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Original article

Intensity modulated radiotherapy in locally advanced thyroid cancer: Outcomes of a sequential phase I dose-escalation study

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ABSTRACT

Background and purpose: To determine the safety and tolerability of dose-escalation using modestly accelerated IMRT in high-risk locally advanced thyroid cancer requiring post-operative radiotherapy, and to report preliminary data on efficacy.

Materials and methods: A sequential Phase I dose-escalation design was used. Dose level one (DL1) received 58.8 Gy/28F to the post-operative bed and 50 Gy/28F to elective nodes. DL2 received 66.6 Gy/30F to the thyroid bed, 60 Gy/30F to post-operative nodal levels and 54 Gy/30F to elective nodal levels. Acute (NCICTCv.2.0) and late toxicities (RTOG and modified LENTSOM) were recorded. The primary endpoint was the number of patients with ≥Grade 3 (G3) toxicity at 12 months post-treatment.

Results: Fifteen patients were recruited to DL1 and twenty-nine to DL2. At 12 months ≥G3 toxicities were 8.3% in both DL1 and DL2. At 60 months, ≥G3 toxicity was reported in 3 (33%) patients in DL1 and 1 (7%) in DL2. One patient in DL2 died at 24 months from radiation-induced toxicity. Time to relapse and overall survival rates were higher in DL2, but this was not statistically significant.

Results: Dose-escalation using this accelerated regimen can be safely performed with a toxicity profile similar to reported series using conventional doses.

External beam radiotherapy is used in high-risk thyroid cancer postoperatively to reduce the risk of recurrence and increase the likelihood of achieving locoregional control [1].

Dosimetric planning studies have demonstrated that intensity-modulated radiotherapy reduces dose to organs-at-risk in thyroid cancer while maintaining PTV coverage [2].

There has been no prospective trial assessing dose-fractionation in thyroid cancer, although retrospective series suggest a dose–response curve [3].

It is generally accepted that a dose of 60 Gy in 30 fractions or a biologically equivalent dose is required, although some centres have explored the use of boosts above this to the at-risk areas [4,5].

We have previously reported acute toxicities in DL1 of the study investigating the effect of modest acceleration using IMRT to deliver 58.8 Gy in 28 fractions to tumour bed or involved nodal sites and 50 Gy in 28 fractions to elective nodes [6]. This was well tolerated with one G3 toxicity and the trial proceeded to DL2 with an expanded dose-escalated cohort. This cohort received 66.6 Gy in 30 fractions to the primary tumour bed, 60 Gy in 30 fractions to the involved nodes and 54 Gy in 30 fractions to the elective nodes. The aim of this sequential Phase I study was to assess the safety and tolerability of dose-escalation using IMRT, and gain preliminary data on efficacy.

We have previously reported the acute toxicities of the expanded cohort, which were similar between the two groups [7]. We now report the long-term toxicity and survival outcomes at five years.

Materials and methods

Study objectives and patient eligibility

Patients with histologically proven, locally advanced differentiated and medullary thyroid carcinoma with radiological and pathological features warranting post-operative external beam radiotherapy were eligible (T4 disease; positive neck nodes; recurrent disease; residual macroscopic disease or medullary carcinoma). Patients aged <18 years or with an anaplastic thyroid

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cancer were excluded. Pre-treatment evaluations comprised history, examination, pre-operative computed tomography of head, neck and chest, optimal surgical resection and institutional pathological review. The disease was staged according to AJCC 1997 criteria. All patients provided written informed consent and the Institutional Research and Ethics Committee approved the study (Royal Marsden Hospital CCR 1978, NCT02055989).

Trial design

A sequential cohort Phase I dose-escalation design was used. This was a single institution study with standard departmental protocol used for target volume delineation. The aim of the first phase was to determine feasibility of using IMRT in delivering a modestly accelerated fractionation regimen. Dose-escalation followed once feasibility was demonstrated in the Phase I study. Initially, 15 patients were enroled to dose level 1 (DL1). The planning target volume 1 (PTV1) comprised the post-operative surgical bed (the thyroid bed, level VI nodal group and post-operative nodal groups) and received 58.8 Gy in 28 fractions. The elective nodal levels, PTV2 (remaining level II–V and upper mediastinum) received 50 Gy in 28 fractions.

Dose level 2 (DL2) represented an increase in biologically equivalent dose of 12% to the primary tumour, thus delivering 66.6 Gy in 30 fractions to thyroid bed and level VI lymph node group, 60 Gy in 30 fractions to post-operative nodal levels and 54 Gy in 30 fractions to elective nodal levels.

Radiotherapy technique

Patients were immobilized with a custom-made mask. Target volumes and organs-at-risk (brainstem, spinal cord and parotid glands) were delineated according to ICRU as previously described [6], using a standard protocol across both recruiting centres within the same institution (Royal Marsden Hospital) for both DL1 and DL2. Radiotherapy was delivered using five or seven-beam simultaneous integrated boost IMRT techniques. Radiation dose was prescribed to the median of the PTV1 dose–volume histogram such that 95% of each PTV was encompassed by 95% of the prescription dose. The maximum dose constraints to 1 cm^3 of the spinal cord and brainstem were 46 Gy and 54 Gy, respectively, and a mean dose constraint of 24 Gy was applied to each parotid gland. Radiotherapy was delivered in once daily fractions, 5 fractions weekly excluding the weekend.

Outcome assessment

Recurrence was defined as clinical, biochemical, radiological and/or histopathological evidence of disease presenting three months after completing radiotherapy. Where possible, patients proceeded to salvage surgery for persistent or recurrent disease.

Acute and late toxicity

Acute toxicity scores were recorded using NCI-CTCAE v.2.0 weekly during IMRT, for 4 weeks of recovery and at week 14. Indications for enteral feeding were: weight loss >10%, risk of aspiration and inability to maintain adequate calorific intake. Late toxicity scores (RTOG/EORTC and LENTSOMA) were recorded at follow-up at 3, 6, 12, 18 and 24 months after radiotherapy and yearly thereafter to 60 months.

Statistical analysis

The primary endpoint was the number of patients with G3/4 complication at 12 months after treatment. DL1 was designed as a feasibility study of modestly accelerated IMRT equivalent to 60 Gy in 30 fractions. Dose-escalation to DL2 was scheduled once feasibility was demonstrated. The stopping rules determined that if 0 (n = 15) patients had ≥G3 late complications at 1 year then a ≥20% risk of G3 late complication rate would be excluded with 95% power. If any patient developed ≥G3 late complications at DL1 and DL2, then the number of patients recruited at that level would be increased to 30 to improve statistical power and escalation to DL2 would only be allowed if no more than two patients developed G3 late toxicity (incidence of ≥G3 late complication rate predicted to be 0–17% and 0–22%, respectively, with 95% power).

If more than 2 patients suffered a ≥G3 late complication then recruitment to that level would be stopped (incidence of ≥G3 complication predicted to be 2–27% with 95% power). The dose-limiting toxicity was defined as the number of patients with ≥G3 toxicity at 1 year following completion of treatment. The 2 dose cohorts are sequential studies and their outcomes are reported separately.

Descriptive statistics are used to present the data. The incidence of an acute or late toxicity was defined as the total number of patients reaching that grade at any time, divided by the total number of assessable patients. The prevalence of a reaction at a specified point in time was defined as the number of patients scored as having that grade of reaction relative to the total number of patients assessed at that specific time point. Outcome measures following IMRT were described by local (at primary site) and regional (neck and upper mediastinum) control. Time to locoregional recurrence interval was calculated as time from diagnosis to recurrent local or nodal disease. Patients with persistent disease at primary site or neck were included as locoregional events. Time to relapse rate (TTR) was defined as time from diagnosis to development of locoregional and/or distant disease. Overall survival (OS) was measured from diagnosis to death from any cause. Survival analyses were estimated using the Kaplan–Meier method. All outcomes were recorded at patient visits or gained retrospectively from patient records.

Results

From February 2002 to December 2010, 15 patients were treated in DL1 and 30 in DL2 as outlined in the CONSORT diagram (Fig. 1). One patient with anaplastic thyroid cancer was removed from analysis in DL2. Table 1 (Supplemental data) lists the baseline patient and tumour characteristics. All patients underwent total thyroidectomy with selective neck dissection or optimal surgical resection of recurrent disease. Radioiodine remnant ablation was administered as indicated for differentiated thyroid carcinoma. Median (range) time to complete radiotherapy was 38 days (37–45) in DL1 and 42 days (39–46) in DL2.

All 15 patients in DL1 completed radiotherapy without any interruptions. At 12 months following completion of radiotherapy, 12 patients were assessable for late toxicities.

One patient experienced G3 ‘subjective difficulty in breathing’ at twelve months, which resolved and was not reported after this. There was no associated respiratory toxicity in the ‘objective’ and ‘management’ domains at any point. They had previously experienced G3 dysphagia, pain and salivary gland changes during radiotherapy at week 5 and 6 extending to week 2 and 3 post-radiotherapy. Therefore, after case review it was felt safe to proceed to DL2.

Fifteen patients were initially enroled in DL2. One patient experienced G3 dysphagia and a radiation-induced stricture at 12 months. The cohort was then expanded to 30 patients. A total of 24 patients were assessable for late toxicities at 12 months. A further patient experienced G3 xerostomia at 12 months which resolved by 18 months. The two patients who experienced G3 tox-

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