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Phase I trial

Intensity Modulated Radiotherapy (IMRT) in locally advanced thyroid cancer: Acute toxicity results of a phase I study

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Abstract

***Background and purpose*: This phase 1 study was designed to determine the toxicity of accelerated fractionation IMRT in locally advanced thyroid cancer.**

***Methods*: Patients with high risk locally advanced thyroid cancer who required post-operative EBRT were recruited. A single-phase inverse-planned-simultaneous-boost was delivered by IMRT: 58.8 Gy/28F (daily) to the primary tumour and involved nodes and 50 Gy/28F to the elective nodes. Acute (NCICTCv.2.0) and late toxicity (RTOG and modified LENTSOM) was collected.**

***Results*: Thirteen patients were treated (7 medullary thyroid, 2 Hurthle cell and 4 well differentiated thyroid cancer). G3 and G2 radiation dermatitis rates were 38.5% and 31%; G3 and G2 mucositis rates 8% and 53% and G3 and G2 pain 23% and 54%. Thirty-one percentage required enteral feeding. G3 and G2 xerostomia rates were 0% and 31%. Recovery was seen, with 62% patients having dysphagia $G \leqslant 1$ 2 months after IMRT. Thirty percent of patients developed L'Hermitte's syndrome. No grade 4 toxicity was observed. No dose limiting toxicity was found.**

***Conclusions*: Accelerated fractionation IMRT in this group of patients is feasible and safe. The acute toxicity appeared acceptable and early indicators of late toxicity moderate and similar to what would be expected with conventional RT. Longer follow up is required to quantify late side effects.**
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Keywords: Thyroid cancer; IMRT; Toxicity

Patients with locally advanced thyroid cancer who have residual disease after surgical excision and those with differentiated tumours that do not take up radioactive iodine present a therapeutic challenge. Although these tumours have been regarded as radioresistant [6,7], external beam radiotherapy (EBRT) has been shown to be of value in several retrospective studies [4,13,16,18].

Doses of 60 Gy in 2 Gy daily fractions and above to the post-operative thyroid bed and involved nodal areas have been shown to have the highest chance of achieving local control [13]. However, with current radiation techniques, the anatomical position of the tumour and regional lymph nodes surrounding the spinal cord often precludes the delivery of such a high dose [20]. Partial reductions of spinal cord dose are possible with 3D conformal radiotherapy (CRT) [8], but usually do not reduce the maximum spinal cord dose.

In a radiotherapy planning study of thyroid cancer, IMRT has been shown to significantly reduce the maximal spinal cord dose compared to CRT. In addition, it significantly improved the coverage of the target volume allowing potential for dose escalation [12]. With present radiotherapy techniques, 30—40% of patients with gross disease do not obtain a complete response (CR) [13] and dose escalation to the thyroid bed and/or nodal areas represents a reasonable strategy to improve local control. We present here the initial results of patients treated within the first dose level of a phase 1 dose escalation study of IMRT in patients with locally advanced thyroid cancer.

Materials and methods

Patients and treatment

Patients with histologically proven locally advanced thyroid cancer who required post-operative external beam radiotherapy because of high risk of local recurrence (T4

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disease, N+ neck, recurrent disease, residual macroscopic disease, or medullary carcinoma) were eligible. Patients with anaplastic thyroid cancer were excluded. The study was approved by the Royal Marsden Hospital ethics committee and all patients gave written informed consent to their participation.

A single-phase simultaneous integrated boost technique (SIB) [3,11] was used to deliver 58.8 Gy in 28 daily (5 fractions per week) fractions of 2.1 Gy to the tumour bed and involved nodal areas and 50 Gy in 28 daily fractions of 1.8 Gy to the elective lymph nodes. These doses were calculated using the formula EQD2 = $D(d + \alpha/\beta)/2 + \alpha/\beta$ [1], with α/β of 10 for tumour and 3 for late toxicity.

A single phase dose escalation trial design was used. The aim of this first phase was to define the toxicity profile of this new treatment. Dose escalation was planned once feasibility was demonstrated in the first cohort, with 15 patients planned to be enrolled in each dose level.

IMRT technique

All patients underwent a radiotherapy planning CT scan of the head and neck, immobilised using a custom-made cabulite mask, from the supra-orbital ridge to 2 cm below the carina on a 4 slice GE CT scanner.

ICRU 50 and 62 guidelines provided the basis for defining the different target volumes. The primary or high dose CTV1 encompassed any residual disease, the post-operative thyroid bed, from at least the cricoid cartilage to the sternal notch and the pathologically positive post-operative nodal bed. Level 6 nodes were also included in the high dose volume from the cricoid to the sternal notch, and in the elective CTV2 from the cricoid to the hyoid. The rest of the CTV2 included the uninvolved nodal levels II–V, supraclavicular fossa (SCF) nodes bilaterally and upper mediastinal nodes. Uninvolved barriers to tumour spread, such as bone and fasciae were excluded. Adjacent structures (i.e. muscle) infiltrated by tumour were included in the CTV1. A 3 mm margin was added to the CTV to account for patient motion, organ motion and set up inaccuracies to obtain the PTV [10]. The organs at risk delineated were the spinal cord and parotid glands, with a dose constraint to the spinal cord of 48 Gy.

The inverse planning module of CadPlan v6.3.5 (Varian Medical Systems, Palo Alto, CA) was used to create five or seven field clinically acceptable IMRT plans for dynamic delivery on a Varian 2100CD linear accelerator and PINNACLE^3 (Philips Radiation Oncology Systems, Milpitas, CA) for step and shoot delivery on an Elekta linear accelerator (Elekta Oncology Systems, Crawley, UK), all using 6MV photons.

Follow up (FU)

All patients were assessed prior to commencement of IMRT. Acute toxicity was evaluated weekly during the course of IMRT and at 4 and 8 weeks following completion of treatment. Toxicity scoring was performed according to the NCI CTC v.2.0 criteria. Late toxicity data were collected at 3, 6, 12, 18 and 24 months and annually thereafter using the RTOG and LENT SOM scoring systems.

Statistical analysis

Descriptive statistics are used to present the data. The prevalence of a reaction at a specified point in time was defined as the proportion of patients scored as having that grade of reaction relative to the total number of patients assessed at that specific time point [2]. The incidence was defined as the total number of patients reaching a grade reaction at any time, divided by the total number of evaluable patients [2]. The mean time with a specific grade 3 early reaction was defined as the time in weeks spent with that reaction divided by the number of patients who reached that grade.

For the calculation of the duration of the reactions, incidence and prevalence, specific rules were applied to substitute missing values [2]. Single missing scores were substituted by the average of the scores in the preceding and following week. If the week 1 assessment was missing, it was substituted by the week 2 assessment, and the one from week 8 by the one from week 4. If two consecutive assessments were missing, they were left as missing data.

Results

Thirteen patients with histologically proven thyroid cancer were treated. Median follow up was 37 (range 25–169) weeks. Patient characteristics are shown in Table 1. Mean primary PTV dose delivered to 95% of the volume (D95%) was 56.4 Gy (55.2–61.4) and mean elective nodal D95% was 46.4 Gy (45.8–49.1). Fig. 1 depicts typical isodose curves. Overall, mean treatment time was 39 ± 2 days.

Acute toxicity

No patients experienced acute grade 4 toxicity. The incidence of acute toxicity observed is shown in Table 2. Overall, median minimum Karnofsky PS was 80 (50–100) and median maximum fatigue was grade 2 (0–3).

The peak prevalence of moist desquamation (G3) was 25% in week 5 of treatment. Fig. 2 shows the time course of the prevalence of all grades of dermatitis. Erythema commenced early, in the first week of IMRT. More severe skin reactions were not seen until week 5, and by week 9 (i.e. 3 weeks post-treatment) no patient had persistent moist desquamation. Healing was complete in all patients by week 14. The average time with G3 dermatitis, in patients who reached that grade, was 1.2 ± 0.4 weeks.

Fig. 3 shows the prevalence of mucositis, dysphagia and pain as a function of time. The peak prevalence of G3 (confluent) mucositis was in 9% at week 8 (i.e. 2 weeks post-treatment). The peak prevalence of dysphagia was G3 (enteral feeding), in 27% patients, seen in week 6 of treatment. This was, however, short-lived, with a mean time with G3 dysphagia of 2.7 ± 1.7 weeks. This toxicity resolved by week 10 (i.e. 4 weeks post-treatment), with only one patient requiring a soft diet by week 14.

For pain, the peak prevalence of G3 pain (pain that interfered with function and activities of daily living) was 30% and was seen in week 7 (i.e. 1 week post-treatment). This was also short-lived, with a mean duration of 2 ± 1 weeks. Thirty-eight percent of patients required opioids for pain control.

Table 1
Patient characteristics

Median age (range)	57 (29—75)
Gender	
Male	4
Female	9
Planning system	
Pinnacle	3
Cadplan	10
Histology	
Papillary	3
Follicular	1
Medullary	7
Hurthle cell	2
T stage	
Recurrence	3
T2	1
T3	1
T4	8
N stage	
Nx	2
N0	4
N1a	2
N1b	5

Fig. 2 also shows the time course of the prevalence of all grades of xerostomia. The peak prevalence of xerostomia was G2, 44.4%, seen in week 7 (i.e. 1 week post-treatment). No patient experienced xerostomia G3. A feeling of dry mouth commenced early, in week 1 of IMRT. There was gradual deterioration, up until week 7 and progressive recovery thereafter with 58.3% patients experiencing xerostomia G0-1 at 14 weeks (i.e. 8 weeks post-treatment). The average time spent with G2 xerostomia in those patients who reached that grade was 5.2 ± 3.2 weeks.

Late toxicity

Although follow up is still too short to draw meaningful conclusions, 2 patients experienced mild dysphagia, but were able to tolerate a normal diet. Four patients developed L'Hermitte's syndrome, starting at 3 months post-treatment and lasting 6—9 months, and with all patients making a full recovery. One patient complained of moderate xerostomia, 2 had altered taste sensation and 3 complained of mild hoarseness.

Outcome

Of the 13 patients, all had a complete response (CR) to treatment, but 3 developed recurrent disease. One patient with medullary carcinoma of the thyroid developed an in-field recurrence 36 months following completion of treatment. One patient with Hurthle cell carcinoma progressed both in the mediastinum (in-field) and the lungs at 7 months. A third patient, with medullary carcinoma, developed bone and lung metastases 3 months after IMRT. Both patients with metastatic disease subsequently died. A third patient died of unrelated causes. Nine patients (69%) remain alive and disease free.

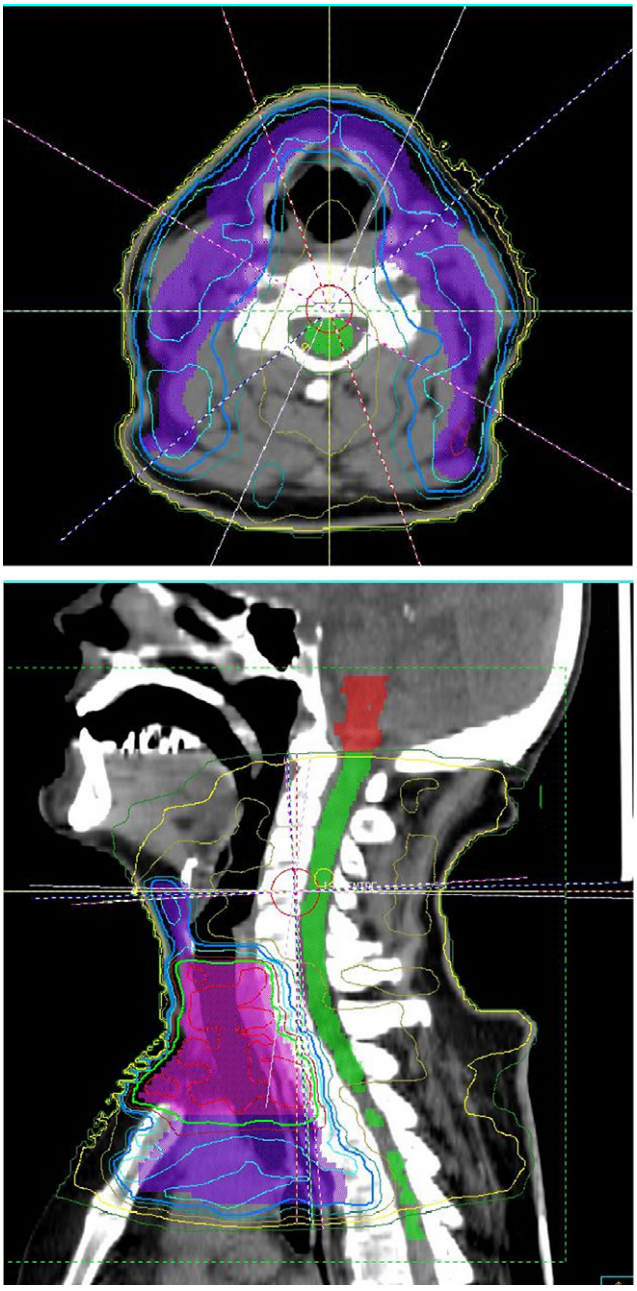

Fig. 1. Simultaneous-integrated-boost (SIB)-IMRT technique characterised by the delivery of a different dose per fraction to different target volumes. Primary target volume (PTV1: dark grey) and elective nodal target volume (PTV2: light grey). The light grey line represents the 95% isodose and the dark grey line the 90% isodose for the 58.8 Gy prescription. The dark blue line represents the 95% isodose and the dark green line the 90% isodose for the 50.0 Gy prescription.

Discussion

The acute toxicity of delivering high dose radiotherapy to the thyroid bed and bilateral neck for patients with high risk carcinoma of the thyroid was manageable with supportive care. Although the overall incidence of dysphagia was high, only 31% of patients required enteral feeding and this was short-term. Recovery was complete in 85% of patients, with

Table 2
Incidence of acute grade 2 and grade 3 toxicity

	G2 (%)	G3 (%)
Dermatitis	31	38.5
Mucositis	53	8
Dysphagia	61.5	31
Pain	54	23
Xerostomia	31	0

only 15% having late mild discomfort on swallowing. The lower incidence observed in our study than in the only other report of IMRT in thyroid cancer is likely to be a function of both the different prescription doses and the volume of tissue irradiated to high dose levels [15]. A correlation between the incidence of grades 3–4 mucositis and the proportion of patients requiring enteral feeding has been reported in patients with head and neck cancer [2,19]. Objective assessment of acute pharyngeal and oesophageal mucositis is, however, difficult in thyroid tumours, where its clinical manifestations, i.e. dysphagia and pain, can be used as surrogates. In our study the incidence of G3 mucositis was 7.7%, but this figure is likely to underestimate the true incidence of this toxicity as the area assessed (posterior oropharyngeal wall and the supraglottic larynx) was in most cases above the high dose volume. Radiation oesophagitis has been found to correlate with dosimetric parameters such as maximum and mean doses and volume and length irradiated [9,14,17], but our dataset was too small to derive any such correlations. The late toxicity observed to date was low, but further follow up is required to assess this further.

Overall, two patients developed local recurrence, one with medullary and the other with Hurthle cell thyroid cancer, giving a local control rate of 85% for the whole group. Half of the patients in our study had non-familial medullary carcinoma, which is known to have a poor prognosis with 50% patients having cervical nodal metastases at diagnosis and a 10-year disease-free survival rate of 50% in patients over 40 years old [5]. Recently, an 82% 2-year local progression free rate was reported in thyroid cancer with the use of IMRT [15]. In this study, out of a total of 20 patients, most had papillary thyroid cancer and the doses delivered to the primary/high dose volume ranged from 54 to 70 Gy.

IMRT achieved mean doses to 95% of the high dose volume of 56.4 Gy at 2.1 Gy per fraction. This technique has the potential to allow doses to both the primary and elective volumes to be increased whilst keeping the spinal cord dose within tolerance. Given the reported poor prognosis of patients with locally advanced disease it could be considered that they might benefit from dose escalation. One such strategy has been proposed as part of this study, where dose

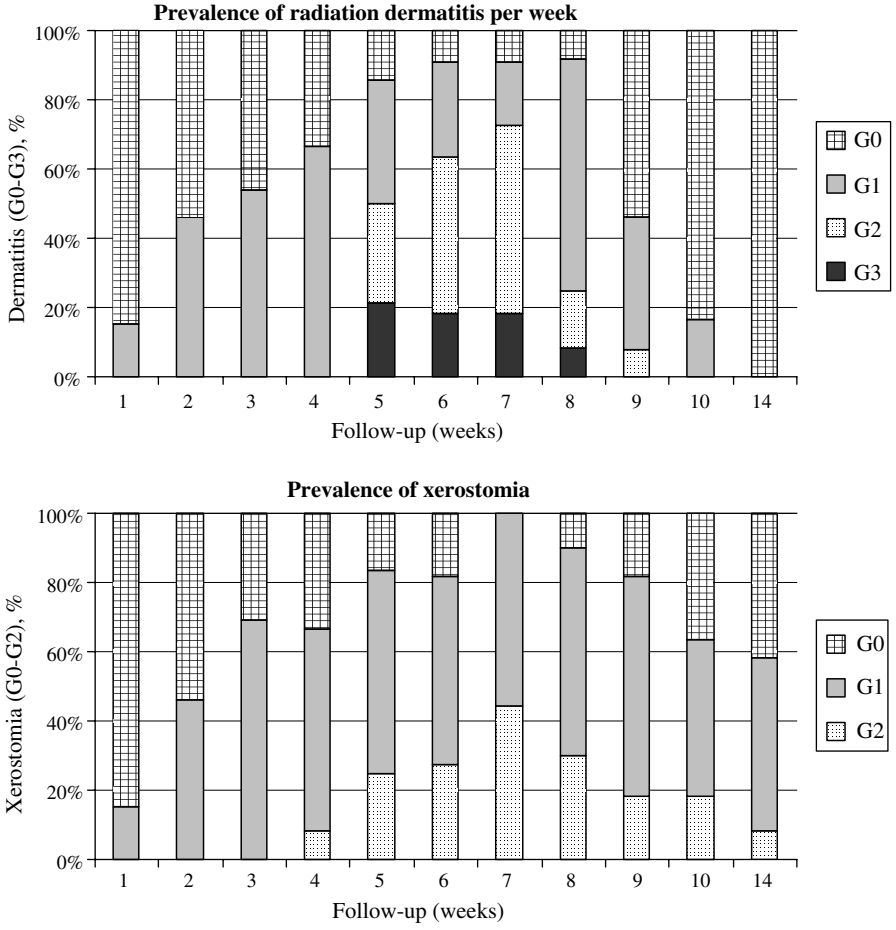

Fig. 2. Prevalence of radiation dermatitis and xerostomia over time.

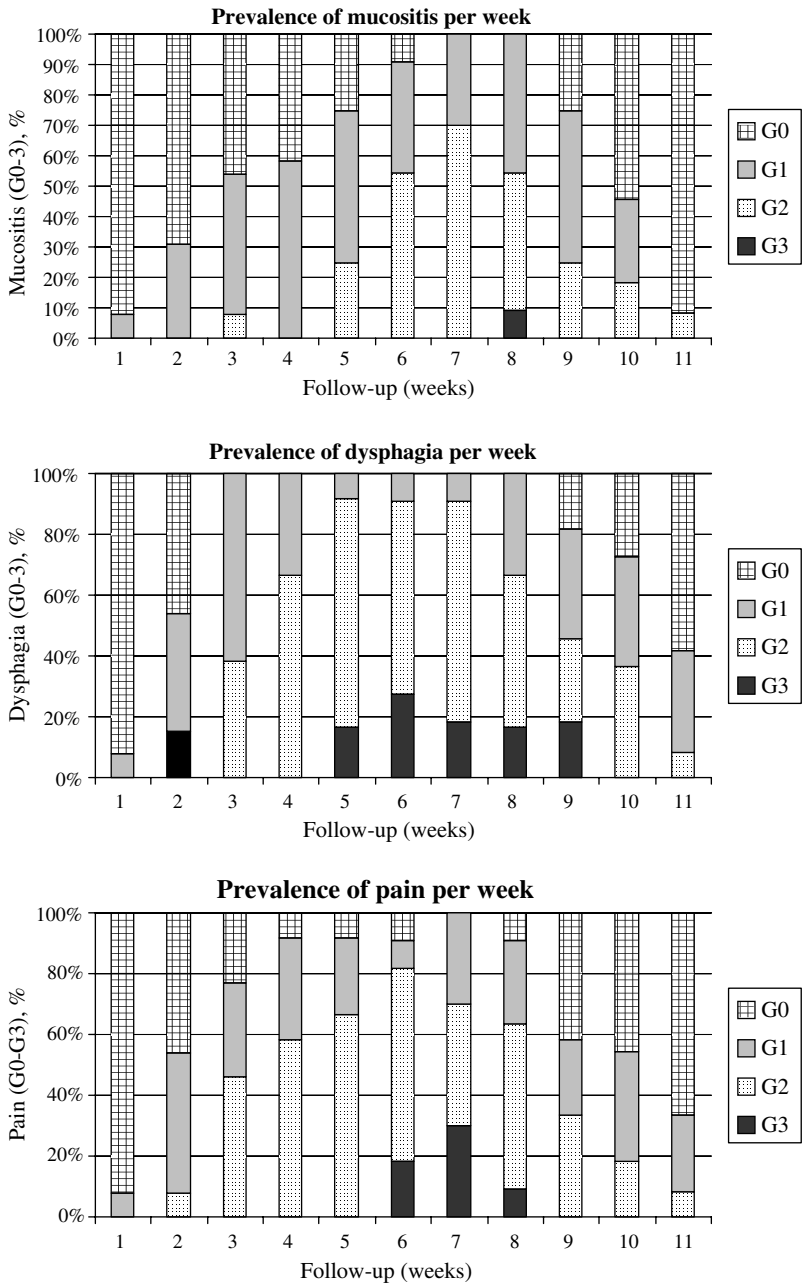

Fig. 3. Prevalence of radiation mucositis, dysphagia and pain over time.

escalation to the primary volume to 66.6 Gy in 30 daily fractions has now been undertaken.

In summary, we have shown that IMRT is feasible and safe in this group of patients. The acute toxicity of IMRT appeared acceptable and early indicators of late toxicity moderate and similar to what would be expected with conventional RT.

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