median follow-up period of 65.1 months [12]. Most notably, when compared to no surgery by multivariable analysis, RS had a higher HR for death than both complete tumor removal and incomplete tumor removal. However, they included

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Table 2
Univariate and multivariable Cox proportional hazards model analysis of selected patient variables and their associations with overall survival.

Characteristic	Variable	Univariate analysis		Multivariable analysis	
		HR (95% CI)	p-Value	HR (95% CI)	p-Value
Treatment group	Local resection	–	–	–	–
	Radical surgery	0.38 (0.09, 1.54)	0.174	0.43 (0.10, 1.83)	0.255
Age	18–54	–	–	–	–
	55–64	1.13 (0.59, 2.13)	0.721	1.15 (0.60, 2.20)	0.682
	65–74	2.32 (1.33, 4.08)	0.003	1.43 (0.73, 2.80)	0.295
	≥75	4.85 (2.76, 8.60)	<0.001	2.87 (1.42, 5.77)	0.003
Ethnicity	White	–	–	–	–
	Black	1.79 (1.07, 3.00)	0.026	1.65 (0.94, 2.88)	0.079
	Hispanic	0.87 (0.35, 2.17)	0.762	0.80 (0.31, 2.07)	0.639
	Other	0.93 (0.23, 3.85)	0.927	1.01 (0.24, 4.24)	0.989
	Unknown	2.44 (1.24, 4.78)	0.010	2.38 (1.19, 4.74)	0.014
Income	Below median	–	–	–	–
	Above median	0.66 (0.43, 0.99)	0.046	0.71 (0.46, 1.09)	0.119
	Unknown	0.00 (0.00, Inf)	0.995	0.00 (0.00, Inf)	0.994
Insurance	Private	–	–	–	–
	Government	3.67 (2.29, 5.91)	<0.001	2.11 (1.10, 4.06)	0.024
	None	1.36 (0.41, 4.52)	0.616	1.30 (0.37, 4.51)	0.680
	Unknown	1.90 (0.57, 6.29)	0.298	1.96 (0.56, 6.84)	0.289
Charlson/Deyo score	0 (none)	–	–	–	–
	1 (mild)	2.18 (1.32, 3.62)	0.002	2.12 (1.25, 3.60)	0.005
	≥2 (moderate/severe)	4.62 (2.29, 9.39)	<0.001	2.73 (1.32, 5.67)	0.007
Pathologic nodal status	Negative	–	–	–	–
	Positive	0.66 (0.09, 4.95)	0.691	0.66 (0.09, 5.03)	0.692
	Unknown	1.79 (1.09, 2.91)	0.020	1.30 (0.78, 2.17)	0.311
Sex	Female	–	–		
	Male	1.07 (0.71, 1.63)	0.724		
Year of diagnosis	2004–2007	–	–		
	2008–2011	0.99 (0.61, 1.61)	0.964		
	2012–2015	0.61 (0.25, 1.51)	0.290		
Area	Metropolitan	–	–		
	Unknown	1.01 (0.14, 7.27)	0.994		
	Urban/rural	0.95 (0.49, 1.84)	0.884		
Treatment facility	Academic	–	–		
	Community	0.90 (0.58, 1.41)	0.657		
	Other/unknown	0.61 (0.32, 1.16)	0.132		
Surgical margins	Negative	–	–		
	Positive	0.79 (0.44, 1.42)	0.424		
	Unknown	1.00 (0.60, 1.65)	0.991		
Radiotherapy	No	–	–		
	Yes	0.72 (0.36, 1.43)	0.350		

HR, hazard ratio; Inf, infinity.

patients with metastatic disease, which precluded making any conclusions about LR for localized PC. Finally, a study of patients in California with PC analyzed a total of 136 patients, 60 of whom were treated with LR, 58 with RS, and 18 with LR followed by RS. Overall survival did not differ between groups, nor did rates of disease-related complications, over a median follow-up period of 63.6 months [10]. All of these results, including our study, challenge the belief that RS is superior to LR in preventing metastatic disease and improving survival.

The NCDB captures more than 70% of incident cancer cases in the United States every year and is continuously audited for accuracy. Despite this, there are several limitations to this study inherent to the nature of the database. The retrospective nature of the study is subject to selection and misclassification bias. There is no information on recurrence or disease specific survival, nor is there information regarding surgeries prior to the procedure classified as each patient's definitive surgery. Morbidity data is lacking in the dataset, including information regarding emergency department visits, hospital admissions, calcium levels, or complications related to local invasion. Data regarding whether surgeries involved debulking to prevent or address aerodigestive complications are also lacking in the dataset. However, these types of surgeries are most often palliative and performed in very advanced cases where metastatic disease is present – a subset of patients that we did not include in our study [16,20]. Coding of surgical procedures provided sufficient detail to distinguish local resection from radical surgery, but further information regarding extent of lymphadenectomy, specific adjacent organs removed, and dissection planes was not available. Calcium-related morbidity could not be evaluated due to limitations of the database, including hypercalcemic crisis events and development of chronic renal failure directly attributed to hypercalcemia.

Conclusions

Extent of surgery did not impact overall survival (OS) in patients with localized parathyroid carcinoma in our study. We propose that patients who are found to have parathyroid carcinoma after undergoing LR for a presumed benign indication may be safely and closely monitored for recurrence, rather than be committed to the morbidity of RS. This affirms current guidelines that recommend against routine ipsilateral thyroidectomy and lymphadenectomy. Studies addressing parathyroid carcinoma disease-specific morbidity are required to further clarify the role of LR compared to RS.

The National Cancer Database (NCDB) is a joint project of the Commission on Cancer of the American College of Surgeons and the American Cancer Society. The NCDB includes approximately 70% of

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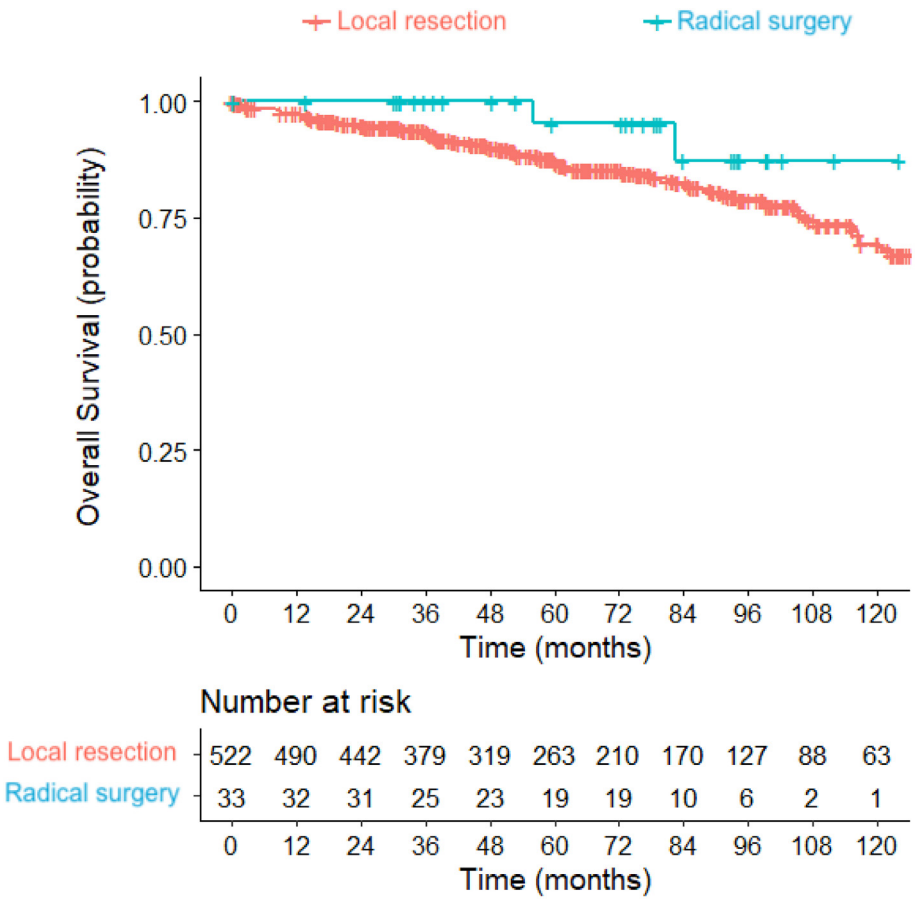

Fig. 2. Kaplan-Meier curves of overall survival for local resection (LR) versus radical surgery (RS) groups extended to 10 years. Median survival not reached by either group at 10 years, with median follow-up time of 60.4 months. Logrank test: p = 0.20.

incident cancer cases in the United States. The Commission on Cancer's NCDB and the hospitals participating in the Commission on Cancer's NCDB are the source of the de-identified data used herein; they have not verified and are not responsible for the statistical validity of the data analysis or the conclusions derived by the authors.

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CRediT authorship contribution statement

Shravan Leonard-Murali: Conceptualization, Methodology, Data acquisition, Quality control of data and algorithms, Formal analysis, and interpretation, Statistical analysis, Writing – original draft, Writing – review &; editing, Manuscript review. **Tommy Ivanics:** Conceptualization, Data acquisition, Formal analysis, and interpretation, Writing – review &; editing, Manuscript review. **David S. Kwon:** Conceptualization, Methodology, Data acquisition, Quality control of data and algorithms, Formal analysis, and interpretation, Writing – original draft, Writing – review &; editing, Manuscript review. **Xiaoxia Han:** Methodology, Quality control of data and algorithms, Formal analysis, and interpretation, Statistical analysis. **Christopher P. Steffes:** Data acquisition, Writing – review &; editing, Manuscript review. **Rupen Shah:** Writing – review &; editing, Manuscript review.

Declaration of competing interest

David S. Kwon is a paid consultant for Ethicon, Inc. This affiliation did not represent a conflict of interest. The authors have no other disclosures to report.

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