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ORIGINAL ARTICLE – ENDOCRINE TUMORS

Well-Differentiated Thyroid Cancer: Who Should Get Postoperative Radiation?

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ABSTRACT

Background. The mainstay of treatment of well-differentiated thyroid cancer (WDTC) is surgery followed by adjuvant radioactive iodine therapy. Postoperative radiation therapy (PORT) is rarely used.

Objective. The aim of our study was to report our experience of patients with WDTC who were selected to receive PORT.

Materials and Methods. After Institutional Review Board approval, patients who received PORT were identified from a departmental database of 6259 patients with WDTC treated with primary surgery from 1986 to 2015. We carried out propensity matching to compare outcomes with a cohort of patients who did not receive PORT. The main outcome of interest was central neck recurrence-free probability (CNRFP), while secondary outcomes were lateral neck recurrence-free probability (LNRFP), disease-specific survival (DSS), and overall survival (OS).

Results. From 6259 patients, 32 (0.5%) patients with a median age of 65.2 years received PORT. Tall-cell variant papillary thyroid carcinoma was the most common pathology (45%). Patients who received PORT had no difference in CNRFP compared with patients treated without PORT (10-year CNRFP 88% vs. 73%; $p = 0.18$). Furthermore, patients who received PORT had superior LNRFP (10-year LNRFP 100% vs. 62%; $p = 0.001$) compared with the no-PORT cohort. Despite this, patients who received PORT had similar DSS (71% PORT vs. 75% no-PORT) and OS (65% PORT vs. 58% no-PORT group) as the no-PORT cohort.

Conclusions. Our data show that select patients who received PORT had improved locoregional recurrence-free probability; however, this did not translate into improved DSS and OS. At our institution, we recommend the use of PORT only in highly selected patients with locally advanced primary tumors who are deemed to have a high risk of central neck recurrence for which salvage surgery would result in unacceptable risk to the airway.

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The incidence of differentiated thyroid cancer is increasing worldwide. Every year in the US alone more than 64,000 new cases are diagnosed and the increase is mostly attributable to papillary thyroid cancer.[1] This dramatic increase in early-stage thyroid cancer is largely due to improved early diagnosis.[2] However, the incidence of stage IV thyroid cancer is also increasing. Differentiated thyroid cancer is treated surgically by lobectomy or total thyroidectomy with or without neck dissection.[3] Postoperative radioactive iodine (RAI) therapy is administered to select patients in the intermediate-risk group and nearly all patients in the high-risk group according to the recommendations of the American Thyriod Association (ATA) or other similar guidelines.[4]

External-beam radiotherapy (EBRT) is rarely utilized in the management of patients with well-differentiated thyroid cancer (WDTC), with publications typically from single institutions.[5,6] National Comprehensive Cancer

Network (NCCN) guidelines recommend that EBRT should be considered for unresectable disease or gross residual tumor after surgical resection.[7] These indications apply mainly to patients with locally advanced primary thyroid tumors with invasion of surrounding structures such as the larynx, trachea, or esophagus. In these cases, positive margins, microscopic residual disease, or gross residual disease may be present. Often patients with positive margins and microscopic residual disease can be managed with RAI or observation. Patients with gross residual disease after surgery are relatively uncommon as the vast majority of patients with differentiated thyroid cancer present with surgically resectable disease. EBRT is therefore rarely indicated in the management of patients with WDTC. The decision to use EBRT must always be weighed against the potential adverse effects and long-term sequela of treatment, including swallowing and speech problems as a result of radiation to the central compartment neck structures. This is why EBRT is rarely administered in patients with microscopic positive margins, relying on RAI to achieve local control with the avoidance of toxicity from EBRT. Consequently, there are no prospective randomized trials comparing the use of EBRT with other options, such as surgical salvage, observation, or RAI treatment. Existing literature from retrospective data report conflicting results, with some reporting no improvement in outcome whereas others report EBRT prolongs recurrence-free survival and even disease-specific survival (DSS) of patients with advanced thyroid cancer.[8] However, these studies contained a heterogeneous cohort of patients that included not only patients who had EBRT performed after surgery (PORT) but also patients who had EBRT as palliative treatment for inoperable recurrence. The radiation dose used in these studies also varied. In addition, these studies included patients with mixed histology and included poorly differentiated thyroid cancer as well as WDTC.

The aim of our study was to report our experience of patients with WDTC managed with surgery followed by postoperative radiation therapy (PORT). The primary outcomes we were interested in were central neck recurrence-free probability (CNRFP) and impact on survival. We carried out propensity matching using a cohort of patients with similar clinical and pathological characteristics who did not receive PORT to oncological outcomes.

MATERIALS AND METHODS

Patients included in this study were selected from our existing database of 6259 patients with WDTC primarily treated with surgery by our service between 1986 and 2015. The study was approved by the Institutional Review Board at our center.

Of the entire database, only 32 (0.5%) patients received PORT. Most patients in this group received PORT due to incomplete tumor resection or microscopic positive margins in high-risk areas of the central neck. Patients were pathologically staged according to the 8th Edition of the American Joint Committee on Cancer (AJCC).

Propensity Matching

Statistical analysis was performed using R version 3.6.2 (The R Foundation for Statistical Computing, Vienna, Austria). To select the control group of patients who did not receive PORT in order to compare with the patients treated with PORT, we specified age, sex, histology type, and TNM stage as our propensity score matching criteria. The R package 'MatchIt' and 'optmatch' were used at a 1:1 ratio, as the the most precise match pairs are achieved using 1:1 matching, not with 1:2 or 1:3 matching.[9,10] Optimal matching finds the matched samples with the smallest average absolute distance across all matched pairs. The Pearson Chi-square test or Fisher's exact test were used for the comparison of categorical covariates between the two groups, and Student's *t*-test was used for comparison of the continuous variable age.

Outcomes Analysis

The main outcome of interest was CNRFP, which includes thyroid bed and level VI node recurrences. We analyzed secondary outcomes, including lateral neck recurrence-free probability (LNRFP), distant recurrence-free probability (DRFP), DSS, and overall survival (OS). Cumulative incidence function was used to compare CNRFP, LNRFP and DRFP, with death as a competing risk, and a Gray's test was performed to compare the groups. The Kaplan–Meier method was used to compare the remaining outcomes and a log-rank test was performed to compare the two groups. All local and regional recurrences were structural biopsy-proven recurrences. Thyroglobulin data were not available for these cases and thus biochemical recurrence was not recorded. The follow-up interval was calculated in months from the date of initial surgery. A *p*-value of <0.05 was considered statistically significant.

RESULTS

Clinical and Pathological Characteristics of the Postoperative Radiation Therapy (PORT) Group

The clinical and pathological characteristics of the selected patients are shown in Table 1. The median age of

TABLE 1 Patient and histologic characteristics of patients treated with PORT compared with a propensity matched cohort of patients who did not receive PORT

Characteristics	PORT [$n = 32$]	No PORT [$n = 32$]	p value
Age, years (SD)	65.2 (SD 11.3)	60.1 (SD 18.8)	0.32
Female	9 (28)	10 (31)	0.79
Male	23 (72)	22 (69)	
Histology			
PTC classical variant	6 (19)	3 (9)	0.57
PTC follicular variant	2 (6)	0 (0)	
Hurthle cell carcinoma	3 (9)	4 (13)	
PTC unknown	7 (22)	9 (28)	
Tall cell variant	14 (44)	16 (50)	
T-stage			
T1a	1 (3)	0 (0)	0.63
T3a	2 (6)	5 (16)	
T3b	1 (3)	0 (0)	
T4a	25 (78)	25 (78)	
T4b	3 (9)	2 (6)	
N-stage			
N0a	3 (9)	3 (9)	0.63
N0b	3 (9)	3 (9)	
N1a	10 (31)	9 (28)	
N1b	16 (50)	17 (53)	
M-stage			
0	30 (94)	28 (87)	0.71
1	2 (6)	4 (13)	
ETE			
Strap muscles	26 (81)	30 (94)	0.87
Esophagus	11 (34)	14 (44)	
Trachea	19 (59)	17 (53)	
Recurrent laryngeal nerve	19 (59)	19 (59)	
Larynx	6 (19)	10 (31)	
RAI therapy			
Yes	21 (66)	26 (81)	0.16
No	11 (34)	6 (19)	
Margins			
Negative	10 (31)	10 (31)	0.78
Positive	20 (63)	17 (53)	
Extent of thyroid surgery			
Total thyroidectomy	25	29	0.26
Completion thyroidectomy	6	3	
Neck dissection			
No	7	10	0.22
Central	8	4	
Lateral	7	3	
Lateral and central	10	15	

Data are expressed as n (%) unless otherwise specified

PTC papillary thyroid cancer, *PORT* postoperative radiotherapy, *ETE* extrathyroid extension, *RAI* radioactive iodine, *SD* standard deviation the patients receiving PORT was 65.2 years (range 34.7–83.7 years) and the majority of cases were male ($n = 23$, 72%). Aggressive types of WDTC were prevalent in this group of patients; 14 (44%) patients had tall cell variant papillary thyroid carcinoma (PTC) and 3 (9%) patients had Hurthle cell carcinoma. Twenty six patients (81%) had a primary tumor invading strap muscles, and 29 (91%) additionally invaded adjacent structures such as the trachea, larynx, recurrent laryngeal nerves, and esophagus. One case (3%) had gross residual disease, while the remaining patients had microscopic positive margins in high-risk areas of the central neck. Metastases to regional lymph nodes in the central and lateral neck were present in 26 patients (81%). The majority of cases (66%) had RAI therapy, with a median dose of 193 mCi (interquartile range 144–216) (electronic supplementary Table 1).

The median time from surgery to PORT was 3.2 months (range 0.9–8.4 months), and patients received PORT with a median dose of 62 Gy (range 50–70 Gy). The central and lateral necks were included in the target volume in 25 patients (76%), thyroid bed with central neck in four patients (12%), and in four cases (12%) the radiation fields were unknown (electronic supplementary Table 2).

Clinical and Pathological Characteristics of the Propensity Matched No-PORT Group

We achieved similar clinical and pathologic characteristics of the matched cohort (Table 1). The median age was 60.1 years (range 25.5–91.3 years), with males being the most common sex (69%). There were no significant differences in age, sex, histology, TNM stage, RAI and extrathyroidal extension (ETE) between the PORT and no-PORT groups. In addition, there was no significant difference in the positive margin rate or extent of initial surgery between groups. In the matched control group obtained using optimal matching, the absolute standardized difference ranged from 0.069 to 0.471.

Central Neck and Lateral Neck Recurrence-Free Probability

The median follow-up of the PORT group was 91.7 months (range 7–281 months), and 90.6 months (range 12–385 months) for the control no-PORT group. Patients treated with PORT had no difference in CNRFP compared with patients treated without PORT (10-year CNRFP 88% vs. 73%; Grays's test $p = 0.18$) (Fig. 1a). The PORT group had three local recurrences and no central neck nodal recurrences, compared with the matched no-PORT group, where three local and four central neck nodal recurrences occurred.

Patients treated with PORT had superior LNRFP compared with patients treated without PORT (10-year LNRFP 100% vs. 62%; Grays's test $p = 0.001$) (Fig. 1b). In the PORT group, no patients had a lateral neck recurrence, compared with nine in the no-PORT group. The majority of patients (76%) in the PORT group had the lateral neck included in the target field for RT. Univariate analysis showed that the PORT group had a hazard ratio (HR) of 0.227 (95% confidence interval 0.042–1.221; $p = 0.0232$) compared with the matched control group.

Disease-Specific and Overall Survival

To determine if the improved LNRFP translated into improved survival, we compared DSS and OS between the groups. Thirty deaths were recorded in both groups, 13 of which were disease-specific.

There was no difference in OS between the groups (OS: 5- and 10-year OS was 87.8% and 64.8% for the PORT group compared with 71.1% and 57.8% for the no-PORT group, respectively; $p = 0.41$) [electronic supplementary Fig. 1]. Furthermore, there was no difference in DSS between the groups (DSS: 5- and 10-year DSS was 89.7% and 71% for the PORT group compared with 80.6% and 75.2% for the no-PORT group, respectively; $p = 0.88$) (Fig. 1c).

Distant Recurrence-Free Probability

To determine if the lack of improved DSS in the PORT group was due to poorer DRFP, we compared the DRFP between the groups. There was no difference in DRFP (10-year DRFP 70% vs. 65%; Grays's test $p = 0.65$) (Fig. 1d). In those patients who received PORT, eight developed distant metastasis during the follow-up period compared with six patients in the no-PORT group.

Salvage Treatment in Patients Treated Without PORT

We next analyzed the treatment of recurrence in patients who did not receive PORT in comparison with patients who did receive PORT (details are shown in Table 2). Of 11 recurrences, two (18%) were local, two (18%) were central with lateral neck node, and seven (64%) were lateral neck node recurrences. Of those patients who did not receive PORT, six (55%) with recurrence were able to be treated with surgery; two had a bilateral neck dissection, three had a lateral neck dissection, and one had a central neck dissection. Of the remaining five patients, three had observation only, due to distant metastasis or concurrent diseases preventing safe surgery, and two patients were treated with RAI. The detailed characteristics of each patient with recurrence are given in Table 3. The ability to salvage a significant portion of recurrences explains the similar OS and DSS in the PORT and no-PORT groups.

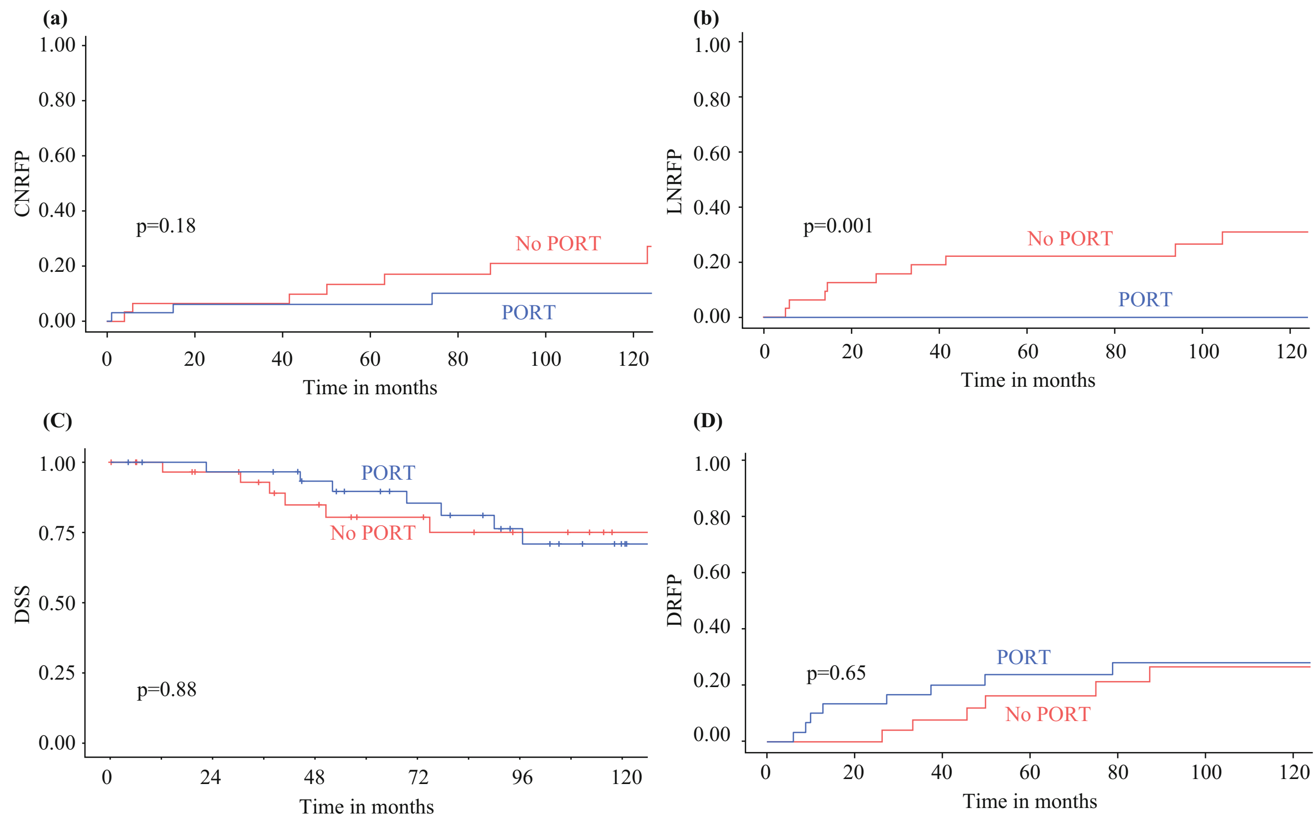

FIG. 1 Estimated cumulative incidence curves with death as a competing factor of **A** central local recurrence-free probability, **B** lateral neck recurrence-free probability, and **D** distant recurrence-free probability, and Kaplan–Meier curves of (**C**) disease-specific survival. *CNRFP* central neck recurrence-free probability, *LNRFP* lateral neck recurrence-free probability, *DRFP* distant recurrence-free probability, *DSS* disease-specific survival, *PORT* postoperative radiotherapy

TABLE 2 Treatment of locoregional recurrences

Characteristic	PORT [$n = 3$]	No PORT [$n = 11$]	p value
Recurrence type			0.06
Only local	3 (100)	2 (18)	
Central/local with lateral neck node	0	6 (55)	
Only lateral neck node	0	3 (27)	
Treatment			0.06
Surgery	0	6 (55)	
RAI	1 (33)	2 (18)	
RT	1 (33)	0	
Chemotherapy	1 (33)	0	
Observation	0	3 (27)	
Surgery type	NA		NA
Bilateral neck		2 (33)	
Lateral neck		3 (50)	
Central neck		1 (17)	

Data are expressed as n (%)

PORT postoperative radiotherapy, *NA* not available, *RAI* radioactive iodine, *RT* radiation therapy

TABLE 3 Clinical and pathologic characteristics of patients with locoregional recurrence from the no-PORT and PORT groups

No.	Age, years	Sex	pTNM	Histology	Recurrence type	Treatment	Distant metastasis
No-PORT group							
1	91.3	Male	T4aN1aM0	PTC: Tall cell variant	Lateral neck	LND	No
2	51.2	Male	T4aN1bM0	PTC: Tall cell variant	Central + lateral neck	CND+LND	Lung
3	82.0	Male	T4aN1bM0	PTC: Tall cell variant	Lateral neck	Obs	Lung
4	60.7	Male	T4aN1bM0	PTC	Lateral neck	LND	No
5	57.3	Male	T4aN1bM0	PTC: Tall cell variant	Central + lateral neck	CND+LND	Lung, bone
6	31.0	Female	T4aN1aM0	PTC	Local + lateral neck	RAI	No
7	54.5	Male	T4aN1bM0	PTC: Tall cell variant	Central + lateral neck	CND+LND	Bone
8	76.2	Female	T4aN1bM1	PTC: Tall cell variant	Central + lateral neck	RAI	Lung
9	75.7	Female	T4bN1bM0	PTC: Tall cell variant	Central + lateral neck	CND+LND	Lung
10	78.5	Female	T4aN1aM0	PTC: Tall cell variant	Local	Obs	Lung
11	66.8	Male	T4aN1aM0	PTC: Tall cell variant	Local	Obs (died of other cause)	No
PORT group							
1	76.2	Male	T4bN1bM0	Hurthle cell carcinoma	Local	Chemotherapy	Lung
2	65.2	Male	T4bN1bM0	PTC: Tall cell variant	Local	RT (palliative)	No
3	48.7	Female	T4aN1bM1	PTC: Tall cell variant	Local	RT (palliative)	No

LND lateral neck dissection, *CND* central neck dissection, *Obs* observation only, *RAI* radioactive iodine therapy, *PTC* papillary thyroid cancer, *PORT* postoperative radiotherapy, *RT* radiation therapy

TABLE 4 Early and late toxicities of PORT[a] (CTCAE v.5)

Toxicity	Acute [*n* (%)]	Late [*n* (%)]
Dermatitis		
Grade 1–2	22 (71)	1 (3)
Grade 3–4	1 (3)	0
Mucositis		
Grade 1–2	28 (90)	0
Grade 3–4	1 (3)	0
Xerostomia		
Grade 1–2	30 (97)	20 (65)
Grade 3–4	0	0
Dysphagia		
Grade 1–2	27 (87)	13 (42)
Grade 3–4	3 (10)	2 (6)
Fatigue		
Grade 1–2	24 (77)	6 (19)
Grade 3	0	0
PEG	3 (10)	2 (6)
Tracheostomy	1 (3)	0

CTCAE common terminology criteria for adverse events, *PEG* percutaneous endoscopic gastrostomy

[a]Toxicity information was available for 31 patients

Toxicity of Radiation Treatment

Adverse effects from PORT are shown in Table 4. Data on toxicity were available for 31 patients. The majority of patients experienced grade 1–2 mucositis, xerostomia, and dermatitis. Grade 3–4 toxicities were rare—one case each of dermatitis and mucositis and three cases of dysphagia. Three patients (10%) required placement of the feeding tube during RT and one patient (3%) had a tracheostomy due to severe laryngeal congestion. Two patients (6%) required feeding tube placement in a late post-RT period.

DISCUSSION

The use of EBRT in patients with WDTC is a very controversial topic with scarce published research and no prospective randomized clinical data. All existing papers have only a small number of patients, with a mixture of well and poorly differentiated pathology and comprising patients managed by surgery with PORT and also those treated with palliative RT without surgery. For example, a recently published paper by Samhouri et al.[5] included a group of patients with diverse pathology, including medullary and anaplastic thyroid cancers. The study included EBRT administered both as PORT and also for metastatic cancer sites. Some earlier published studies excluded anaplastic thyroid cancers, focusing on differentiated thyroid cancer, and they also included medullary thyroid cancers.[11] Medullary thyroid cancers are a specific pathological entity that should be studied in separate trials. Another paper published by Romesser et al. excluded both anaplastic and medullary thyroid cancers, concentrating on PTC and follicular thyroid carcinoma (FTC), but at least half of the patients were classified as having poorly differentiated thyroid cancers.[12] That study also included patients with gross residual disease after surgery and also patients who did not have surgery because of unresectable disease. Conventional radiation techniques as well as intensity-modulated radiation therapy (IMRT) were reported. Beckham et al. reported on a more homogenous group of patients treated only with IMRT and only patients with PTC and FTC;[13] however, that study still included unresectable disease at the time of presentation and those with unresectable recurrence in the cohort. Therefore, the current literature that includes this heterogeneity in histology and radiation indications makes it difficult to interpret the results of these studies and make any meaningful recommendations for PORT treatment in patients with WDTC.

PORT is rarely administered in patients with WDTC because surgery is considered to be safe and effective as a salvage procedure. This is especially true for salvage of lateral neck recurrence, which is usually achievable with a neck dissection with limited morbidity. Recurrence in the central neck, either due to local thyroid bed recurrence or paratracheal lymph node recurrence, is much more challenging. Surgical salvage carries increased risk in the central neck with possible injury to the recurrent laryngeal nerves and of permanent hypoparathyroidism. Surgical treatment of central neck recurrence may also require tracheal resection, laryngectomy, or even pharyngectomy and esophagectomy, resulting in diminished quality of life.[14] Therefore, the site of possible recurrence will dramatically influence the surgeons' decision to recommend PORT. Early series reported recurrence in the central neck as the most common reason of death in the management of DTC.[15,16] However, due to improvements in surgery and the appropriate use of PORT, failure in the central neck with subsequent death is now quite rare. Nowadays, most deaths occur due to distant metastatic disease.[17]

Papers investigating the role of PORT usually use local and/or locoregional recurrence probability as the main outcome of interest;[5,18,19] however, using only local recurrence-free probability underestimates failure in the central neck due to central neck node recurrences. In addition, locoregional recurrence-free probability includes both lateral and central neck recurrence.[13] Since control of the central neck is the most important aspect in patients with locally advanced thyroid cancer, we used CNRFP as our primary endpoint, as this includes both the local thyroid bed and also level VI node recurrences.

The decision to use PORT also results in local toxicity, with detrimental effects on speech and especially on swallowing.[20] Schuck et al. reported an increased rate of skin, mucosal, and salivary toxicity, and many patients experienced difficulty with swallowing. Although the toxicity markedly decreased 100 days after EBRT, a substantial number of patients still had salivary gland and swallowing issues. Similar results were reported by Shugard et al., with around one-third of patients receiving PORT reporting grade 2 dermatitis, mucositis, and xerostomia. Moreover, at 90 days post RT, 10–17% of cases still had symptoms of dysphagia and xerostomia.[21]

In our study, we report that patients selected to receive PORT had improved LNRFP compared with a propensity-matched no-PORT control group. At the same time, there was no difference in CNRFP. This may be due to the small number of cases and limited number of central neck recurrences. A larger dataset would be necessary to show the potential difference. Despite improved locoregional-free recurrence probability, this did not translate into improved OS and DSS compared with the propensity matched cohort of patients who did not receive PORT. We postulated that one possible explanation for the similar survival outcomes could be poorer DRFP in the PORT group. For this reason, we compared DRFP in each group. In fact, there was no significant difference between groups, which suggests that despite poorer locoregional recurrence-free probability, patients treated with surgery without PORT were able to be salvaged. In the propensity matched group, 11 patients had recurrence, of whom 55% were salvaged surgically and 27% of cases were managed with observation alone. This successful salvage treatment explains the similar survival outcomes in the two groups.

At our institution, the decision to treat patients with PORT is highly selective and involves a multidisciplinary team (MDT) decision. In general, PORT is only administered if the surgeon believes that there is a high risk of central neck recurrence for which salvage surgery is associated with a significant risk of RLN sacrifice, tracheal resection, or laryngectomy. In the majority of patients, surgical salvage is favored if possible. The rationale to favor surgical salvage is mainly due to the presumed toxicity of radiation. In the past, parallel opposed field radiation, and later three-dimensional (3D) conformal radiation encompassing the central and lateral neck from the hyoid bone to the mediastinum, were traditionally used. Such a wide field resulted in severe toxicity with regard to swallowing and speech dysfunction;[11,22] however, nowadays it is possible to deliver more accurate and focused fields using IMRT. It is possible to spare the lateral neck, deliver less radiation to the pharyngeal constrictor muscles, and spare the submandibular gland function focusing only on the areas of high-risk of recurrence.[11] This results in a better adverse effect profile.[11,19,23,24] Therefore, one may argue that with present-day technology, a greater number of patients at risk for central neck recurrence may benefit from PORT and spare them future surgical salvage procedures. Another important factor is the patients' preferences, which should be considered with a clear explanation of the different possible outcomes and the possible adverse effects of each treatment option. The possible indolent course of the disease should also be weighed against the possible toxicity of PORT. Lastly, other factors such as advanced age, extensive previous surgery, and the presence of distant disease also play an important role in the decision to administer PORT.

We recognize that our study has limitations due to its retrospective nature and that the data were from a single institution. We were limited by the fraction of patients who received PORT from this large cohort of patients with differentiated thyroid cancer. Moreover, our cohort received several different types of PORT techniques, including two-dimensional (2D; 2 cases), 3D conformal, and IMRT, over a span of several decades. Additionally, 11 patients did not receive RAI. These factors could impact outcomes, although in our cohort the difference between the PORT and no-PORT groups, based on some of the mentioned parameters, did not show significant difference. The strength of the study is that participants were selected from a large cohort of well-documented patients with differentiated thyroid cancer treated within the same comprehensive cancer center with a uniform institutional philosophy. Using our large database has allowed us to identify only patients with WDTC who received PORT, and allowed us to exclude patients with poorly differentiated or anaplastic thyroid cancer and also patients with unresectable disease treated without surgery. Given the lack of any prospective randomized trial, we believe the use of propensity matching allows more meaningful conclusions to be achieved for the use of PORT in these patients.

CONCLUSION

The decision to treat patients with PORT is highly selective and requires a comprehensive MDT discussion, taking into account patient preferences. Our data show that select patients who received PORT had improved locoregional recurrence-free probability with an acceptable adverse effect profile from radiation. At our institution, we recommend the use of PORT in highly selected patients who undergo surgery for locally advanced primary tumors (T4a) and/or significant central nodal disease and who have a high risk of central neck recurrence in whom surgical salvage is deemed to be unattractive due to unacceptable risks to the airway.

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