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Published

2017

Journal Title

Current Oncology

Version

Version of Record (VoR)

DOI

10.3747/co.24.3551

CURRENT ONCOLOGY
A Canadian Cancer Research Journal

ORIGINAL ARTICLE

Patterns of failure in anaplastic and differentiated thyroid carcinoma treated with intensity-modulated radiotherapy

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ABSTRACT

Background The radiotherapy (RT) volumes in anaplastic (ATC) and differentiated thyroid carcinoma (DTC) are controversial.

Methods We retrospectively examined the patterns of failure after postoperative intensity-modulated RT for ATC and DTC. Computed tomography images were rigidly registered with the original RT plans. Recurrences were considered in-field if more than 95% of the recurrence volume received 95% of the prescribed dose, out-of-field if less than 20% received 95% of the dose, and marginal otherwise.

Results Of 30 DTC patients, 4 developed regional recurrence: 1 being in-field (level III), and 3 being out-of-field (all level II). Of 5 ATC patients, all 5 recurred at 7 sites: 2 recurrences being local, and 5 being regional [2 marginal (intramuscular to the digastric and sternocleidomastoid), 3 out-of-field (retropharyngeal, soft tissues near the manubrium, and lateral to the sternocleidomastoid)].

Conclusions In DTC, locoregional recurrence is unusual after RT. Out-of-field DTC recurrences infrequently occurred in level II. Enlarged treatment volumes to level II must be balanced against a potentially greater risk of toxicity.

Key Words Thyroid neoplasms, recurrence, radiotherapy, anaplastic thyroid carcinoma, papillary carcinoma

Curr Oncol. **2017 June;24(3):e226-e232** **www.current-oncology.com**

INTRODUCTION

External-beam radiotherapy (RT) is an established treatment modality in the management of anaplastic thyroid cancer (ATC). These undifferentiated tumours are extremely aggressive, recurring both locally and distantly. Radiotherapy decreases local recurrence, reduces the morbidity associated with ATC progression, and might increase cancer-specific survival[1–5].

Given in the adjuvant setting, RT has also been shown to reduce recurrence in selected patients with high-risk differentiated thyroid cancer (DTC, including follicular and papillary carcinoma)[6–9]. Several features have been proposed to confer a high risk of recurrence, including pathologic stage T4a, gross extrathyroidal extension, macroscopic or microscopic positive margins, lack of radioactive iodine uptake, tall-cell variant, and older age[1,8–12]. Uncontrolled locoregional disease is a major cause of morbidity and mortality in DTC[13].

Despite several studies investigating the role of RT in DTC and ATC, no clear consensus has been reached concerning the optimal RT volume, and institutional practice varies. At the Princess Margaret Cancer Centre, the standard is to include levels III–VI, with levels V and II partially included, in the clinical target volume for both ATC and DTC. Larger volumes are described in the literature, especially for ATC (including in the currently open Radiation Therapy Oncology Group 0912 trial), often extending from the mastoid to the carina[6,7,14,15]. In the case of ATC, the use of larger fields must be balanced against the potential for increased acute and late toxicities in this population with a very poor prognosis.

Surgery to achieve complete resection of disease is occasionally possible for ATC, particularly when it is a

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smaller component within a tumour mass consisting of DTC. For DTC, the philosophy at Princess Margaret has been to control disease in the postoperative thyroid bed, especially in the region of the larynx and tracheoesophageal groove, wherein salvage surgery would involve extensive procedures such as laryngectomy. We consider that nodal recurrences of DTC can usually be surgically salvaged. However, in the intensity-modulated RT (IMRT) era, the locoregional pattern of failure after RT has not been well established, and it is possible that treating a larger volume could prevent additional recurrences in both ATC and high-risk DTC.

The purpose of the present study was to determine the patterns of failure after postoperative IMRT in ATC and DTC patients and to determine the location of those failures in relation to the RT volume.

METHODS

Study Design and Patient Population

A research ethics board–approved retrospective chart review was performed for all patients diagnosed with ATC or DTC from 2006 to 2012. That period was chosen to limit the review to IMRT-treated patients. Patients who were treated with postoperative RT for ATC and DTC were included. Patients who received 40 Gy in 16 fractions—and higher cumulative doses—were included. The adjuvant dose for DTC patients was 60–66 Gy in 30–33 fractions to the high-risk volume and 54–56 Gy in 30–33 fractions to lower-risk volumes. Patients with ATC were treated with a range of fractionations, including 60 Gy in 40 fractions delivered twice daily in 1.5 Gy fractions[16]. We excluded patients who received primary RT, patients treated for recurrent disease, and patients who received split-course 40 Gy in 10 fractions or other palliative regimens (n = 245). All pathology was centrally reviewed at our institution.

All patients underwent computed tomography (CT) simulation with a thermoplastic mask for immobilization. Radiation treatment plans were created using the Pinnacle treatment planning system (Philips Medical Systems, Andover, MA, U.S.A.). All patients were treated using an IMRT technique. The RT volumes routinely included the thyroidectomy bed (levels III–VI, with levels II and V partially included) for both ATC and DTC[17].

Follow-up was at the discretion of the treating physician. Patients with DTC were seen as necessary until acute toxicity resolved, and then every 6 months for 5 years, with care usually being shared between the surgeon and other members of the team. Patients with DTC routinely received additional therapy with radioactive iodine. Thyroglobulin levels were routinely assessed, and in DTC patients, we aimed for suppression of thyroid-stimulating hormone. Toxicity was reported by retrospective review and was graded according to the *Common Terminology Criteria for Adverse Events*, version 4.0.

Recurrence Analysis

Local recurrences were defined as occurring within the thyroid bed. Regional recurrence was defined as occurring in the lymph node regions or soft tissues of the neck or the upper mediastinum.

Computed tomography imaging demonstrating local or regional recurrence was rigidly registered with the original planning CT imaging. Priority was given to accuracy of registration in the area of the recurrence. We performed separate registrations in cases in which 2 recurrence volumes were identified at a significant distance from one another. The recurrence volumes were then contoured, with the original dose distribution overlaid. The dose delivered to the area of the recurrence volume was calculated. In instances in which the recurrence volume extended outside the limit of the original patient volume, the recurrence volume was limited to the boundaries of the original CT images. The dose to that truncated volume was calculated.

Recurrences were defined as in-field if more than 95% of the recurrence received 95% of the dose; marginal, if 95%–20% received 95% of the dose; and out-of-field, if less than 20% received 95% of the dose[18]. When a clinical target volume was created, with a lower dose prescribed to elective nodal volumes (typically 54–56 Gy in 30 or 33 fractions), the 95% isodose of that dose was used in the analysis for nodal recurrence.

Statistical Analysis

Patient demographics and disease and treatment characteristics are summarized using descriptive statistics. Time-to-event statistics for overall survival (OS), locoregional recurrence (LRR), and distant recurrence (DR) were calculated from the date of diagnosis to the event date (death for OS, local or regional recurrence for LRR, and distant recurrence for DR) or to the last date of follow-up. The Kaplan–Meier method was used to calculate OS. The cumulative incidence for LRR and DR was calculated using the competing-risks approach.

RESULTS

We identified 30 patients with DTC and 5 with ATC who completed postoperative RT. The results are presented here by histologic type.

ATC

Patient, Tumour, and Treatment Characteristics

All 5 of the identified patients had ATC within a larger non-anaplastic tumour. The anaplastic component was detected either preoperatively by fine-needle aspiration or within the final thyroidectomy specimen. Table I presents the patient, tumour, and treatment characteristics.

Patterns of LRR

All 5 patients with ATC experienced recurrence after RT. Table II sets out the surgical and RT treatment details. There were 7 recurrence volumes: 2 local and 5 regional. Both local recurrences were in-field. Of the regional recurrences, 2 were marginal (1 intramuscular to the anterior belly of the digastric, 1 in the lateral aspect of the sternocleidomastoid at the level of the cricoid), and 3 were out-of-field (1 retropharyngeal, 1 lateral to the sternocleidomastoid at the level of the hyoid, and 1 in the soft tissues anterior to the upper manubrium). Median time from completion of RT to LRR was 8.4 months (range: 2–16 months). Because of poor performance status, metastatic

TABLE I Patient, tumour, and treatment characteristics

Variable	Thyroid cancer histology	
	Anaplastic	Differentiated
Demographics		
Patients (*n*)	5	30
Age at Dx (years)		
Median	62	59
Range	51–69	34–78
Sex [*n* (%)]		
Men	3 (60)	10 (33)
Women	2 (40)	20 (67)
Pathology		
Papillary histology	NA	30 (100)
T Stage		
T1	NA	1 (3)
T2	NA	2 (7)
T3	NA	12 (40)
T4a	3 (60)	15 (50)
T4b	2 (40)	0 (0)
N Stage		
N0	1 (20)	7 (23)
N1a	2 (40)	5 (17)
N1b	2 (40)	16 (53)
Nx	0 (0)	2 (7)
M Stage		
M0	4 (80)	29 (97)
M1	1 (20)	1 (3)
Margins		
Positive	5 (100)	24 (80)
Close (<1 mm)	0 (0)	1 (3)
Extrathyroid extension	5 (100)	25 (83)
Lymphovascular invasion	4 (80)	20 (67)
Widely invading the capsule	NA	20 (67)
Differentiation		
Tall cell	NA	9 (28)
Hurtle cell	NA	2 (6)
Insular	NA	1 (3)
Treatment		
RT dose (Gy)		
Median	52	66
Range	40–66	60–66
Duration from Dx to start of RT (days)		
Average	77	192
Range	41–97	53–642
RAI treatment	NA	25 (83)
Median first dose of RAI (mCi)		
Median	NA	153
Range		102–212
Pre-RT thyroglobulin level (µg/L)[a]		
Median	NA	6
Range	<0.8 to 442	

[a] Available for 28 of the 30 patients.
Dx = diagnosis; NA = not applicable; RT = radiotherapy; RAI = radioactive iodine.

disease, and clinical deterioration, no patient underwent salvage surgery for recurrence.

Survival and Recurrence

All 5 patients died. Median survival duration was 1.2 years [95% confidence interval (CI): 1.2 years to not applicable]. The 1-year OS rate was 80% (95% CI: 52% to not applicable); it was 0% at 2 years (Figure 1). The LRR rate was 60% at 1 year (95% CI: 7% to 91%) and 100% at 2 years. The DR rate was 100% at 1 year. All 5 patients developed lung metastases. Additionally, 1 patient developed bone metastases, and 1, abdominal metastases.

Toxicity

Of the 5 patients, 3 experienced acute grade 3 esophagitis. For nutritional support, 1 patient required a gastrostomy tube which was inserted before RT and remained *in situ*. In 1 patient who required it, a tracheostomy tube was inserted after surgery and removed before the start of RT. No grade 3 or greater dermatitis was reported.

DTC

Patient, Tumour, and Treatment Characteristics

All 30 DTC patients had tumours with papillary histology. The RT dose in 4 patients (13%) was 60 Gy in 30 fractions; in the remaining 26 patients (87%), it was 66 Gy in 33 fractions. The radioactive iodine dose was available in all but 1 of the 25 patients who received it. Most patients had positive margins, extrathyroid extension, and involved lymph nodes. Table I presents complete patient, tumour, and treatment characteristics.

Patterns of LRR

Of the DTC patients, 4 experienced regional recurrence; there were no local recurrences. Table II sets out the surgical and RT details for those patients. Of the regional recurrences, 1 was in-field in level III, and 3 were out-of-field, all in level II. Of the level II recurrences, 2 were found at the level of the hyoid, and 1, mid-way between the hyoid and the C1 transverse process. There were no marginal recurrences.

Median time from completion of RT to recurrence was 29 months (range: 2–52 months). Of the 4 patients with LRR, 2 underwent salvage neck dissection. The others had progressive metastatic disease and were unsuitable for salvage surgery.

Survival and Recurrence

Median follow-up duration was 5.1 years (95% CI: 4.3 to 6.2 years). Of the 30 patients, 3 died during the observation period. The 5-year OS was 93% (95% CI: 84% to 100%; Figure 1). Median survival duration was not reached. The 5-year LRR rate was 17% (95% CI: 5% to 35%). The 5-year DR rate was 23% (95% CI: 9% to 41%). All 6 patients with DR developed lung metastases. One patient additionally developed mediastinal adenopathy, and one developed bone metastases.

Toxicity

Acute grade 3 radiation dermatitis was reported in 1 of the 30 patients. Acute grade 3 esophagitis was reported in 4 patients, and grade 4 esophagitis, in 1 patient. Late grade 3

TABLE II Treatment and recurrence details for patients with locoregional recurrence after radiotherapy

Histology	TNM stage	Surgery	Radiotherapy			Recurrence	
			Dose (Gy)	Fr. (*n*)	Nodal volumes	Site	Pattern
Anaplastic	pT4b pN1b cM0	Thyroidectomy (R1), partial pharyngectomy, and esophagectomy; right neck level II-IV, anterior V, bilateral central compartment, posterior pharyngeal muscle, tissue of right proximal trachea and posterior cricoid, superior mediastinal node	40	16	Bilateral III, IV, V,Via, VIb, mediastinum above carina	Regional: retropharyngeal	Out-of-field
Anaplastic	pT4a pN1a cM1	Thyroidectomy (R1), partial thymectomy; bilateral central compartment, anterior mediastinal nodes	52	20	Right low-level IB and II (in vicinity of gross tumour volume); bilateral III, IV, V, Via, VIb, mediastinum down to carina	Regional: lateral to the sternocleidomastoid muscle, at the level of the hyoid	Out-of-field
Anaplastic	pT4a pN0 cM0	Thyroidectomy (R1); left level III, IV, VI and right functional neck dissection; posterior cricoid and tracheal resection, with primary tracheal repair	66	33	Bilateral III, IV, V, Via, VIb	Regional: in subcutaneous tissues near to the superior edge of the manubrium Regional: lateral to the sternocleidomastoid muscle, at the level of the cricoid	Out-of-field Marginal
Anaplastic	pT4b cN1b M0	Thyroidectomy (R2), residual on trachea; no lymph node dissection	50	20	Bilateral III, IV, V, Via, VIb	Regional: intramuscular to the anterior belly of digastric Local: right surgical bed and piriform sinus	Marginal In-field
Anaplastic	pT4a pN1a cM0	Thyroidectomy (R1); bilateral central compartment and Delphian node resection	60	40 (twice daily)	Bilateral partial level III (from top of cricoid), IV, V, Via, VIb	Local: left surgical bed	In-field
Differentiated	pT3 pN1a cM0	Thyroidectomy (R0); right central neck dissection	66	33	Bilateral III, IV, VIa, VIb	Regional: level II, at the level of the hyoid	Out-of-field
Differentiated	pT4a pN1b cM0	Thyroidectomy (R1); right central neck dissection	66	33	Bilateral III, IV, Via, VIb, and partial V	Regional: level II, at the level of the hyoid	Out-of-field
Differentiated	pT4a pN0 cM1	Thyroidectomy (R1); bilateral neck dissection	66	33	Bilateral III, IV, VIa	Regional: level II, midway between the hyoid and the C1 transverse process	Out-of-field
Differentiated	pT3 pN0 cM0	Thyroidectomy (R1); limited central neck dissection	66	33	Bilateral III, IV, V, Via, VIb	Regional: level III	In-field

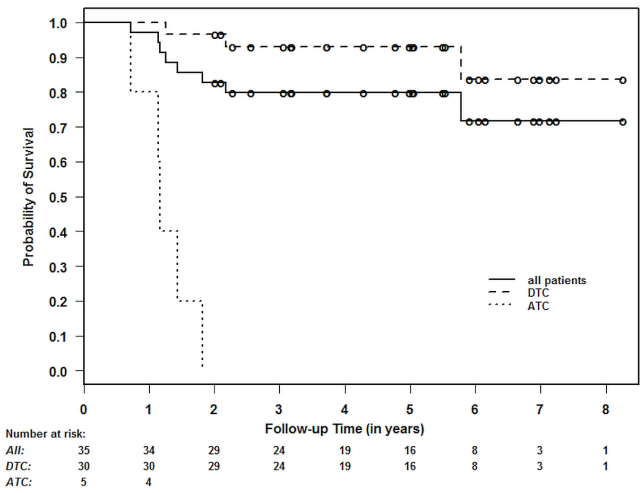

FIGURE 1 Overall survival for differentiated (DTC) and anaplastic thyroid cancer (ATC). Patients with ATC experienced significantly worse survival.

esophagitis was reported in 1 patient, and 1 patient with lung metastases developed late grade 4 tracheal obstruction and hemorrhage requiring emergency tracheostomy and bronchial artery embolization. In total, 2 patients experienced permanent tracheostomy tube insertion, one before RT and the other, 6 years later. Gastrostomy tubes were required in the same 2 patients, permanently in the former and for 3 months in the latter.

DISCUSSION

The optimal volume for external-beam radiation in the IMRT era for ATC and DTC is a significant clinical challenge. Little published evidence is available to justify what might be considered optimal RT volumes in the treatment of ATC and DTC. Several studies have investigated the role of RT in both ATC and DTC, but the RT volume is not always described, and no randomized comparisons have been published. In addition, because of the rarity of disease presentations requiring consideration of RT, many of the studies span decades and do not address modern IMRT techniques.

ATC

Radiation volumes for ATC frequently include the entire neck and the superior mediastinum[19,20]. In a series from Germany, the field borders most commonly extended from the mastoid to the tracheal bifurcation[21]. The Radiation Therapy Oncology Group 0912 trial (https://www.rtog.org/ClinicalTrials/ProtocolTable/StudyDetails.aspx?study=0912), a randomized study currently accruing patients with ATC, mandates generous coverage of the tracheoesophageal groove, levels II–VI, the upper mediastinum to the level of the carina, plus level I and the retropharyngeal nodes at the discretion of the treating physician.

When treating patients with ATC, the primary goal of RT is local control to prevent the morbidity and mortality associated with disease recurrence and progression. Patients with ATC are at risk of dying of uncontrolled local disease even in the presence of distant metastasis[22]. At Princess Margaret, policy has been to limit the volume to the thyroid bed and adjacent nodal regions, including levels III, IV, and VIa–b, with parts of level V (the nodal levels considered at our institution to be most at risk for spread in both the adjuvant and primary RT setting), but omitting level II and the superior mediastinum[23]. Extending the treated volume superiorly might increase the radiation dose to normal structures such as the parotids, mandible, and submandibular glands, increasing the risk of toxicity. An attempt has been made to balance the need for local control against the potential for severe toxicity in this group of patients with generally very poor outcomes.

In a study of 39 patients treated to a median total dose of 50 Gy, with a larger volume (as in Radiation Therapy Oncology Group 0912), 28% of patients developed grade 3 or greater dysphagia requiring a feeding tube or parenteral nutrition, 18% needed emergency tracheostomy, and almost half experienced recurrent laryngeal nerve palsy[21]. Using IMRT and a smaller volume, we found that, of 5 patients, 1 required a gastrostomy, and 1, a tracheostomy. Acute grade 3 esophagitis developed in 3 patients, including in 1 patient who received hyperfractionated twice-daily RT. In the case of rapidly dividing tumours such as ATC, hyperfractionated RT might have improved activity without increased toxicity. In a previous report from Princess Margaret, 9 patients with unresectable ATC received twice-daily RT to 60 Gy. Toxicity was found to be acceptable, although the treatment was reserved for patients with a good performance status[23]. In a larger study of hyperfractionated RT from the Royal Marsden Hospital, acute toxicity was found to be unacceptably high, with grade 3 or greater esophagitis occurring in 79% of patients, leading to discontinuation of the treatment regimen[19]. However, only a small proportion of their patients received postoperative RT. Whether hyperfractionated RT in the adjuvant setting improves outcomes for ATC patients remains unknown.

The marginal and out-of-field ATC recurrences identified in the present study appeared in the tissues lateral to the sternocleidomastoid, intramuscularly in the digastric, in the retropharyngeal nodes, and in soft tissue near the manubrium. To routinely cover all those structures in the clinical target volume would result in a significantly larger volume and would probably result in unacceptable toxicity. The location of the observed recurrences suggests that the pattern of spread is not an orderly progression through nodal echelons, but an aggressive pattern that is not entirely predictable.

DTC

Patients with DTC are treated using a volume similar to that described for ATC. In general, recurrences in nodal regions are deemed to be amenable to salvage surgery. The use of RT to the whole cervical lymph node region is reserved for patients at high risk of relapse who have extranodal extension or multiple nodal recurrences despite surgical neck dissections and radioactive iodine treatment.

Published reports about the pattern of nodal involvement at surgery, or the pattern of failure after surgery alone, often combine nodal levels II–IV[24–28]. It is therefore not possible to tailor RT volumes on the basis

of those studies. More recently, Kruijiff *et al.*[29] examined the location of 94 postoperative recurrences in 1183 patients with papillary thyroid carcinoma by individual nodal levels in the neck. They found that 12% recurred in level II; 18%, in level III; 18%, in level IV; 17%. in level V; 32%, in level VI; and 2%, in the superior mediastinum. Such detailed pattern-of-failure analyses after RT are sparse. Azrif *et al.*[15] reported the patterns of failure after RT in 49 patients treated with either non-coplanar lateral fields (with the superior border above the hyoid bone) or with anterior–posterior parallel opposed portal fields (with a superior border at the tip of the mastoid process). Superior mediastinal nodes were not included. Patients experienced 4 upper mediastinal, 8 nodal, and 6 local recurrences. Because the target volumes were defined using orthogonal simulator fields, no analysis of the location of the nodal recurrences with respect to the dose distribution was possible. However, the 4 superior mediastinal recurrences were likely out-of-field, given that treatment to that area was purposefully omitted. Kim *et al.*[14] reported on 11 DTC patients treated with RT limited to the operative bed or gross relapse, and 12 patients who received additional elective RT to the cervical and mediastinal lymph nodes. Out-of-field recurrences were defined broadly as "outside the RT field". There were 7 LRRs in the limited-RT group (6 out-of-field, 1 in-field) and only 1 LRR (in-field) in the elective-RT group. In another report from Korea, 3 of 6 recurrences were situated in level II, and all were reported as in-field, although no dosimetric analysis was performed[30]. In our pattern-of-failure analysis under IMRT, all 3 out-of-field DTC recurrences occurred in level II.

The toxicity from a large RT volume for DTC was recorded in a multicentric study of three-dimensional conformal RT that prescribed 50.4–54 Gy to lymph nodes from the mastoid to the tracheal bifurcation. Acute grade 3 toxicity was reported in only 14% of patients (3 of 22), and all incidences had resolved at first follow-up[31]. Kim *et al.* recorded grade 3 or greater toxicity in only 8% (1 of 12) patients treated with large elective RT volumes[14]. The present study of a larger group of DTC patients supports the observation that current treatments produce grade 3 or greater toxicities in a small number of patients. Using IMRT, we documented acute grade 3 or greater esophagitis in 17% of patients (5 of 30). Two patients required tracheostomy and gastrostomy tube insertion during follow-up. Further technical improvements in IMRT or optimized volumetric modulated arc therapy with an aim to reduce the dose to organs at risk could further reduce treatment-related toxicity in this patient population[6,31,32].

In the era of IMRT, expanding the RT volume for patients with high-risk DTC to include level II might improve the recurrence rate, with lessened toxicity. On the other hand, the overall locoregional failure rate remains relatively low even when accounting for competing risks (17% at 5 years), and the benefit of a larger RT field for the population as a whole would likely be small.

Limitations

Our study has several limitations. First, the sample size was relatively small, and the prescribed doses and fractionations in the ATC group were heterogeneous.

Further, the categorization of failures using the "20%–95%" analysis has its own limitations. For example, it is not possible to know whether a marginal recurrence started within the 95% isodose volume, growing outside of it, or outside the 95% isodose volume, growing within. We occasionally had to truncate the part of the recurrence volume situated outside the original planning CT imaging, partly because of the limitations of rigid registration between the planning and recurrence CT imaging when the patient contours differed significantly. The reduced volume could lead to an overestimation of the proportion of the recurrence that was covered by the 95% isodose line. However, in reviewing the 2 patients for whom modified volumes were used, deformable registration would not have changed the categorization of the recurrences.

Another limitation is that toxicities might have been underreported because they were not prospectively scored during treatment. With respect to ATC, we recognize that a more common clinical scenario is that of unresectable disease treated with upfront RT. However, such patients have a poor prognosis and might not receive routine serial follow-ups and CT imaging, such that we chose to omit them from the analysis. Our results should not be extrapolated beyond the adjuvant setting.

Finally, 2 patients in the present analysis had low-volume lung metastases at presentation. Nevertheless, follow-up duration was 2–6 years in those patients, showing that local control is essential even in the presence of distant metastasis.

CONCLUSIONS

Out-of-field regional recurrences in patients with high-risk DTC treated with a limited RT volume were located in nodal regions adjacent to the treated volumes. However, the overall regional failure rate remains modest, and expanding the RT fields to cover additional nodal echelons would benefit only a small number of patients and could increase toxicity. Out-of-field ATC recurrences were scattered in a non-contiguous fashion, raising the question of whether an extended RT volume would improve locoregional control.

CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology*'s policy on disclosing conflicts of interest, and we declare that we have none.

AUTHOR AFFILIATIONS

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