

**INTENSITY MODULATED RADIOTHERAPY IN LOCALLY ADVANCED THYROID CANCER: OUTCOMES OF  
A SEQUENTIAL PHASE I DOSE-ESCALATION STUDY**

Rooney KP<sup>1</sup>, Miah AB<sup>2,3</sup>, Bhide SA<sup>2,3</sup>, Guerrero-Urbano MT<sup>2,3</sup>, Sharabiani MT<sup>5</sup>,  
Newbold KL<sup>2</sup>, Grove L<sup>2</sup>, \*Harrington KJ<sup>2,3</sup> and \*Nutting CM<sup>2,3</sup>

<sup>1</sup>N. Ireland Cancer Centre, Belfast City Hospital, Belfast, UK. <sup>2</sup>Head and Neck  
and Thyroid Unit, The Royal Marsden NHS Foundation Trust, UK; <sup>3</sup>The Institute  
of Cancer Research, London, UK; <sup>4</sup>Department of Physics, The Royal Marsden  
NHS Foundation Trust; <sup>5</sup>Clinical Statistics Unit, The Royal Marsden NHS  
Foundation Trust

\*KJH and CMN are joint senior authors

Corresponding author

Professor CM Nutting  
Consultant Clinical Oncologist  
The Royal Marsden NHS Foundation Trust  
Fulham Road  
London SW3 6JJ

Tel: 0207 808 2586  
Fax: 0207 808 2235  
Email : [chris.nutting@rmh.nhs.uk](mailto:chris.nutting@rmh.nhs.uk)

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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  $\geq$  Grade 3 (G3) toxicity at 12 months post-treatment.

### **Results**

Fifteen patients were recruited to DL1 and twenty-nine to DL2. At 12 months,  $\geq$  G3 toxicities were 8.3% in both DL1 and DL2. At 60 months,  $\geq$  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 interval and overall survival rates were higher in DL2, but this was not statistically significant.

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

## Introduction

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 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 enrolled 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 immobilised 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 technique. 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<sup>3</sup> 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 caloric 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  $\geq$  G3 late complications at 1 year then a  $\geq$  20% risk of G3 late complication rate would be excluded with 95% power. If any patient developed  $\geq$  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  $\geq$  G3 late complication rate predicted to be 0-17% and 0-22%, respectively, with 95% power).



If more than 2 patients suffered a  $\geq$  G3 late complication then recruitment to that level would be stopped (incidence of  $\geq$  G3 complication predicted to be 2–27% with 95% power). The dose-limiting toxicity was defined as the number of patients with  $\geq$  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 interval 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 (Figure 1). One patient with anaplastic thyroid cancer was removed from analysis in DL2. Baseline demographics (Table 1) were comparable between the groups. 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 enrolled 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 that resolved by the next visit at 18 months. The two patients who experienced G3 toxicities at 12 months were alive at 5 years with no evidence of relapse.

An additional patient experienced G3 dysphagia requiring enteral feeding at the end of treatment until 6 months. At 11 months the patient developed wheeze and subglottic stenosis that settled with steroids. This deteriorated by 18 months requiring a tracheostomy. At 24 months they required a laryngectomy and unfortunately, the patient died from haemorrhage shortly after.

There was no significant difference in the frequency of  $\geq$  G3 toxicities between DL1 (8.3%) and DL2 (8.3%) at twelve months (Figure 2).

This remained the case out to year 5 with three patients reporting xerostomia in DL1 and one developing skin fibrosis in DL2 (supplementary material: Table 1, Figure 1).

Tables 2 and 3 (supplementary material) report the number of patients who had at least one G3 /4 toxicity at each visit at which toxicity was assessed.

Tables 4, 5, 6 and 7 (supplementary material) display the total frequency for each category of toxicity. During the five years of follow-up, a total of 12  $\geq$  G3 late toxicities occurred for DL1 and 24 for DL2. This includes patients who had the same persistent toxicity recorded several times.

The number of patients with recorded data at each visit is shown in table 8 (supplementary material), deaths included: two patients in DL1 during year one, one due to a non-cancer cause and the other due to cancer progression. A further three died in the third year of follow-up due to disease relapse (supplemental material: Figure 2a).

Two patients in DL2 were lost to follow-up after 6 months. Four patients died within the follow-up period, all due to disease relapse.

In DL1, there were 3 locoregional recurrences (supplemental material: Figure 2b). Five patients developed metastatic disease (3 medullary, 1 papillary and 1 Hurthle cell).

In DL2, two patients developed recurrent disease within the high-dose irradiated volume; both had macroscopic residual disease at the time of radiotherapy and relapsed within 3 months following completion of radiotherapy. Four patients in DL2 developed metastatic disease (1 medullary, 1 recurrent papillary, 1 undifferentiated small cell/papillary and 1 recurrent Hurthle cell).

## Discussion

External beam radiotherapy has been used in thyroid cancer for over fifty years, although the patient group that benefits from it has been the subject of much debate. There has been no successful randomized controlled trial to address this and the majority of evidence informing its use has been derived from retrospective analyses. Key evidence from trials such as Farahati et al (1996) [8] suggested radiotherapy increased the time to relapse in high-risk individuals who were aged over 40 with extrathyroideal extension treated standardly with surgery, radioiodine ablation and TSH suppression.

On the basis of reviews into the retrospective data, the British Thyroid Association [1] and American Thyroid Association [9] support the use of radiotherapy in selected high-risk groups, such as those with significant macroscopic disease or where further surgery or radioiodine is not an option.

Dose-response has been investigated over the past 2 decades; Ford et al (2003) [3] noted an improved loco-regional control rate as doses rose to over 54 Gy in retrospective analysis.

More recently, IMRT has been used to deliver homogeneous radiotherapy doses with steeper dose gradients. Schwartz et al (2009) [4] reported their single institution experience in MD Anderson using doses of 60 Gy to the post-operative bed with boosts up to 70 Gy to areas of microscopic and macroscopic involvement. They reviewed 131 patients, 44% of who were treated with IMRT and noted a

decrease in severe late morbidity in the IMRT group (2%) compared to the non-IMRT group (12%).

Teriazakis et al (2009) [5] published data from retrospective analysis of 76 patients treated between 1989 and 2006, including 47 who received IMRT. Patients received 59.4-70 Gy (depending on macroscopic involvement), late enteral feeding tube rate was 5% and two patients required a long-term tracheostomy due to laryngeal oedema; there was no noted difference in toxicity between IMRT and non-IMRT patients. Although retrospective analysis suggests that dose-escalation above 60 Gy using IMRT is safe, this has not been demonstrated in a randomized trial.

We first evaluated the outcomes in a modestly accelerated course of 58.8 Gy in 28 fractions (EQD2 of 60 Gy in 30 fractions) using IMRT and then investigated the safety of dose-escalation above this. Urbano et al (2007) [6] previously reported the initial results of the DL1 cohort demonstrating its safety and rationale for moving onto dose-escalation in DL2. The acute toxicities of DL2 previously reported by Zaidi et al (2011) [7] were comparable to DL1.

We now report the mature long-term results and have demonstrated that dose-escalation of 12% (66.6 Gy in 30 fractions) to the thyroid bed can be safely performed and is tolerable when compared to a dose of 58.8 Gy in 28 fractions.

The study has demonstrated similar  $\geq$  G3 toxicity at 12 months in DL1 and DL2. This was consistent when patients were followed up to trial completion at five years.

However, the study was limited by a decrease in number of assessable patients at the 12 month primary endpoint (DL1 = 12, DL2 = 24)

The recorded long-term toxicities in this trial compare favourably with other studies of thyroid dose-escalation as shown in Table 9 (supplemental material).

These studies had a dysphagia toxicity rate ( $\geq$  G2) of 8% to 20%, similar to our reported rate of 12% in DL2. Stricture or enteral-feeding dependence ranged from 5.4% to 10% compared to 4% in DL2. There was one patient (8%) on nutritional supplements in DL1 but none required long-term enteral feeding.

Although the rates of  $\geq$  G3 toxicities were similar between DL1 and DL2, more subjects in DL2 had persistent grade 1 subjective difficulty in eating solids (DL1: 10% v DL2: 25%). Although low grade, this toxicity may be due to the dose-escalation.

There was also one toxicity-related death after 24 months after laryngectomy for radiation-induced stricture. This serves to remind us of the need for accurate target volume delineation and good patient selection to minimize the normal tissue irradiated. It is reassuring that dysphagia-related toxicities for the remaining patients in DL2 were similar to other studies, as noted above.

Xerostomia at 5 years was higher in DL1 (33% experienced  $\geq$  G3), however this was a small sample (3 out of 9 patients) and it is possible that improvements in radiotherapy planning technique with an increasing focus on parotid-sparing IMRT may account for this improvement.

Survival outcomes were generally better in DL2 with 5-year overall survival of 83.7% in DL2 and 65.5% in DL1. This compares favourably with other series (overall survival rates = 54-73%, supplementary material, Table 9).

The lower overall survival in DL1 compared to DL2 may be accounted for by the older age of its subjects (DL1: 55 v DL2: 52) and the increased number of T4 cases (DL1: 80% v DL2: 41%). However, there were more node positive cases in DL2 (DL1: 53% v DL2: 93%).

DL2 also had better 5-year time to relapse (DL1: 70.4% v DL2: 79.6%, Figure 3) and time to locoregional recurrence than DL1 (DL1: 76.9% v DL2: 91.5%). This difference was not statistically significant and it must be noted that the trial was neither designed nor powered to detect these outcomes (Table 2).

It would be interesting to assess if the higher overall survival and time to relapse noted in DL2 could achieve statistical significance in an adequately powered phase III trial.

This study was hindered by the small sample size and long accrual time with subsequent patient drop out and loss of information at follow up visits.

Despite this we have provided evidence that investigation into dose escalation can be performed safely, however the long term toxicity of radiotherapy remains a concern and current research options are evaluating alternative strategies aimed at enhancing the effectiveness of radioiodine in patients using drugs such as selumetinib [10], a MEK inhibitor, in trials including the US based ASTRA trial (NCT01843062) [11].

The continuing evolution of intensity-modulated radiotherapy provides new opportunities to create steep dose gradients. This combined with careful delineation



of planning target volumes and organs at risk allows for potential sparing of important structures causing long-term toxicity such as the swallowing muscles. This concept is already being realised in oropharyngeal and hypopharyngeal cancer through the UK DARS trial (ISRCTN 25458988). This is evaluating the impact of reducing dose to the pharyngeal constrictor muscles that are involved in swallowing on long-term swallowing outcomes in an international, multicentre phase III setting [12]. Future phase III thyroid radiotherapy studies could utilize these improved techniques with dose escalation to minimize toxicity while ensuring accurate dose delivery to planning target volumes.

Dose-escalation for thyroid cancer can be safely performed with a toxicity profile similar to conventional radiotherapy dose-fractionation schedules and should be investigated in further clinical trials.

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## Figures

**Figure 1: CONSORT diagram**

**Figure 2: LENTSOMA toxicity at 12 months (%).**

**Figure 3: Kaplan-Meier estimates of time to relapse interval at 2 and 5 years**

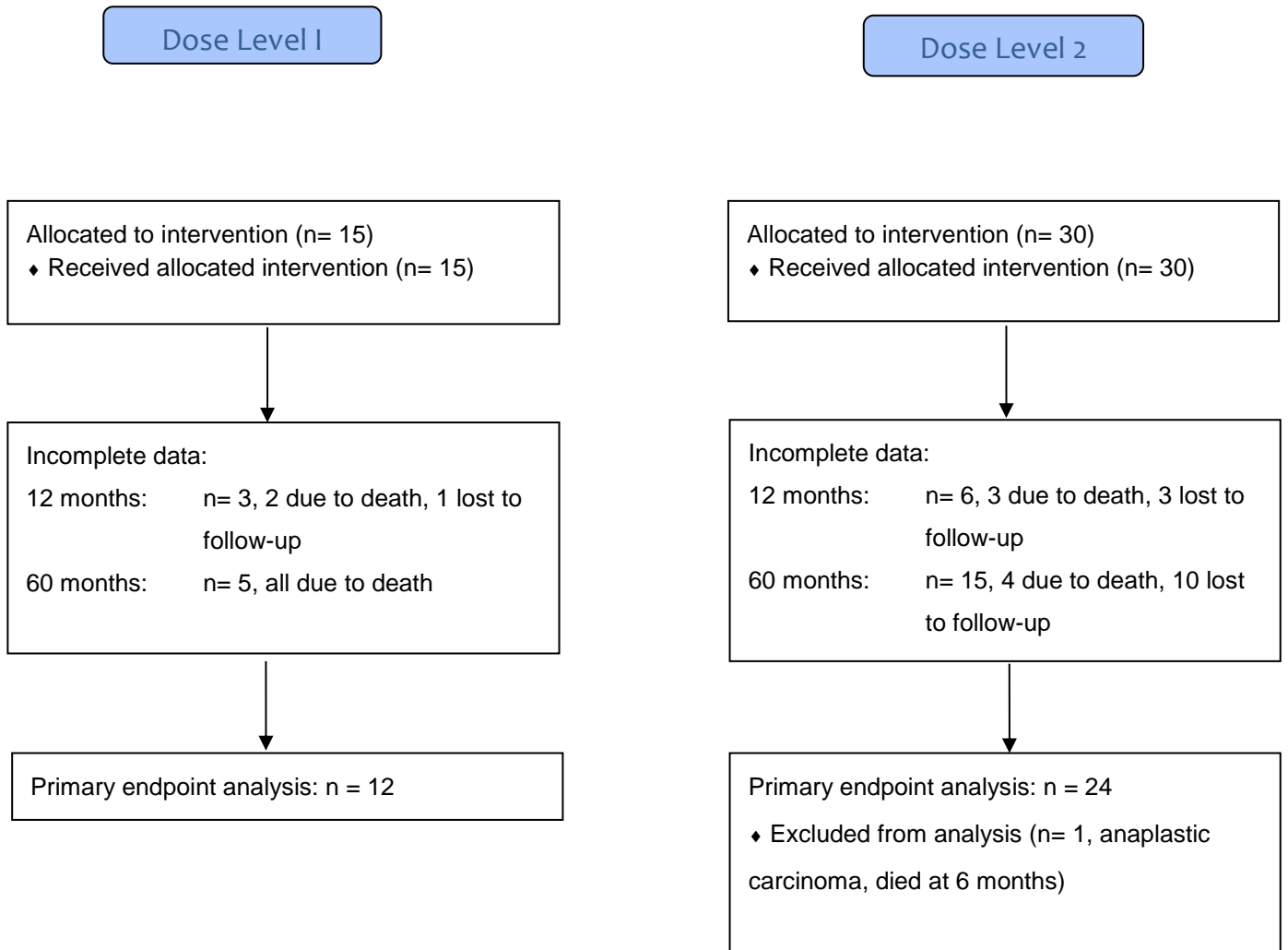
### **Abbreviations:**

**DL1 = Dose level 1**

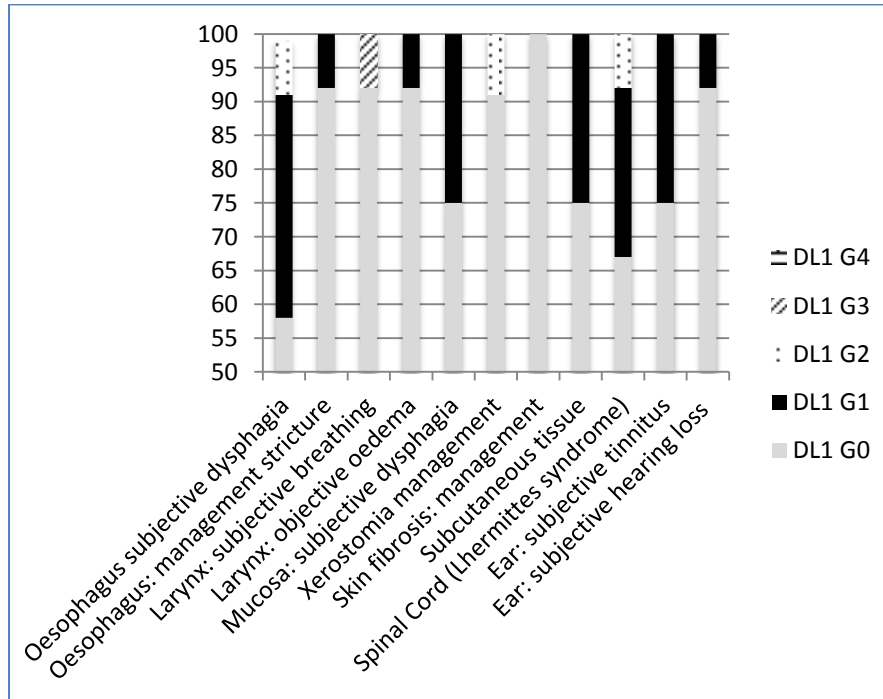
**DL2 = Dose level 2**

**G0, G1.. = Grade 0 toxicity, Grade 1 toxicity etc.**

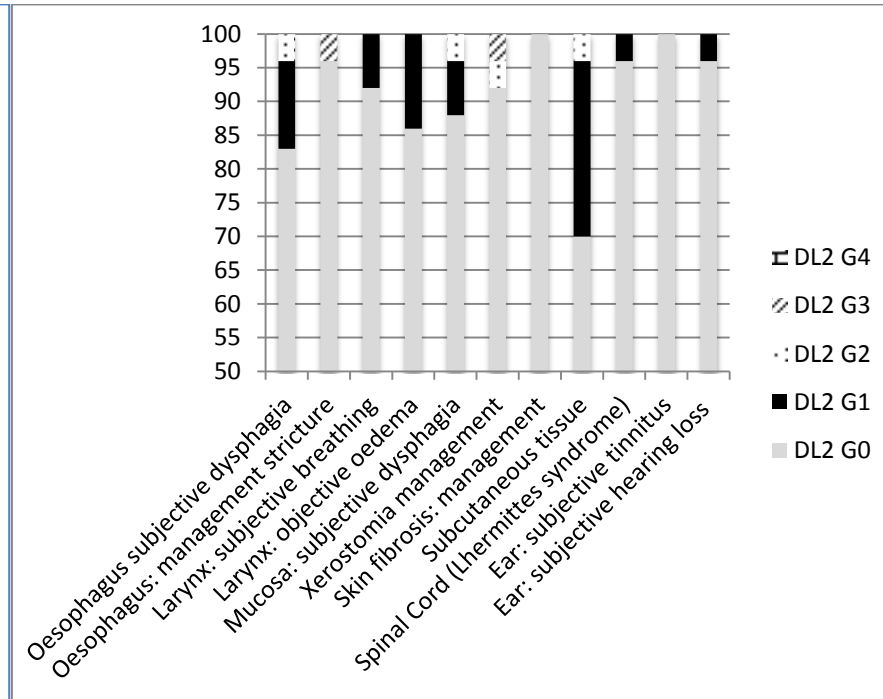
## CONSORT Diagram



**Figure 2: LENTSOMA toxicity at 12 months (%).**  
**DL1 (n=12)**



**DL2 (n=24)**



**No significant difference in frequency of  $\geq$  Grade 3 toxicity at 12 months (DL1 and DL2 = 8.3%).**

**Figure 3: Kaplan-Meier survivor estimates of time to relapse interval at 2 and 5 years (p=0.33).**

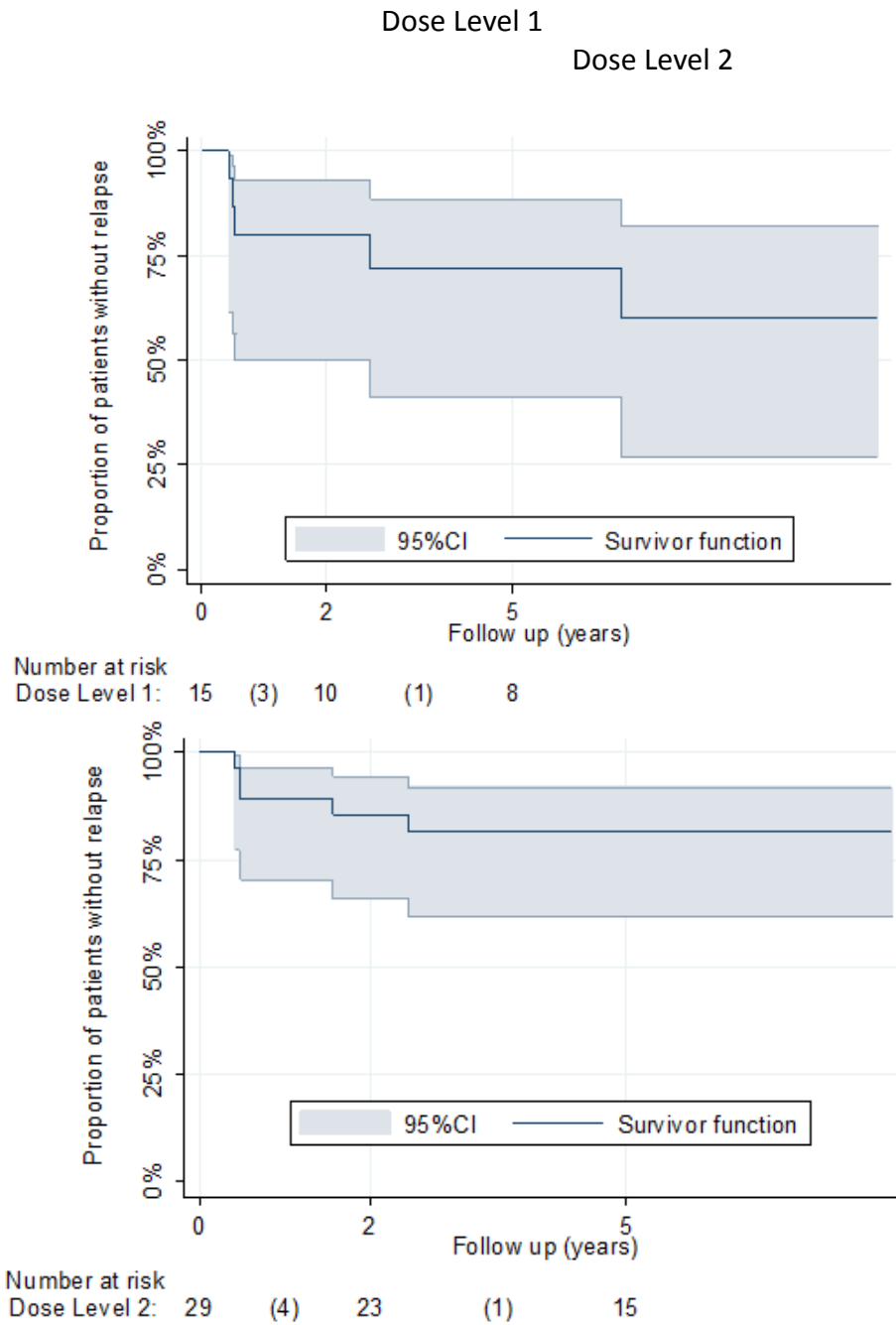


Figure in bracket = number who have relapsed



## Tables

**Table 1: Baseline demographics (n=44)**

**Table 2: Two and five year survival & recurrence outcomes**

**Table 1: Baseline demographics (n=44)**

	DL1 (n=15)		DL2 (n=29)	
	n	%	n	%
<b>Female</b>	10	67	13	45
<b>Male</b>	5	33	16	55
<b>pT1</b>	0	0	3	10
<b>pT2</b>	0	0	10	34.5
<b>pT3</b>	3	20	4	14
<b>pT4a</b>	9	60	10	34.5
<b>pT4b</b>	3	20	2	7
<b>pN0</b>	7	47	2	7
<b>pN1a</b>	1	6	10	34
<b>pN1b</b>	7	47	17	59
<b>Total</b>	<b>15</b>	<b>100</b>	<b>29</b>	<b>100</b>
<b>WHO performance status = 0</b>	14	93	23	79
<b>WHO performance status = 1</b>	1	7	6	21
<b>Histology</b>				
Medullary	7	47	14	48
Papillary	5	33	14	48
Follicular	1	7	0	0
Hurthle cell	2	13	1	4
<b>Mean Age (SD)</b>	55.1 (12.0)		51.8 (10.6)	

**SD = standard deviation**

**Table 2: Two- and five-year survival and recurrence outcomes**

Category	Dose Level	number of patients*	number of events in 5 years	Log- rank p-value	2-year survival (95% CI)	5-year survival (95% CI)
Overall survival (OS)	<b>DL 1</b>	15	5	0.09	73.3 (43.6, 89.1)	65.5 (36.0, 84.0)
	<b>DL 2</b>	29	4		92.9 (74.4, 98.2)	83.7 (62.2, 93.5)
Time to relapse interval	<b>DL 1</b>	15	4	0.33	78.6 (47.3, 92.5)	70.4 (39.0, 87.70)
	<b>DL 2</b>	29	5		85.7 (66.3, 94.4)	79.6 (57.7, 91.0)
Time to locoregional recurrence interval	<b>DL 1</b>	15	3	0.23	85.2 (52.6, 96.0)	76.9 (44.2, 91.9)
	<b>DL 2</b>	29	2		92.9 (74.4, 98.2)	91.5 (70.1, 97.8)

**CI = confidence interval**