

## Supplementary material

- Table 1:** Comparison of LENTSOMA toxicity at 60 months between DL1 & DL2
- Figure 1:** LENTSOMA toxicity at 60 months (%)
- Table 2:** Comparison of LENTSOMA toxicity at 12 months between DL1 & DL2
- Table 3:** Comparison (%) between DL1 and DL2 of LENTSOMA toxicity at 12 months and at 60 months.
- Table 4:** Frequency of  $\geq$ G3 LENTSOMA toxicity up to 12 months
- Table 5:** Frequency of all grades of LENTSOMA toxicity in those experiencing  $\geq$ G3 toxicities up to 12 months
- Table 6:** Frequency of  $\geq$ G3 LENTSOMA toxicity up to 60 months
- Table 7:** Frequency of all grades of LENTSOMA toxicity in those experiencing  $\geq$ G3 toxicities up to 60 months
- Table 8:** Number of assessable patients for each time-point (incomplete data due to death, not recorded or lost to follow up)
- Figure 2a:** Kaplan-Meier survivor estimates of Overall Survival
- Figure 2b:** Kaplan-Meier survivor estimates of time to locoregional recurrence interval
- Table 9:** Previous radiotherapy studies in thyroid cancer

### Abbreviations:

DL1 = Dose level 1

DL2 = Dose level 2

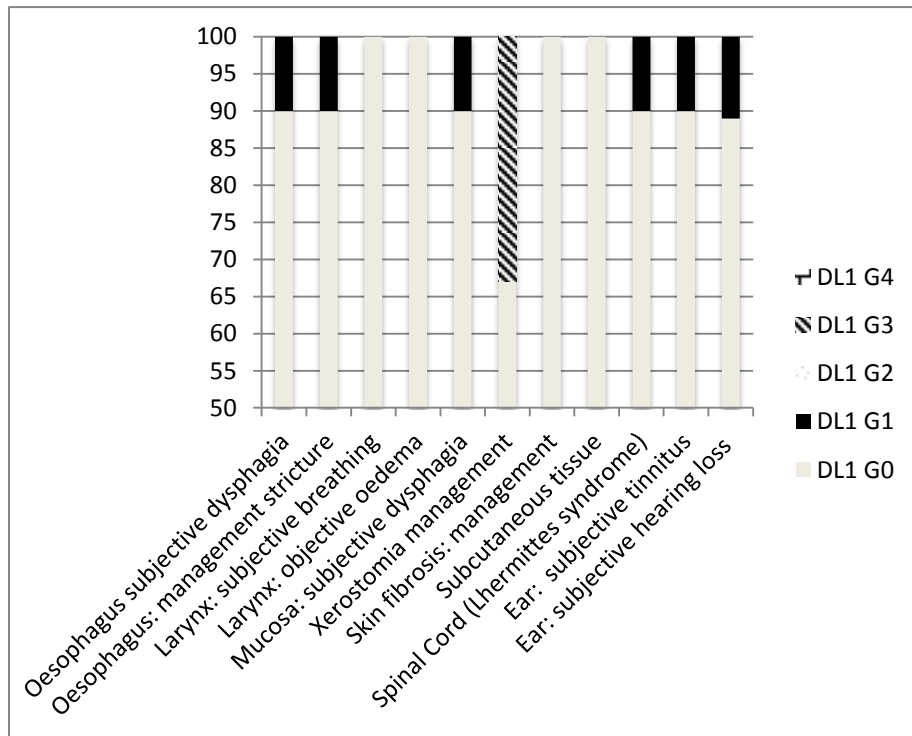
G0, G1.. = Grade 0 toxicity, Grade 1 toxicity etc.

**Table 1: Comparison of LENTSOMA toxicity at 12 months between DL1 & DL2, values are number (percentage)**

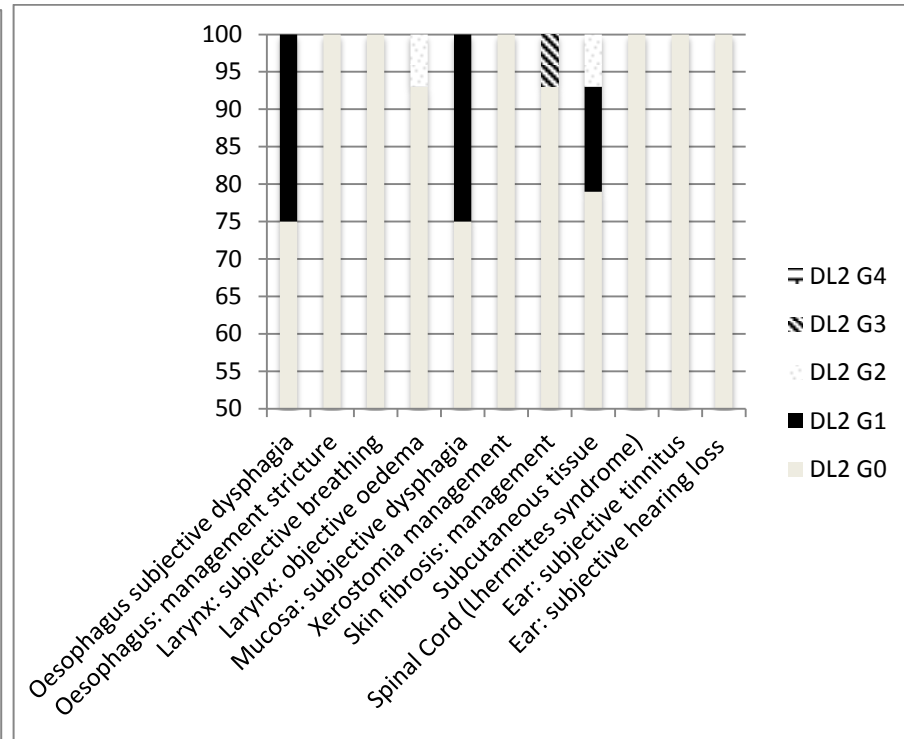
Symptom	Toxicity grade in each Dose Level (number of assessable subjects: DL1: n=12; DL2: n=24, unless otherwise stated)									
	G0		G1		G2		G3		G4	
	DL1	DL2	DL1	DL2	DL1	DL2	DL1	DL2	DL1	DL2
Oesophagus subjective dysphagia	7 (58)	19 (83) (n=23)	4 (33)	3 (13)	1 (8)	1 (4)	0	0	0	0
Oesophagus: management dysphagia/stricture	11 (92)	23 (96)	1 (8)	0	0	0	0	1 (4)	0	0
Larynx: subjective breathing	11 (92)	22 (92)	0	2 (8)	0	0	1 (8)	0	0	0
Larynx: objective oedema	11 (92)	19 (86) (n=22)	1 (8)	3 (14)	0	0	0	0	0	0
Mucosa: subjective dysphagia	9 (75)	21 (88)	3 (25)	2 (8)	0	1 (4)	0	0	0	0
Xerostomia management	10 (91) (n=11)	21 (92) (n=23)	0	0	1 (9)	1 (4)	0	1 (4)	0	0
Skin fibrosis: management	12 (100)	22 (100) (n=22)	0	0	0	0	0	0	0	0
Subcutaneous tissue	9 (75)	16 (70) (n=23)	3 (25)	6 (26)	0	1 (4)	0	0	0	0
Spinal Cord (L'hermitte's syndrome)	8 (67)	23 (96)	3 (25)	1 (4)	1 (8)	0	0	0	0	0
Ear – subjective tinnitus	9 (75)	24 (100)	3 (25)	0	0	0	0	0	0	0
Ear – subjective hearing loss	11 (92)	23 (96)	1 (8)	1 (4)	0	0	0	0	0	0

Figure 1: LENTSOMA toxicity at 60 months (%)

DL1



DL2



**Table 2: Comparison of LENTSOMA toxicity at 60 months between DL1 & DL2, values are number (percentage)**

Toxicity	Toxicity grade in each Dose Level (number of assessable subjects: DL1: n=10; DL2: n=15, unless otherwise stated)									
	G0		G1		G2		G3		G4	
	DL1	DL2	DL1	DL2	DL1	DL2	DL1	DL2	DL1	DL2
Oesophagus subjective dysphagia	9 (90)	12 (75)	1 (10)	3 (25)	0	0	0	0	0	0
Oesophagus: management dysphagia/stricture	9 (90)	15 (100)	1 (10)	0	0	0	0	0	0	0
Larynx: subjective breathing	10 (100)	15 (100)	0	0	0	0	0	0	0	0
Larynx: objective oedema	10 (100)	14 (93)	0	0	0	1 (7)	0	0	0	0
Mucosa: subjective dysphagia	9 (90)	12 (75)	1 (10)	3 (75)	0	0	0	0	0	0
Xerostomia management	6 (67) (n=9)	14 (100) (n=14)	0	0	0	0	3 (33)	0	0	0
Skin fibrosis: management	10 (100)	14 (93)	0	0	0	0	0	1 (7)	0	0
Subcut tissue	8 (100) (n=8)	11 (79) (n=14)	0	2 (14)	0	1 (7)	0	0	0	0
Spinal Cord (Lhermittes syndrome)	9 (90)	15 (100)	1 (10)	0	0	0	0	0	0	0
Ear – subjective tinnitus	9 (90)	15 (100)	1 (10)	0	0	0	0	0	0	0
Ear – subjective hearing loss	8 (89) (n=9)	15 (100)	1 (11)	0	0	0	0	0	0	0

**Table 3: Comparison of LENTSOMA toxicity at 12 months and at 60 months (values are percentage)**

Toxicity	G0				G1				G2				G3				G4			
	DL1		DL2		DL1		DL2		DL1		DL2		DL1		DL2		DL1		DL2	
	12	60	12	60	12	60	12	60	12	60	12	60	12	60	12	60	12	60	12	60
Oesophagus subjective dysphagia	58	90	83	75	33	10	13	25	8	0	4	0	0	0	0	0	0	0	0	0
Oesophagus: management dysphagia/stricture	92	90	96	100	8	10	0	0	0	0	0	0	0	0	4	0	0	0	0	0
Larynx: subjective breathing	92	100	92	100	0	0	8	0	0	0	0	0	8	0	0	0	0	0	0	0
Larynx: objective oedema	92	100	86	93	8	0	14	0	0	0	0	7	0	0	0	0	0	0	0	0
Mucosa: subjective dysphagia	75	90	88	75	25	10	8	25	0	0	4	0	0	0	0	0	0	0	0	0
Xerostomia management	91	67	92	100	0	0	0	0	9	0	4	0	0	33	4	0	0	0	0	0
Skin fibrosis: management	100	100	100	93	0	0	0	0	0	0	0	0	0	0	0	7	0	0	0	0
Subcutaneous tissue	75	100	70	79	25	0	26	14	0	0	4	7	0	0	0	0	0	0	0	0
Spinal Cord (Lhermittes syndrome)	67	90	96	100	25	10	4	0	8	0	0	0	0	0	0	0	0	0	0	0
Ear – subjective tinnitus	75	90	100	100	25	10	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Ear – subjective hearing loss	92	89	96	100	8	11	4	0	0	0	0	0	0	0	0	0	0	0	0	0

**Table 4: Frequency of  $\geq$ G3 LENTSOMA toxicity including all time points up to 12 months**

	DL1 = Dose Level 1 (n=15); DL2 = Dose Level 2 (n=29)			
Late toxicity	Grade 3		Grade 4	
	DL1	DL2	DL1	DL2
Oesophagus	0	2	0	1
Mucosa	3	1	0	1
Larynx	1	0	0	0
Xerostomia	0	2	0	0
Ear	0	1	1	0
Mandible	0	0	0	0
Spinal Cord	0	0	0	0
Skin	0	3	0	0

**Table 5: Frequency of all grades of toxicity in those experiencing  $\geq$ G3 LENTSOMA toxicity up to 12 months**

Late toxicity		DL1 = Dose Level 1 (n=15) DL2 = Dose Level 2 (n=29)							
		G0/1		G2		G3		G4	
		DL1	DL2	DL1	DL2	DL1	DL2	DL1	DL2
Oesophagus	Subjective Dysphagia	12	26	2	2	0	1	0	0
	Management Dysphagia	12	27	1	0	0	1	0	1
Mucosa	Subjective Pain	13	28	0	0	1	0	0	0
	Altered Taste	11	29	1	0	2	0	0	0
	Subjective Dysphagia	14	26	0	3	0	0	0	0
	Management Dysphagia	13	27	0	0	0	1	0	1
Larynx	Subjective Breathing	13	29	0	0	1	0	0	0
Xerostomia	Management*	11	24	2	3	0	2	0	0
Ear	Subjective Tinnitus	13	29	0	0	0	0	1	0
	Management Hearing Loss**	14	28	0	0	0	1	0	0
Skin	Management Dryness**	14	28	0	0	0	1	0	0
	Management Oedema**	13	27	0	0	0	1	0	0
	Management Fibrosis/Scar**	13	27	0	0	0	1	0	0

\* No grade 1 option

\*\* No grade 1 or grade 2 option

**Table 6: Frequency of  $\geq$ G3 LENTSOMA toxicity up to 60 months**

	DL1 = Dose Level 1 (n=15) DL2 = Dose Level 2 (n=29)			
Late toxicity	Grade 3		Grade 4	
	DL1	DL2	DL1	DL2
Oesophagus	0	4	0	1
Mucosa	3	2	0	1
Larynx	2	5	0	0
Xerostomia	6	2	0	0
Ear	0	1	1	0
Mandible	0	0	0	0
Spinal Cord	0	0	0	0
Skin	0	8	0	0



**Table 7: Frequency of all grades of LENTSOMA toxicity in those experiencing  $\geq$ G3 toxicities up to 60 months**

Late toxicity		DL1 = Dose Level 1 (n=15) DL2 = Dose Level 2 (n=29)							
		G0/1		G2		G3		G4	
		DL1	DL2	DL1	DL2	DL1	DL2	DL1	DL2
Oesophagus	Subjective Dysphagia	11	26	3	1	0	2	0	0
	Objective Stricture	13	28	0	0	0	1	0	0
	Management Dysphagia	12	27	1	0	0	1	0	1
Mucosa	Subjective Pain	13	28	0	0	1	0	0	0
	Subjective Altered Taste	11	28	1	1	2	0	0	0
	Subjective Dysphagia	13	26	1	2	0	1	0	0
	Management Dysphagia	13	27	0	0	0	1	0	1
Larynx	Subjective Hoarseness	12	23	2	4	0	2	0	0
	Management Hoarseness	12	26	1	2	0	1	0	0
	Subjective Breathing	13	28	0	1	1	0	0	0
	Objective Oedema	13	26	0	2	1	1	0	0
	Objective/ Management Respiration	13	28	0	0	0	1	0	0
Salivary gland	Subjective	8	23	5	6	1	0	0	0
	Objective	9	23	4	5	1	0	0	0
	Management*	9	22	0	5	4	2	0	0
Ear	Subjective Tinnitus	13	28	0	1	0	0	1	0
	Management Hearing Loss**	14	28	0	0	0	1	0	0
Skin	Management Dryness**	14	27	0	0	0	2	0	0
	Management Ulcer**	13	28	0	0	0	1	0	0
	Management Oedema**	13	27	0	0	0	2	0	0
	Management Fibrosis/Scar**	13	26	0	0	0	3	0	0

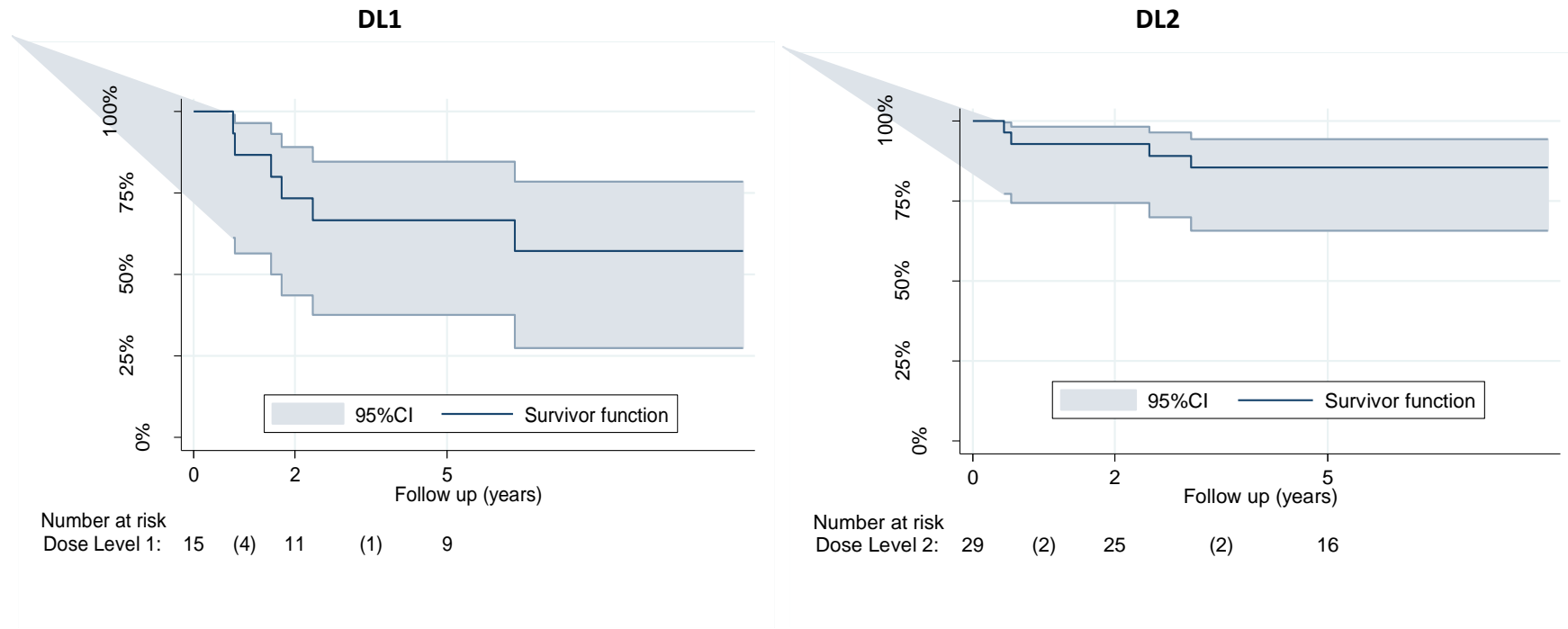
\* No grade 1 option

\*\* No grade 1 or grade 2 option

**Table 8: number of assessable patients for each time-point (incomplete data due to death, not recorded or lost to follow up)**

	Months								
	0	3	6	12	18	24	36	48	60
<b>DL1</b>	15	12	12	12	10	10	10	10	10
<b>DL2</b>	29	25	24	24	22	23	21	21	15

**Figure 2a: Kaplan-Meier survivor estimates of Overall Survival (p=0.09)**



**Figure in bracket = number who have died**

Figure 2b: Kaplan-Meier survivor estimates of time to locoregional recurrence interval ( $p=0.23$ )

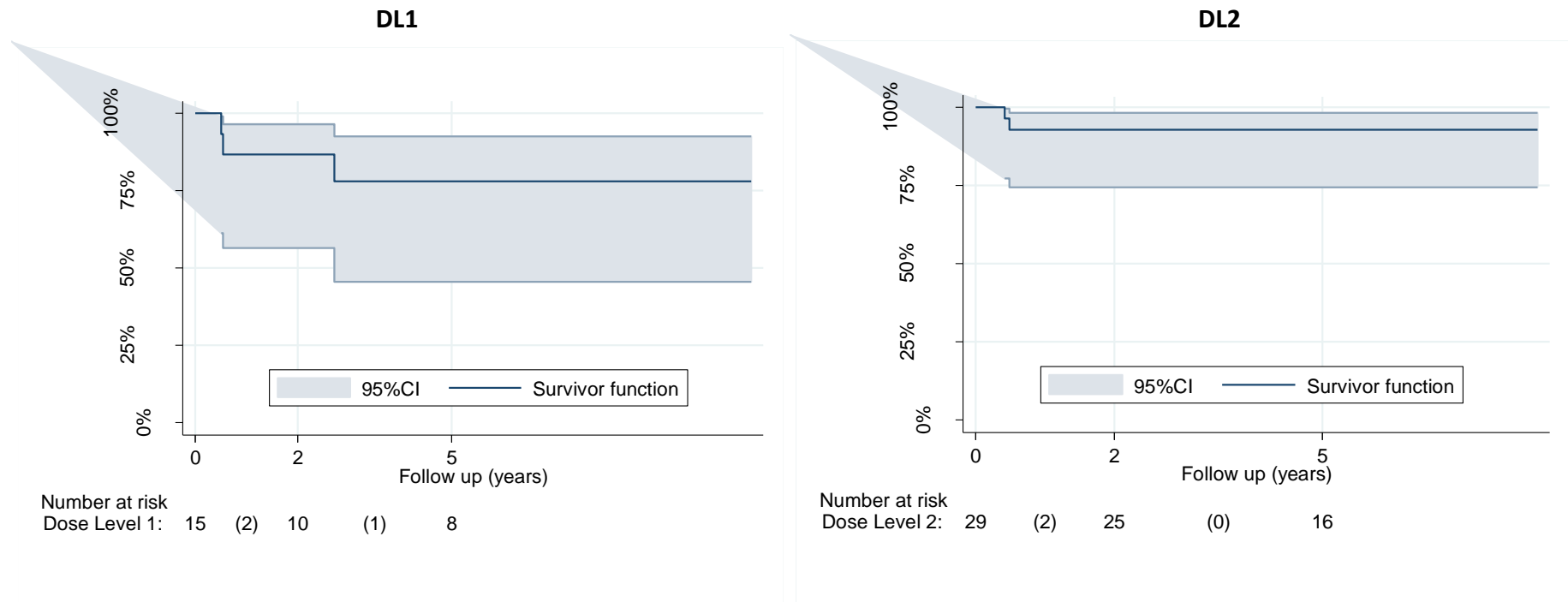


Figure in bracket = number who have locoregional relapse

**Table 9: Previous radiotherapy studies in thyroid cancer**

Author	Median follow-up (months)	Number of Patients	Stage (%)	Dose / fractionation	Late Toxicity (%)	Locoregional control	Survival
<b>Schwartz et al [4]. 1996-2005</b>	38	131 (IMRT = 57)	Stage III = 2 Stage IV = 98 Recurrence = 58	Median = 60 Gy / 30# IMRT: PTV1 = 57-70 Gy PTV2 = 54 Gy	<b>3DRT (56%):</b> oesophageal stricture = 6/74 Feeding tube dependent = 1/74 Subglottic stenosis = 1/74 <b>IMRT (44%):</b> Oesophageal stricture = 1/44	4 yr LRFS = 79%	4 yr DSS = 76% 4 yr OS = 73%
<b>Romesser et al [13]. 1990-2012</b>	24.5	66 (IMRT = 51)	T2 = 8, T3 = 6, T4 = 86, N1 = 83 M1 = 49	PTV1 = 60-70 Gy PTV2 = 54 Gy	RTOG >= G2 late toxicity Dysphagia = 18% - 20% Xerostomia = 20%; Hoarseness = 0 - 5%	3 yr LPFS = 77%: M0 = 88% M1 = 61%	3 yr DMFS: (M0 cohort) = 59% 3 yr OS = 54%
<b>Terezakis et al [5]. 1989-2006</b>	35.3	76 (IMRT = 47)	T2 = 7, T3 = 7, T4 = 84, N1 = 79 M1 = 36	Median = 63 Gy / 33# PTV1 = 63-70 Gy PTV2 = 59.4-63 Gy	"no significant difference between IMRT and non-IMRT" G3 Dysphagia = 5% (PEG, n=4), G2 = 11% G3 Xerostomia = 1%; G4 Laryngeal oedema = 2%	2 yr LCR = 86% 4 yr LCR = 72%	2 yr OS = 74% 4 yr OS = 55%
<b>Meadows et al [14]. 1962-2003</b>	49	42 (IMRT from 2002, number not recorded)	Stage IVa = 29 Stage IVb = 24 Recurrent = 48 M1 = 21	Median = 64.9 Gy / 32# IMRT: Up to 72 Gy/42#	No reported G3 or 4 late toxicity	5 yr LRC: M0 = 89% M1 = 88%	5 yr CSS: M0 = 86% M1 = 80% 5 yr DMFS = 82%
<b>Current trial (2002-2011)</b>	60	44 (all IMRT)	T4a = 19 T4b = 5 N0 = 9 N1a = 11 N1b = 24	DL1: PTV1 = 58.8 Gy / 28#; PTV2 = 50 Gy/28# DL2: PTV1 = 66.6 Gy/30#; PTV2 = 60 Gy/30#; PTV3 = 54 Gy/30#	12 months (G3): DL1 = 8.3%, DL2 = 8.3% 60 months (G3): DL1 = 33%, DL2 = 7%	5 yr TTRI: DL1: 76.9%  DL2: 91.5%	5 yr OS: DL1: 65.5%  DL2: 83.6%

Abbreviations: DMFS = distant metastases-free survival;  
DSS = Disease specific survival;  
LRC = locoregional control;  
OS = overall survival;  
PTV1 = tumour bed or nodal bed if extracapsular spread;  
PTV2 = nodal bed if R0/R1 resection  
TTRI = time to relapse interval