RESEARCH

Postoperative external beam radiotherapy for locoregional control in iodine refractory differentiated thyroid cancer

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Abstract

Background: The role of postoperative external beam radiotherapy (EBRT) in patients with residual iodine refractory-differentiated thyroid cancer (IR-DTC) is still inconclusive. The aim of this retrospective study was to evaluate locoregional control (LRC) and overall survival (OS), and potential side effects after postoperative EBRT for both microscopic and macroscopic non-radically reseted, locally advanced IR-DTC.
Methods: Between 1990 and 2016, 49 patients with locally advanced IR-DTC received EBRT for microscopic (R1; *n* = 28) or macroscopic (R2; *n* = 21) locoregional residual disease. For more insight into the added effect of EBRT, we performed an intrapatient sub-analysis in 32 patients who had undergone more than 1 surgical intervention, comparing LRC after primary, curative-intended surgery with LRC after repeated surgery plus EBRT. To estimate LRC and OS, we used Kaplan–Meier curves. From 2007 onward, we prospectively recorded toxicity data in our head and neck cancer database (*n* = 10).
Results: LRC rates 5 years after EBRT were higher for R1 (84.3%) than for R2 (44.9%) residual disease (*P* = 0.016). The 5-year OS rate after EBRT was 72.1% for R1 and 33.1% for R2 disease (*P* = 0.003). In the intrapatient analysis (*n* = 32), LRC rates were 6.3% 5 years after only initial surgery and 77.9% after repeated surgery with EBRT (*P* < 0.001). Acute toxicity was limited to grade I and II xerostomia, mucositis, and hoarseness; only one patient developed late grade III dysphagia.
Conclusions: Postoperative EBRT is associated with long-lasting LRC and OS with acceptable toxicity in patients with locally advanced IR-DTC, especially in microscopic residual disease.

Introduction

Patients with differentiated thyroid cancer (DTC) commonly have a good prognosis, with 10-year survival rates of 80–95% ([1]). In 10–20% of the patients, recurrences occur within 5 years after initial surgical treatment followed by radioactive iodine (^{131}I) and thyroid-stimulating hormone suppression therapy ([2], [3], [4]).

However, 15–33% of DTC patients have a primary iodine refractory-differentiated thyroid cancer (IR-DTC) or develop IR-DTC after several sessions of ^{131}I therapy ([5], [6], [7], [8]), as defined in the American Thyroid Association (ATA) guidelines ([4]). The ineffectiveness of ^{131}I therapy is related to a loss of iodine uptake or sodium iodide symporter

expression and activation of the mitogen-activated protein kinase pathway (8, 9). IR-DTC is commonly correlated with advanced disease, a high tumor burden, and multiple metastases along with a less-differentiated tumor state (6).

The value of external beam radiotherapy (EBRT) has been studied mainly in locally advanced DTC, but not specifically evaluated in IR-DTC patients (10, 11, 12, 13, 14). The ATA Guidelines recommend surgery combined with ^{131}I and/or EBRT for unresectable DTC involving the upper aerodigestive tract (4). However, the indications for EBRT remain inconsistent because of some contradictory results (15, 16, 17, 18, 19), especially in cases involving microscopic residual (R1) disease. Though prospective data are lacking, recent retrospective studies have reported beneficial effects of EBRT on selected patients (20, 21, 22). Based on these results, EBRT after final incomplete resections of IR-DTC may offer locoregional control (LRC) and probably overall survival (OS), although radiation-related morbidity after extensive repeated surgery will probably influence the quality of life (23).

The aim of this study was to evaluate LRC and OS after postoperative EBRT for both microscopic and macroscopic non-radically resected, locally advanced IR-DTC and to assess the potential side effects.

Materials and methods

Between January 1990 and October 2016, in our tertiary referral center, we included 49 patients who had locally advanced IR-DTC and had received postoperative EBRT for LRC of residual disease. The IR-DTC patients were divided according to the four categories in the ATA guidelines: (i) the malignant/metastatic tissue does not ever concentrate radioiodine (no uptake outside the thyroid bed at the first diagnostic or therapeutic whole body scan); (ii) the tumor tissue loses the ability to concentrate radioiodine after previous evidence of RAI-avid disease (in the absence of stable iodine contamination); (iii) radioiodine is concentrated in some lesions but not in others; (iv) metastatic disease progresses despite significant concentration of radioiodine (4). Next, we used the Charlson Comorbidity Index (CCI) score, which predicts long-term survival in patients with multiple comorbidities based on patients' disease status and past medical history (24).

Adequate initial surgery consisted of total thyroidectomy en bloc with resection of infiltrated surrounding structures (strap muscles, jugular vein, esophageal external muscular wall, or pretracheal fascia) and modified or radical lymph node dissection when indicated. A subset of 35 patients underwent more than 1 surgical intervention. As the dates of initial surgery were missing for 3 patients, we performed an intrapatient analysis among 32 patients, comparing the LRC after curative-intended surgery with LRC after revision surgery plus EBRT to get more insight into the added effect of EBRT. We performed this study according to national Dutch guidelines at the time of inclusion. Based on the design of the study, the Institutional Review Board waived approval.

Staging and pathologic findings

To determine the extent of the disease at the time of initial presentation and restaging, we used the tumor node metastases (TNM) according to the eighth edition of the American Joint Committee on Cancer for DTC (25). Local tumor extension and distant metastases were recorded before radiation based on 18F-fluorodeoxyglucose PET (18F-FDG-PET) and MRI scans, also used for targeting tumor volume. Re-examination of the resected specimens by an experienced pathologist (BvH) confirmed our pathological findings. Pathologic radicality of the final resection was defined as R1 if microscopic tumor was present at the resection margins and as R2 if macroscopic tumor remained.

Radiotherapy

The indication for postoperative EBRT in all patients was decided after discussion in the institutional multidisciplinary tumor board. Until 2008, EBRT was delivered with 3D-conformal radiotherapy (3D-CRT; $n = 26$), using six MegaVoltage photon beams from three different directions (one anterior field and two bilateral fields) to focus precisely on the tumor, while avoiding the healthy surrounding tissue. From 2008 onward, intensity-modulated radiotherapy (IMRT; $n = 23$) with seven-field equidistant non-opposing beams was used. IMRT patients were treated with a simultaneous integrated boost technique, by delivery of different dose levels to different target volumes within a single treatment fraction. After R1 resection or extranodal spread, the surgical bed was treated to a total dose of 52.8 Gy in 33 fractions of 1.6 Gy with a simultaneous integrated boost to the high-risk areas up to 66 Gy, in fractions of 2 Gy. In cases with R2 resections, we treated the surgical bed to 54.25 Gy in fractions of 1.55 Gy. The boost dose to the macroscopic residual disease was

70 Gy in fractions of 2 Gy. No additional elective radiation therapy was applied to the neck or upper mediastinum.

Follow-up

Patients received regular follow-up with serum thyroglobulin measurement, clinical examination, US and CT/MRI, and/or 18F-FDG-PET/CT upon clinical suspicion. Progression of locoregional disease was defined as any increase in size of residual tumor and/or suspected regional nodal metastases, usually confirmed by cytohistological examination. Suspicious radiographic lesions outside the cervical neck and upper mediastinum were defined as distant metastases. LRC and OS were determined from the end of radiotherapy until progression of locoregional disease and until death or last follow-up, respectively.

Toxicity

Baseline, early (6-12 weeks), and late (>12 weeks) radiation-induced side effects were assessed regularly in a standardized head and neck follow-up program. From 2007 onward, toxicity data of all DTC patients referred for EBRT were prospectively recorded according to the RTOG/EORTC Radiation Morbidity Scoring Criteria (26), using the head and neck cancer module (EORTC QLQ-H&N35).

Statistics

Clinical endpoints were LRC and OS. Kaplan–Meier estimates were performed for survival, and the log-rank test used to compare survival curves. Comparisons between cohorts were performed using the chi-square test or Fisher's exact test; medians were compared using the Mann–Whitney U test. A P-value <0.05 was considered as statistically significant. Statistical analyses were performed using IBM SPSS for Windows version 26 (SPSS Inc.).

Results

Patient and treatment data

Patient and tumor characteristics are given in Table 1. Mean age was 66.7 years (s.d., 12.4), with a median CCI of 5 (interquartile range (IQR), 4–7) and median follow-up of 45 (IQR, 25–79) months after EBRT. Microscopic residual disease was present in 28 patients (57.1%), and macroscopic residual disease was present in 21 patients (42.9%). At the time of radiation, 27 patients (55.1%) had synchronous regional metastases and 14 patients (28.6%) had distant metastases. Extrathyroidal extension was present in 29 patients (59.2%).

Table 1 Patient and tumor characteristics.

Patient characteristics	All patients (*n* = 49)	Patients with microscopic residue (*n* = 28)	Patients with macroscopic residue (*n* = 21)	*P*-value
Female	29 (59.2%)	17 (60.7%)	12 (57.1%)	
Male	20 (40.8%)	11 (39.3%)	9 (42.9%)	1.000
Age (years, mean with s.d.)[a]	66.7 (12.4)	66.9 (15.7)	66.5 (9.4)	0.424
CCI score (median with IQR)[a]	5 (4–7)	5 (4–7)	6 (3.5–6.5)	0.812
Follow-up (months, median with IQR)[a]	45.2 (24.7–79.2)	60.4 (33.0–98.6)	30.9 (16.0–52.3)	0.008[a]
TNM[b]				
T1-3b	18 (36.7%)	10 (35.7%)	8 (38.1%)	
T4a/b	29 (59.2%)	16 (57.1%)	13 (61.9%)	
Tx	2 (4.1%)	2 (7.1%)	0 (0.0%)	0.457
N0 (a/b)	22 (44.9%)	10 (35.7%)	12 (57.1%)	
N1 (a/b)	27 (55.1)	18 (64.3%)	9 (42.9%)	0.158
M0	35 (71.4%)	19 (67.9)	16 (76.2%)	
M1	14 (28.6%)	9 (32.1%)	5 (23.8%)	0.750
Pathology				
Papillary	29 (59.2%)	15 (53.6%)	14 (66.7%)	
Follicular	20 (40.8%)	13 (46.4%)	7 (33.3%)	0.394
IR category				
I	7 (14.3%)	2 (7.1%)	5 (23.8)	
II	23 (46.9%)	14 (50.0%)	9 (42.9%)	
III	13 (26.5%)	10 (35.7%)	3 (14.3%)	
IV	6 (12.2%)	2 (7.1%)	4 (19.0%)	0.139

[a]Age, CCI score, and follow-up calculated at the start of EBRT. [b]Eighth tumor node metastases classification at initial treatment.
CCI, Charlson comorbidity index; IQR, interquartile range; IR, iodine refractory.

Except for the duration of follow-up, there were no significant differences between the groups with microscopic and macroscopic residual disease (Table 1). In all patients, treatment consisted of one or more surgical procedures (1–5), with additional ^{131}I ablation (Table 2). Fourteen patients received EBRT after primary extensive surgical treatment, and 35 patients after ≥2 surgical procedures. EBRT was delivered with a median dose of 66 (IQR, 60–70) Gy and a median of 33 (IQR, 31–35) fractions. IMRT was applied in 23 patients (46.9%) and 3D-CRT in 26 patients (53.1%).

Clinical endpoints

Locoregional control

All patients Locoregional relapse was detected in 13 patients (26.5%) at a median of 29 months (IQR, 9–42) after EBRT. 1-, 5-, and 10-year LRC rates were 91.2, 71.0, and 59.2%, respectively, for the whole population. Persistent LRC with the appearance of distant metastases outside the radiation field was present in 20 patients.

Patients with R1 vs R2 resection 1-, 5- and 10-year LRC rates were 92.7, 84.3, and 75.8% for R1 residual disease, and 88.8, 44.9, and 22.4% for R2 residual disease, respectively ($P = 0.016$; Fig. 1A).

Intrapatient analysis; surgery vs repeated surgery plus EBRT The effect of EBRT on LRC was further analyzed in an intrapatient subset analysis ($n = 32$). 1-, 5-, and 10-year LRC rates were 59.4, 6.3, and 3.1% after initial surgery, and 93.3, 77.9, and 62.3% after repeated surgery (≥2) plus EBRT, respectively ($P < 0.001$; Fig. 1B). One patient after initial surgery and ten patients after repeated surgery (≥2) had non-resectable macroscopic disease. Comparable results were found when the same intrapatient subset analysis was performed in patients with only microscopic disease ($n = 22$). 1-, 5-, and 10-year LRC rates were 59.1, 4.5, and 4.5% after initial surgery, and 90.9, 80.7, and 71.8% after repeated surgery (≥2) plus EBRT, respectively ($P < 0.001$; Supplementary Fig. 1, see section on supplementary materials given at the end of this article).

Overall survival

All patients 1-, 5-, and 10-year OS rates after EBRT were 87.8, 56.7, and 25.3%, respectively, for the whole population.

Patients with R1 vs R2 resection 1-, 5-, and 10-year OS rates were 92.9, 72.1, and 36.1% in the R1 group, and 81.0, 33.1, and 8.3% in the R2 group ($P = 0.003$; Fig. 1C), respectively.

Table 2 Treatment characteristics.

Characteristic	*n* (%), *n* = 49
Surgery	
Total thyroidectomy	49 (100.0%)
Lymph node dissection	42 (85.7%)
Concomitant	17 (34.7%)
Additional	25 (51.0%)
Microscopic residual disease	28 (57.1%)
Macroscopic residual disease	21 (42.9%)
Total surgical interventions	
1	14 (28.6%)
2	16 (32.7%)
≥3	19 (38.7%)
Radioactive iodine	
Number of ablations (median with IQR)	3 (2–3)
Cumulative activity (MBq, median with IQR)	12,950 (11,100–16,650)
EBRT	
Total dose (Gy, median with IQR)	66 (60–70)
Fractions (median with IQR)	33 (31–35)
IMRT	23 (46.9%)
3D-CRT	26 (53.1%)
Systemic therapy, TKI	3 (6.1%)

Gy, gray; IMRT, intensity-modulated radiotherapy; IQR, interquartile range; MBq, megabecquerel; TKI, tyrosine kinase inhibitor; 3D-CRT, 3D-conformal radiotherapy.
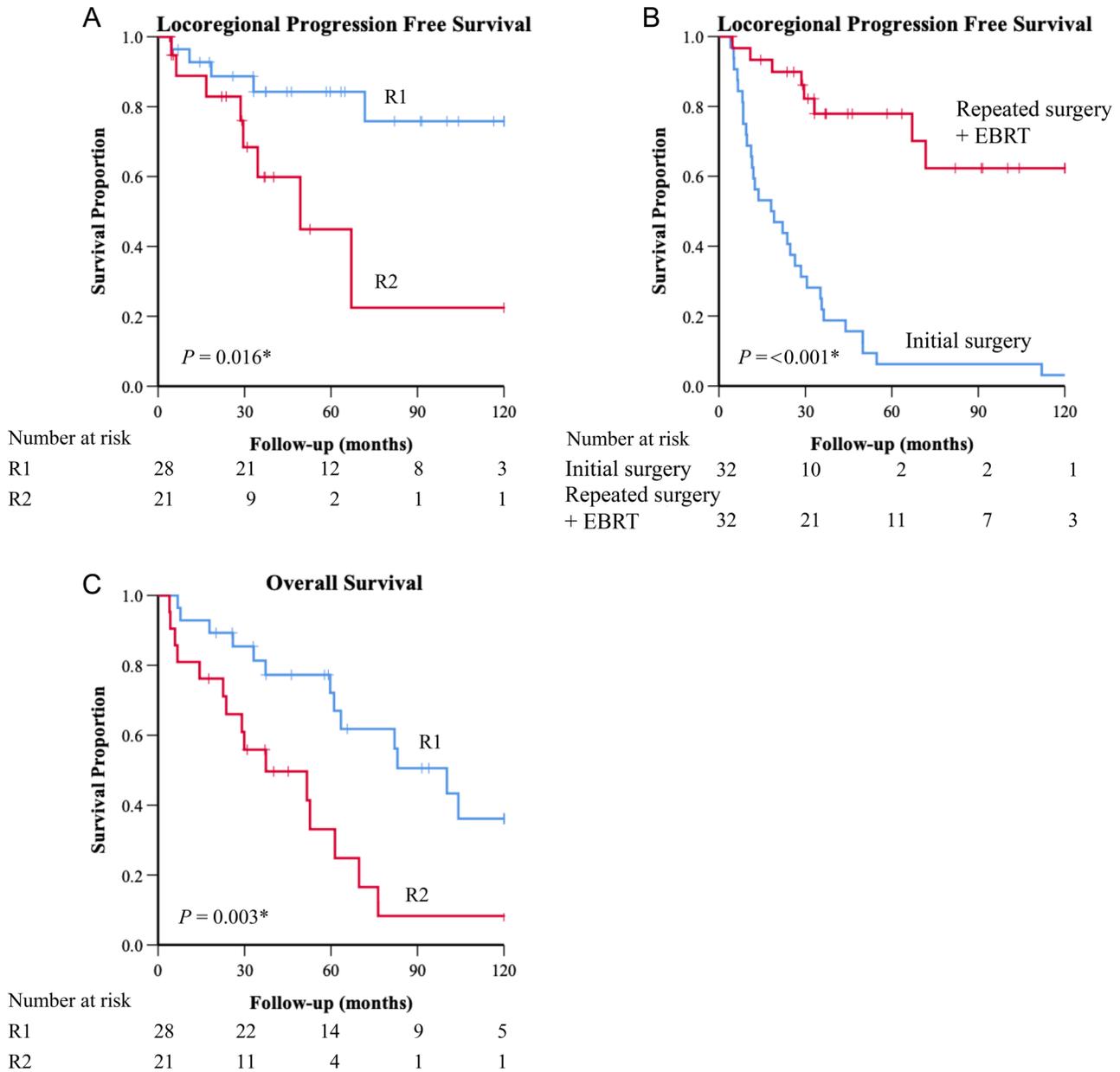
Figure 1

(A) Kaplan–Meier estimate of locoregional progression-free survival based on microscopic (R1) vs macroscopic (R2) residual disease. Blue line represents R1 disease, and red line represents R2 disease (*P* = 0.016). (B) Kaplan–Meier estimate of intrapatient subset analysis (*n* = 32). Locoregional progression-free survival based on initial surgical intervention vs repeated surgery plus EBRT. Blue line represents patients treated with initial surgery (pre-EBRT), and red line represents patients after repeated surgery plus EBRT (*P* < 0.001). (C) Kaplan–Meier estimate of overall survival based on R1 vs R2 residual disease. Blue line represents R1 disease, and red line represents R2 disease (*P* = 0.003).

General

No difference was seen in LRC and OS regarding the TNM status, as well as the radiation technique (3D-CRT vs IMRT). At death (*n* = 18), 8 (16.3%) patients had local and distant disease, 9 (18.4%) had only distant metastases, and 1 patient (2.0%) had only local tumor progression. Distant metastases were commonly detected in the lung (100%) and bones (27.8%).

Toxicity

Radiation-induced toxicity is presented in Table 3. Toxicity was evaluated prospectively in ten patients treated with

Table 3　Prospectively scored toxicity of 10 out of 49 patients.

Start of PORT	Grade 0	Grade I	Grade II	Grade III
Xerostomia	6 (60%)	3 (30%)	1 (10%)	0 (0%)
Mucositis	10 (100%)	0 (0%)	0 (0%)	0 (0%)
Dysphagia	10 (100%)	0 (0%)	0 (0%)	0 (0%)
Hoarseness	5 (50%)	5 (50%)	0 (0%)	0 (0%)
Dermatitis	10 (100%)	0 (0%)	0 (0%)	0 (0%)
Pain (head and neck)	10 (100%)	0 (0%)	0 (0%)	0 (0%)
Acute (<6 weeks)				
Xerostomia	4 (40%)	2 (20%)	2 (20%)	0 (0%)
Mucositis	9 (90%)	1 (10%)	0 (0%)	0 (0%)
Dysphagia	3 (30%)	2 (20%)	5 (50%)	0 (0%)
Hoarseness	4 (40%)	4 (40%)	2 (20%)	0 (0%)
Dermatitis	2 (20%)	2 (20%)	6 (60%)	0 (0%)
Pain (head and neck)	3 (30%)	3 (30%)	4 (40%)	0 (0%)
Late (≥3 months)				
Xerostomia	5 (55.6%)	3 (33.3%)	1 (11.1%)	0 (0%)
Mucositis	9 (100%)	0 (0%)	0 (0%)	0 (0%)
Dysphagia	4 (44.4%)	1 (11.1%)	3 (33.3%)	1 (11.1%)
Hoarseness	2 (22.2%)	5 (55.6%)	2 (22.2%)	0 (0%)
Dermatitis	5 (55.6%)	3 (33.3%)	1 (11.1%)	0 (0%)
Pain (head and neck)	4 (44.4%)	2 (22.2%)	3 (33.3%)	0 (0%)

PORT, postoperative radiotherapy.

IMRT. Only one patient had late grade III toxicity; no grade IV toxicity occurred.

Discussion/conclusion

This study shows that postoperative EBRT is associated with long-lasting LRC and OS with acceptable toxicity in patients with locally advanced IR-DTC, especially in microscopic residual disease. The intrapatient analysis, comparing LRC after primary curative-intended surgery with LRC after revision surgery plus EBRT, showed that EBRT potentially enhances LRC.

LRC is an important clinical endpoint, since locoregional progression accounts for significant morbidity, with reduced quality of life. The American Head & Neck Society recommend EBRT for patients with gross residual or non-resectable locoregional disease, except for patients with limited residual ^{131}I-avid disease (27). Although EBRT is more often offered for patients with macroscopic disease, our study showed additional long-term benefits in patients with microscopic residual IR-DTC who had an inevitable higher risk of locoregional failure with no or limited benefit from additional potentially mutilating surgery. This approach is particularly important in the multidisciplinary discussion, as we should be focused on avoiding too extended and mutilating salvage surgery with associated difficulties and increased severe adverse effects, particularly in the irradiated neck.

Data regarding additional EBRT in patients with IR-DTC are still scarce and remain controversial. Furthermore, we should take care that the benefits of EBRT outweigh the associated morbidity. The sub-analysis in our study suggests that EBRT might increase LRC in these patients. However, the effect of EBRT on OS due to a possible altered natural way of progression is difficult to assess without performing a prospective randomized study with inclusion of a control group not receiving EBRT.

Two retrospective studies from the Memorial Sloan Kettering Cancer Center showed that patients with gross residual and extrathyroidal extension or unresectable DTC, who underwent EBRT with or without low dose concurrent chemotherapy, had an increased LRC (13, 22). Several authors found a beneficial effect on gross residual disease. Chow *et al.* described a comparable significantly increased LRC after 10 years (63.4% vs 24.0%) with an increase of cancer-specific survival (74.1% vs 49.7%) by adding EBRT in non-radically resected gross residual thyroid cancer (28). Brierley *et al.* showed an increased LRC in patients with pT4 disease and no gross residual disease after EBRT as compared with patients without EBRT (10-year LRC 86.4% vs 65.7%) (15). Recently, Kim *et al.* reported a 5-year LRC rate of 95% in the EBRT group and 63% in a non-matched control group, in locally advanced PTC invading the trachea after surgical resection (20). However, others reported no beneficial effects (16, 17, 18, 29). Furthermore, these retrospective observational studies do not include prospective data with proper control groups not receiving EBRT (30).

Therefore, we currently rely on relatively small heterogeneous retrospective cohorts. Thus, when additional surgery involves a high risk of decreased quality of life, EBRT is still considered for a selected group of patients with high likelihood of microscopic residual disease and low likelihood of responding to [131]I. As discussed at multidisciplinary tumor board meetings, to obtain a better LRC, the decision to use EBRT is based on pre- and postoperative imaging, usually PET-CT and/or MRI, as well as intraoperative findings by experienced surgeons.

IMRT offers clear dosimetric advantages on tumor coverage and organ sparing above 3D-CRT, reducing late toxic effects, such as long-term xerostomia, without compromising the tumor dose (31). However, reduced toxicity from IMRT is difficult to be demonstrated in this retrospective study, since toxicity data were not

prospectively collected in the pre-IMRT era. Most studies report these complications retrospectively but seldom consider that these patients have undergone multiple operations and high doses of ^{131}I (32, 33).

In this study, EBRT was given in a carefully selected patient population, indicating its strength with clearly stated selection criteria for administering EBRT. However, this selection bias may also be considered as a limitation for generalizability of the results. Although we collected radiotherapy side effects prospectively since the introduction of IMRT, our study is limited by its small cohort with respect to the toxicity data. Furthermore, there is lack of data to include a matched control arm, and the effect of the extent of each surgical resection in itself could not be assessed. Although the intrapatient analysis of LRC should be interpreted with caution, it supports the beneficial effect of EBRT especially since the frequency of macroscopic disease is higher after repeated surgery plus EBRT.

In order to make appropriate decisions for IR-DTC patients in clinical practice, the meaningful impact of EBRT should be considered, as well as novel-targeted drugs including tyrosine kinase inhibitors (TKIs) and immunotherapy (34, 35). To identify patients with a high likelihood of harboring iodine refractory disease, several specific descriptions of IR-DTC have been added to the definition, and these patients should be considered as potential candidates for early intervention (36, 37). As such, the indication for this systemic approach is generally limited to progressive disease with distant metastases. However, the potentially beneficial effect of combining TKIs with EBRT seems to be a promising new therapeutic strategy for these patients (38). Although relatively rare, we should be aware of bleeding and development of tracheo-oesophageal fistulas in patients treated subsequently with TKIs after radiotherapy (39). Valerio *et al.* showed that EBRT was not significantly associated with the development of fistulas and organ perforation (40). Therefore, we should be cautious to consider TKI treatment too early after EBRT and refrain radiotherapy in poor performance stated patients particularly in the unresectable cases with extended local invasion.

In summary, the effectiveness of postoperative EBRT was demonstrated by a durable LRC with acceptable toxicity for IR-DTC, especially in patients with microscopic residual disease. To improve LRC, these patients should be referred to specialized centers, where multidisciplinary teams should consider postoperative EBRT when in doubt about the best treatment strategy.

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