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A Single Institution Experience with Papillary Thyroid Cancer: Are Outcomes Better at Comprehensive Cancer Centers?

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Abstract

Introduction: Papillary thyroid cancer (PTC) is the most common form of thyroid cancer. Although the survival rate is excellent, recurrence is as high as 20%. The mainstay of therapy is thyroidectomy and lymph node dissection based on risk factors. Data from other cancers suggest that surgical outcomes are most optimal at comprehensive cancer centers. We hypothesize that patients with PTC who had their initial operation at a comprehensive cancer center would have a better oncologic outcome.

Methods: We utilized an IRB-approved cancer care registry database of patients with thyroid cancer who were seen at our institution between 2000 and 2018. Patient records were updated with cancer-specific outcomes including recurrence and need for re-intervention. Clinical and surgical outcomes were then compared between patients who had their initial operation at a comprehensive cancer center (CCC group, n=503) versus those who did not (non-CCC group, n=72).

Results: Mean patient age was 49 ± 16 years and 70% were female. Average tumor size was 1.6 ± 1.6 cm. There was no difference in tumor size, age, gender or race between groups. Pre-operative ultrasound was more frequently performed at the CCC (89%) than at non-CCC's (51%, $p < 0.001$). CCC patients were more likely to undergo initial total thyroidectomies compared to non-CCC patients (76% vs. 21%, $p < 0.001$). Positive surgical margins were more frequently found in patients at non-CCC's (19%) than at the CCC (9.7%, $p = 0.016$). Finally, CCC patients

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Authors' contributions

All authors made substantial contributions to study conception and design, interpretation of data, and drafting and revising of the article. H. Chen was responsible for study conception, interpretation of data, and data quality control. Z. Aryanpour was primarily responsible for writing the manuscript and data analysis.

Disclosure

The authors report no proprietary or commercial interest in any product mentioned or concept discussed in this article.

had a significantly lower cancer recurrence rate (5.0% vs. 37.5%, p <0.001). Therefore, the need for additional cancer operations was much greater in patients who had initial thyroid surgery at non-CCC (31.9% vs. 1.4%, p < 0.001).

Conclusions: Patients with PTC who have their initial thyroidectomy at non-CCC have higher recurrence rates, higher rates of positive tumor margins on pathology, and increased need for additional operations. These data suggest that patients who have their initial procedure at a CCC for PTC have better long-term outcomes.

Keywords

Papillary thyroid cancer; surgery outcomes; comprehensive cancer center; NCI

Introduction

The incidence of thyroid cancer has increased over the past three decades.[1–3] Thyroid cancers are classified as one of four main pathological subtypes: papillary, follicular, medullary and anaplastic.[4–6] Of these subtypes the most common is papillary thyroid cancer (PTC), which also carries the best prognosis. Although the five-year survival rate for PTC is almost 100%, the recurrence rate is as high as 20%.[7, 8] Management of patients with PTC most often includes surgery and/or radioactive iodine therapy. Recently, the relationship between hospital patient volume and surgical mortality outcomes has been under investigation. Multiple studies have shown an inverse relationship between hospital volume and surgical mortality[9–13], some have shown that oncologic outcomes may be better at Comprehensive Cancer Centers[14, 15], and there is evidence showing that admissions to these types of hospitals for thyroidectomies specifically result in shorter lengths-of-stay and lower cost overall.[16] Under the National Cancer Institute (NCI), 71 hospitals across the United States are NCI-Designated Cancer Centers, with 51 being classified Comprehensive Cancer Centers (CCC).[17] The purpose of this study is to examine the differences in surgical outcomes, such as recurrence rates and need for additional operations, between patients who had surgery for their PTC at either a designated CCC or not. We hypothesize that patients who had their initial PTC surgery at a CCC will have better surgical and oncologic outcomes than those who had their initial surgeries at non-CCC.

Methods:

Patient population and setting

The University of Alabama at Birmingham is a tertiary referral center and NCI-designated Comprehensive Cancer Center in Birmingham, Alabama. We utilized a retrospectively collected thyroid cancer database that was approved by the UAB Institutional Review Board. The thyroid cancer database included information from patients with various types of thyroid cancer who were evaluated at our institution from the years 2000 to 2018. Patient population and setting information is summarized in Table I. From this database, we identified 575 patients with pathologically confirmed PTC, with 503 of these patients having their initial PTC surgery at our institution and 72 who had their initial PTC surgery elsewhere.

Among the 72 patients who had their index operation elsewhere, 23 patients had completion thyroidectomy at our institution and 49 patients underwent non-operative active surveillance. Of these 49 non-CCC patients being followed, 27 patients developed locoregional disease progression/recurrence and 22 patients did not. In the absence of thyroglobulin levels, disease progression/recurrence was defined as cytopathologic confirmation of PTC on ultrasound-guided FNA biopsy of radiographically suspicious lymph nodes in a majority of patients and was denoted after excision in a small minority of patients presenting with structural disease (5%). Independent review of patient charts for images and/or radiologic reports was done to assess for the presence of both central and lateral neck pre-operative ultrasound in both patient groups. Patients included in our study were seen at our institution for PTC surveillance every 6–12 months. The mean duration to recurrence was 26 months.

Statistical analysis

Patient records were reviewed and demographic, pre- and post-operative clinical characteristics, and oncologic outcomes were recorded. Statistical analyses were performed using t-test, Chi-Square, and ANOVA as appropriate. Outcomes were compared between patients who had their initial operation at a comprehensive cancer center (CCC group) versus those who did not (non-CCC group). These characteristics and outcomes included significance of other variables such as: performance of pre-operative ultrasound of both the central and lateral neck, initial thyroid surgery type (total vs. subtotal), positive-margins on surgical pathology, cancer recurrence, and need for additional PTC operations on institution-based outcomes. All analyses were conducted with SPSS Statistics (IBM Corp. Released 2019. IBM SPSS Statistics for Windows, Version 26.0. Armonk, NY: IBM Corp.).

Results

Patient demographics are summarized in Table II. Mean patient age was 49 ± 16 years and 70% were female. Average tumor size was 1.6 ± 1.6 cm. There was no difference in tumor size, age, gender, or race between the two groups. The average time to recurrence for CCC (n = 25) and n-CCC (n = 27) patients was 845 days (2.3 years) and 771 days (2.1 years), respectively and was not significant different between groups (t=0.005, p=0.713). All PTC variants were included in the final analysis with a breakdown as follows: 71% classic PTC, 24% follicular variant PTC, and 5% other variant PTC. There were no differences in PTC variant types between the two groups ($p > 0.05$). The statistical power of the study for both groups with a group ratio of 7 and a significance of 0.05 was 80%.

The univariate differences in pre-operative characteristics and post-operative outcomes between the two groups are depicted in Table III. The multivariate result was significant for primary operation site, Pillai's trace = 0.252, $F(4, 567) = 47.84$, $p < .0005$. Pre-operative ultrasound of both the central and lateral neck was performed more frequently in CCC patients (89%) than non-CCC patients (51%, $p < 0.001$). CCC patients were more likely to undergo total thyroidectomies at their index operation compared to non-CCC patients (76% vs. 21%; $p < 0.001$).

Oncologic outcomes were significantly different between the two groups. Positive margins on surgical pathology were found more frequently in patients at non-CCC (19%) than at the

CCC (9.7%, p = 0.016). Importantly, CCC patients had a significantly lower recurrence rate (5.0% vs. 37.5%, p <0.001). Therefore, the need for additional cancer operations was much greater in patients who had initial thyroid surgery at non-CCC facilities (31.9% vs. 1.4%, p < 0.001).

Discussion

To our knowledge, this exploratory study is one of the first to analyze papillary thyroid cancer outcomes based on institution type in terms of NCI comprehensive cancer care center (CCC) designation or not. These data suggest that patients with PTC who had their initial thyroid surgeries at non-CCC are less likely to have pre-operative ultrasounds of both the central and lateral neck, have higher recurrence rates, higher rates of positive tumor margins on pathology, and increased need for additional operations. Conversely, patients who had their initial thyroid surgeries at CCC are more likely to have pre-operative ultrasound of both the central and lateral neck, have less recurrence rates, less rates of positive tumor margins on pathology, and overall a decreased need for reoperation compared to their non-CCC counterparts. These data support our hypothesis that patients who had an initial operation for PTC at a CCC have overall better surgical and oncologic outcomes.

The NCI may designate a hospital as a Cancer Center, a Comprehensive Cancer Center, or a Basic Laboratory Cancer Center. The distinction between the former two is a superior commitment to research with an emphasis on multi-disciplinary collaboration.[17] Comprehensive cancer centers (CCCs) also generally see a higher number of patients, have more specialist physicians, and have more resources and funding than non-comprehensive cancer centers (non-CCCs).[18] Our NCI-designated Comprehensive Cancer Center is a major hub for cancer research and collaboration in the southeast, with state-of-the-art facilities, extensive NIH funding, and a heavy focus on bench to bedside research in the clinical, laboratory, and population settings. These are the characteristics that allow NCI-designation as CCC, and our institution fulfills these requirements.

In attempting to generalize our findings to apply to all CCCs, it is important to note that there are a multitude of possibilities as to why these characteristics allow for better surgical outcomes in cancer treatment, and they are likely multifactorial. As previously stated, some of the core benchmarks in NCI accreditation as a CCC include significant NIH funding and dedication to research, both of which our institution has fulfilled. However, there is no specific requirement by the NCI in designating a center as an advanced thyroid cancer facility. At the current time, extensive funding and research may be the only arbitrary measures of determining an institution’s scope of quality care, and further research may be warranted to determine which quality care measures an institution must meet to qualify as a destination for thyroid cancer care specifically (i.e., adherence to national guidelines). This is one factor that limits the generalizability of our findings to our own institution and not to CCCs nationwide. Perhaps more resources and high-class facilities allow for better surgical training, or there is more reliance on interdisciplinary care and thyroid tumor board discussion at CCCs, or CCCs are under more national scrutiny so there is a more strict compliance with guidelines, or another reason that is not the primary question of our study. Regardless of the reason, these are the characteristics shared by all NCI-designated CCCs,

and our institution is no exception. Further analysis may help to uncover what practices or factors present at CCC's lead to these better outcomes and a thorough understanding of these factors may inform future practice guidelines that can improve patient outcomes beyond CCCs.

Based on discussion on outcomes from the surgeons, patients are often given the choice whether to proceed with a total thyroidectomy (TT) or a thyroid lobectomy in the appropriate clinical setting based on tumor size and presence of high-risk features[20]. In our study, patients who had their initial PTC surgery at a CCC were more likely to proceed with TT compared to PTC patients at non-CCC. We postulate that the differences in approach to TT vs. lobectomy in CCCs vs. n-CCCs are due to regional or hospital-specific protocols or how the surgeons counsel the patients regarding outcomes based on extent of surgery. In terms of the increased rates of TT in lieu of lobectomy at our institution, this may apply to CCCs across the country or uniquely to our center. As being the only CCC and one of three level 1 trauma centers in a state that is historically medically underserved, our CCC may face obstacles that others do not. Low rates of health literacy may lead to many patients being lost to follow-up, and hypothetically these patients may not pursue post-operative or follow-up care that may cause them to be unaware of progressive disease until they re-appear with inoperable recurrence. This may be a reason or confounder as to why our institution or even CCCs in general tend to approach TT more frequently than lobectomy so as to avoid this theoretical risk with loss of surveillance.

Pre-operative ultrasound of both the central and lateral neck was more frequently performed at CCCs than at non-CCCs. This may reflect access to resources or a difference in standard procedures across different hospitals, specifically in adherence to guidelines in CCCs vs. non-CCCs. There is evidence that there is little variation between guideline practices at NCI-designated CCCs compared to their low-volume counterparts.[21] In the assessment and screening of thyroid cancer, the American Thyroid Association recently added recommendations for lateral neck ultrasound in addition to traditional central neck screening.[22] The lower rates of both central and lateral neck pre-operative ultrasound in the non-CCC group may reflect a difference in adherence to ever-changing practice guidelines, as CCCs may be under more pressure to stay up to date than their counterparts. The CCCs also have well trained radiologists who are able to inform the surgeons on the risk of malignancy based on ultrasound characteristics more consistently. In our study, patients who had initial PTC surgery at non-CCCs also had positive margins more often on original surgical pathology. This may be due to differences in approach and expertise of the performing surgeons. Patients who had initial PTC surgery at a CCC had less recurrent disease and therefore less need for reoperation. This may also be due to the fact that CCCs have a higher patient and case volume of PTC as well as greater access to multidisciplinary care with increased resource availability.[23]

Our study has several limitations that warrant discussion. Primarily, better surgical PTC outcomes at CCCs may only apply to our home CCC and not CCCs nationwide. This is likely due to referral and selection bias in the non-CCC cohort: patients who came to our facility after having their primary operation somewhere else may have been actively seeking out a tertiary care center or specifically a CCC. Patients referred to our center may have

also had certain prognostic features that ultimately led them to our center. Additionally, this referral bias may have allowed a significant number of patients who had adequate and equivalent care elsewhere who ultimately did not need remedial care to be unaccounted for, and without knowing the scope of this group our conclusions may not be causal. Future directions that mitigate this issue would include a set of patients that were initially treated at a non-CCC and not referred for follow-up to more accurately address the generalizable role of CCCs in PTC outcomes, and this would likely entail use of a modified dataset of papillary thyroid cancer patients from the National Cancer Database (NCDB) and/or Surveillance Epidemiology and End Results (SEER) database. Secondly, the retrospective nature of our analysis may miss a true causal conclusion. Thirdly, time distribution of the cases may influence the recurrence rate in that patients with recent surgery may not have had time to recur. Fourthly, the lack of thyroglobulin levels in our cohort may be underestimating the actual rates of recurrence, which should be accounted for in future prospective studies as a more accurate indication of disease progression or recurrence. And finally, although no statistical differences were found between demographics of the patient groups, confounders that were not presently evaluated may be present, thus distorting the significance of our findings.

Conclusion

In conclusion, patients with PTC who had their initial thyroid surgeries at non-CCC are less likely to have pre-operative ultrasounds, have higher recurrence rates, higher rates of positive tumor margins on pathology, and increased need for additional operations. Patients who had their initial thyroid surgeries for PTC at CCC are more likely to have a decreased need for reoperation compared to their non-CCC counterparts and ultimately better long-term outcomes.

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Key messages

- PTC, the most common form of thyroid cancer, has an excellent prognosis but a high recurrence rate
- Patients with PTC who have their thyroid surgery at an NCI-designated comprehensive cancer center have lower recurrence rates, less need for additional operations, and less positive margins on surgical pathology
- Patients with PTC are more likely to have better surgical outcomes at high volume comprehensive cancer care centers than their low-volume counterparts

Table I.

Patient population and setting

	CCC* (n)	N-CCC* (n)
Followed only	**471** [a]	**22**
Followed + recurrence	**25**	**27**
Needed re-operation	**7**	**23**
Total	**503**	**72**

[a] All CCC patients for "followed only" is after index operation at our institution

* CCC = Comprehensive Cancer Center

* N-CCC = non-CCC

Table II.

Patient demographics

	CCC* (n)	N-CCC* (n)	Full sample (N)
Age[a] (years)	**49 ± 16**	**50 ± 16**	**49 ± 16**
Race			
African-American	**65** (12.9%)	**4** (5.6%)	**69** (12%)
White	**337** (67%)	**52** (72.2%)	**389** (67.7%)
Asian	**9** (1.8%)	**1** (1.4%)	**10** (1.7%)
Other	**92** (18.3%)	**15** (20.8%)	**107** (18.6%)
Gender			
Female	**351** (69.8%)	**50** (69.4%)	**401** (69.7%)
Male	**152** (30.2%)	**22** (30.6%)	**174** (30.3%)
Total	**503** (100%)	**72** (100%)	**575** (100%)
Tumor size	**1.6 ± 1.6 cm.**	**1.6 ± 1.5 cm.**	**1.6 ± 1.6 cm.**

[a]Standard error of the mean = 0.029

*CCC = Comprehensive Cancer Center

*N-CCC = non-CCC

Table III.

Comparison of pre-operative & post-operative outcomes between the 2 groups

	CCC*	N-CCC*	P-Value
Pre-operative Ultrasound Performed	89%	51%	< 0.001
Total thyroidectomy as initial surgery	76%	21%	< 0.001
Positive margins on surgical pathology	10%	19%	0.016
Cancer recurrence	5%	37%	< 0.001
Additional operations needed	1.4%	32%	< 0.001

* CCC = Comprehensive Cancer Center

* N-CCC = non-CCC