The Use of a Conventional Low Neck Field (LNF) and Intensity-Modulated Radiation Therapy (IMRT): No Clinical Detriment of IMRT to an Anterior LNF during the Treatment of Head and Neck Cancer

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Abstract

Purpose—Appropriate treatment of the lower neck when using IMRT is controversial. Our study tried to determine differences in clinical outcomes using IMRT or a standard LNF to treat low neck.

Methods and Materials—This is a retrospective, single institution study. Ninety-one patients with squamous cell carcinoma of head and neck cancer were treated with curative intent. Based on physician preference, some patients were treated with LNF (PTV3) field using a single anterior photon field matched to the IMRT field. Field junctions were not feathered. The endpoints were time to failure and use of PEG tube (as a surrogate of laryngeal edema causing aspiration) and analysis done with chi-square and the log-rank tests.

Results—Median follow up 21 months (range 2 – 89). The median age 60 years. Thirty seven (41%) were treated with LNF, 84% were stage III or IV. PEG tube was required in 30% as opposed to 33% without the use of LNF. N2 or 3 neck disease was treated more commonly without a LNF (38% vs. 24%, $p = 0.009$). Failures occurred in 12 patients (13%). Only one patient treated with LNF failed regionally, 4.5 cm above the match line. The 3-year disease-free survival rate was 87%, 79% with LNF and without LNF respectively ($p = 0.2$) and the 3-year LR failure rate was 4%, 21% respectively, ($p = 0.04$).

Conclusions—Using LNF to treat the low neck did not increase the risk of regional failure "in early T& early N diseases" or decrease PEG tube requirements.

Keywords

IMRT; Head and Neck cancer; Low neck field; RT toxicities; PEG tube

Introduction

Treatment of head and neck cancers with standard radiation therapy has traditionally consisted of two parallel-opposed lateral portals matched to an anterior supraclavicular field. With the introduction of 3-dimensional conformal techniques (3D-CRT) using intensity modulated radiation therapy (IMRT), there has been an improvement in tumor coverage in certain tumors (i.e. nasopharyngeal carcinoma) and a decrease in dose to certain normal structures (i.e. reducing the dose to the parotid glands[1] has decreased the risk of late Xerostomia) compared with conventional radiation portals. This improved tumor coverage appears to have improved treatment outcomes by lowering loco-regional recurrence rates[2–7]. When using IMRT, it is controversial how to treat the low neck. There are two basic approaches: Using IMRT as a single field/or whole field versus using a split field technique using IMRT to treat the primary tumor matched to a conventional low neck field to treat low neck. Several authors described different techniques for matching the IMRT fields[8–14]. There are advantages and disadvantages for each approach which were described in several recent papers[8, 14–17]. Using a matching (i.e. split field IMRT), the dose inhomogeneities contribute to setup errors leading to either cold or hot spots over the entire treatment course which could lead to increased failures or complications, respectively. The concern with the whole field approach is the increased dose to the larynx, causing laryngeal edema which could cause speech or swallowing difficulties. When there is gross adenopathy at the level of the larynx prior to treat, split field technique is not recommended unless a neck dissection is planned due to a potential risk of regional failures. This retrospective study was performed to determine differences in clinical outcomes using whole-field or split-field IMRT.

Methods and Materials

Between May 2001 and June 2008, 153 patients with head and neck cancer were treated with IMRT at Fox Chase Cancer Center. Among these, 91 (59.5%) had squamous cell carcinoma and were treated with curative intent. The patient, tumor and treatment related demographic data were obtained retrospectively. The distribution of these variables is shown in Tables 1 to 3. The IMRT technique, dose prescription and treatment planning methods at FCCC were described in detail previously[7].

Radiotherapy details

All patients were treated with IMRT using a smart boost[18], which uses the inherent hot spots generated by the IMRT plan to treat different volumes at different doses at the same time. Based on physician preference, some patients receive the radiation to the supraclavicular fossa using a single anterior photon field matched to the IMRT fields. In the definitive treatment setting, IMRT was used to decrease the dose to the parotid gland only if there were no clinically involved lymph nodes on that side of the neck. The high risk volume was prescribed to 70 Gy in 35 fractions, 2 Gy per fraction over 7 weeks duration (clinically evident disease at the primary site and neck with a 1 to 2 cm margin, PTV1) while electively treated neck nodes were treated to 56 Gy (PTV2). An intermediate risk volume was generally not used. When a low neck field (LNF) was treated, the dose was prescribed to 46–50 Gy to a depth of 3 cm. Field junctions were not feathered. The inferior 100 cGy isodose line of the IMRT radiation fields was matched to superior border of supraclavicular fossa facilitated by asymmetric collimation providing half beam blocking, ensuring no cold

spots. In the postoperative setting, the PTV1 (the post-operative bed and regions of pathologic lymph node involvement) was prescribed to 60 to 66 Gy while the PTV2 was prescribed to 54 Gy (elective regional lymph nodes). Normal tissue dose constraints were: spinal cord less than 48 Gy, brain stem less than 54 Gy, mean parotid dose less than 26 Gy, limit larynx dose to less than 40 Gy and optic chiasm to less than 54 Gy. The Corvus inverse treatment planning system was used for the majority of patients (version 3.0, NOMOS Corp., Cranberry Township, PA). The median total dose to the PTV1 was 70 Gy in 35 fractions (range: 42–75 Gy in 21–50 fractions); PTV2 was 56 Gy (range: 39–68 Gy) and PTV3 was 48.6 Gy (range: 44–56 Gy). All patients were treated with once daily fractionation, 2 Gy per fraction over a period of 6 to 7 weeks except 3 patients who were treated using a University of Chicago approach (ClinicalTrials.gov Identifier: NCT00117572) with 75 Gy, 1.5 Gy per fraction, twice daily, one week on and one week off concomitant with chemotherapy. The median duration of treatment was 46 days (range: 29–67 days). The median numbers of beams used were seven (range: 4–17) with IMRT.

Chemotherapy

Fifty-two patients (57%) were treated with various chemotherapy regimens along with radiation therapy; 24/37 (65%) and 28/54 (52%) patients each with or without LNF ($p = 0.28$). Concomitant Cisplatin was most commonly used (n = 29, 32%) at 100 mg/m^2 every three weeks, along with RT. Weekly Cetuximab was used in 11 patients (12%). Cisplatin and cetuximab combination was given to 6 patients (7%). Six patients were treated with combination regimens (3 with docetaxel, fluorouracil, hydroxyurea, one with carboplatin, taxol and cetuximab, one patient with cisplatin and docetaxel and one with carboplatin and taxol). Concurrent chemotherapy was given to 57% in the definitive and 5% in the postoperative setting for patients treated with LNF. The distributions of patients treated with chemotherapy along with different RT methods with and without LNF (definitive versus postoperative setting) are shown in Table 3.

Neck dissection

All patients were assessed by a head and neck surgeon 4 weeks post-radiation for neck dissection. During the interval studied, planned neck dissections were performed when lymph nodes > 3 cm at presentation. In addition, patients with persistent nodes following radiation went on to receive a neck dissection. Thirty nine patients (43%) had neck dissection performed: 12 (32%) and 27 (50%) patients treated with and without LNF.

Complications

Acute and late toxicity were recorded as per the Radiation Therapy Oncology Group (RTOG) toxicity criteria. The use of a PEG (percutaneous endoscopic gastrostomy) tube was used as a surrogate marker of laryngeal edema causing aspiration and the toxicities were analyzed for the patients treated with or without the LNF.

Statistical analysis

All the analyses were performed using the statistical analysis systems (SAS Institute, Cary, NC). Patient, tumor- and treatment-related factors, including T stage (T1, 2, versus T3, 4), N stage (N0,1 vs. N2, 3), tobacco history (yes versus no), alcohol intake (yes versus no), location of primary (oral cavity versus other sites), treatment type (definitive RT versus PORT), concurrent chemotherapy (yes versus no), use of amifostine (yes versus no), use of a third field (yes versus no) and RT duration (< 46 days versus > 46 days) were analyzed for an impact on disease-free survival, patterns of failure and toxicity via the chi-square test and log-rank test. Values of 'p' less than 0.05 were considered statistically significant. Local failures (LF) were defined by persistence/recurrence within the primary site. Regional

failures occurred in the draining lymph nodes in the neck. Marginal failure was defined as a failure that occurred at a region of dose falloff or outside the RT field.

Results

Thirty seven (41%) patients were treated with a LNF. Patient characteristics are shown in Table 1. The median ages were 57 years and 63 years for patients treated with and without LNF. There were no differences between groups based on tobacco use ($p = 1.0$), alcohol intake ($p = 0.61$) and ethnicity ($p = 0.71$). Tumor-related characteristics are shown in Table 2. The plurality of patients (48%) had tumor in the oropharynx (24 and 20 patients in each group) and 24% had oral cavity tumors ($p = 0.16$). There were 6 (7%) patients with laryngeal and two with hypopharyngeal primary cancers. Twenty patients had T3 tumors and 15 T4; 28 patients had N2 nodal stage and 31 and 41 belong to stage III and IV, respectively. N2 or 3 neck disease was treated more commonly without a LNF (38% versus 24%, $p = 0.009$). In patients treated with LNF, 31/37 (84%) belonged to stage III or IV. PORT was given to 29% of patients (24% RT alone and 5% concurrent chemoradiation), while 71% were treated with definitive radiation (19% RT alone and 52% concurrent chemoradiation), $p = 0.24$.

The acute and late toxicities are shown in Tables 3 and 4. Most patients developed grade 2 and 3 skin and mucosal reactions whether treated with or without LNF. Grade 4 toxicity occurred in 3% of patients with LNF. There were no other major grade 3 or 4 toxicities in either group. 33% needed PEG tube as opposed to 29% without the use of a LNF during the course of treatment ($p = 0.82$). The median time at which the PEG tube was taken out was 7 months (range: 1–72 months). Among the 37 patients in the total group with PEG tube use, 7 were dependant for more than one year (1 and 6 patients with and without LNF, respectively.

The Kaplan-Meier estimates of two- and three-year local control rates, locoregional control rates and overall survival are shown in Table 5. The two-year local control rates, loco-regional (LR) control and overall survival were 100% and 89% ($p = 0.06$), 96% and 79% ($p = 0.04$), and 78% and 81%, ($p = 0.98$) for patients treated with and without LNF respectively. The two-year actuarial rate of failure was 18% for the total cohort, 13% and 21% in patients treated with and without LNF ($p = 0.2$, shown in Figures 1 and 2). Failures occurred in 12 patients (13%): 5 local, 2 regional, 1 locoregional, 1 local-regional-distant, 2 distant and 1 regional-distant (shown in Table 6). Only one patient treated with a LNF failed regionally, 4.5 cm above the match line ($p = 0.04$). On univariate analysis, the type of treatment ($p = 0.004$; definitive RT versus PORT), overall stage ($p = 0.05$; I/II versus III/IV) and location of primary ($p = 0.008$; oral cavity versus other sites) were significant predictors of disease free survival (shown in Table 7). The use of LNF did not predict for regional failure ($p = 0.5$) or the need of PEG acutely ($p = 0.82$). The predictors for loco-regional failure were overall stage ($p = 0.02$; I, II, III versus IV), location of primary ($p = 0.01$; oral cavity versus other sites), chemotherapy ($p = 0.04$; yes versus no) and the use of LNF ($p = 0.04$). There was no difference in the overall survival rates.

Discussion

Proper selection of IMRT technique (wide field versus split field) is controversial. The major arguments are the risk of marginal failures with the use of SF-IMRT as opposed to the unnecessary larynx irradiation[17, 19, 20] with the WF-IMRT. There are no clinical studies on outcomes with and without use of LNF with IMRT. This is the first dataset looking at the clinical outcomes. In our study, we did not see any difference in the patterns of failure or the side effects profile (Tables 2–6) including PEG tube dependency in patients treated with and

without LNF. Matching an anterior low neck field (LNF) with a larynx block decreases the dose to the larynx while increasing the uncertainty of dose delivery at the match line. Rosenthal et al[19] described that independent jaw collimation at the junction of the abutting fields corrects the errors with either over-dose or under-dose at the match line. Duan et al[9] compared the conventional single-isocenter and half-beam (SIHB) technique with dynamic field matching IMRT in 10 head and neck cancer patients. To avoid field overlap beyond the match line, the inferior border of IMRT fields were adjusted automatically by the treatment planning system to fit the dynamic MLC fields, 1.5 cm inferior to the match line by the use of collimator jaw before dose calculation. The average inhomogeneity ranged between −1.6% to + 1.6% using dynamic IMRT versus −3.7% to + 3.8% with SIHB. Dabaja et al[17] studied the target volume coverage using different IMRT techniques in 13 patients with early-stage oropharynx cancers. Treatment plans were created with half-beam (HB-IMRT) and wide field (WFIMRT) IMRT techniques and comparisons included coverage to the planning target volume of the primary (PTV 66) and subclinical disease (PTV 54). The mean volume (PTV 66) receiving >110% for all patients planned with WF-IMRT was 9.3% compared with 13.7% with HB-IMRT ($p = 0.09$). The mean doses to all critical structures were comparable except those to larynx. The mean dose to the larynx was significantly less with HB-IMRT (18.7 Gy versus 47 Gy) compared with WF-IMRT ($p = 0.001$). Amdur et al[16] performed a dosimetry evaluation of two IMRT techniques in a model patient with a stage T2N2b carcinoma of the tonsil with adenopathy extending inferiorly to cricoid cartilage. The mean dose to the larynx was higher with the WF-IMRT (35 Gy) compared with the split-field including the LNF (17 Gy). Amdur et al[15] from University of Florida (UF) reviewed all the techniques being used to date in matching the IMRT fields to the LNF, including the method followed at UF from a head and neck cancer symposium. At UF, to minimize the concern about hot or cold spots from collimator misalignment, the position of the collimator was moved 3 mm superior to the central axis after completing one third of the treatment and then 3 mm inferior to the central axis after delivering two thirds of treatment. Lee et al[14] proposed guidelines to select the IMRT technique for treating head and neck cancers in 6 patients. Dosimetric parameters were compared for each patient with split-field (SF) and extended whole-field (WF) IMRT. Target-dose coverage and doses delivered to the critical normal structures were similar between the two treatment techniques. SF-IMRT was preferred to nasopharyngeal and oropharyngeal primary sites to minimize the dose to the glottic larynx. WF-IMRT was preferred for carcinoma of the larynx, hypopharynx and unknown head-and-neck primary sites where the glottic larynx was considered part of the target. Regardless of the primary site of head and neck cancer, WF-IMRT was preferred if there was evidence of enlarged lymph nodes measuring > 3 cm in the lower neck.

Conclusions

Both the techniques are good for treating subclinical disease and do not increase the risk of regional failure "in early T & early N diseases" or decrease the risk of needing a PEG tube. Careful attention to matching the IMRT field with the conventional low neck field will minimize the problems with matching and also to avoid matching when the disease is present in the low neck > 3 cm. Longer follow up and larger patient numbers are needed to confirm these findings.

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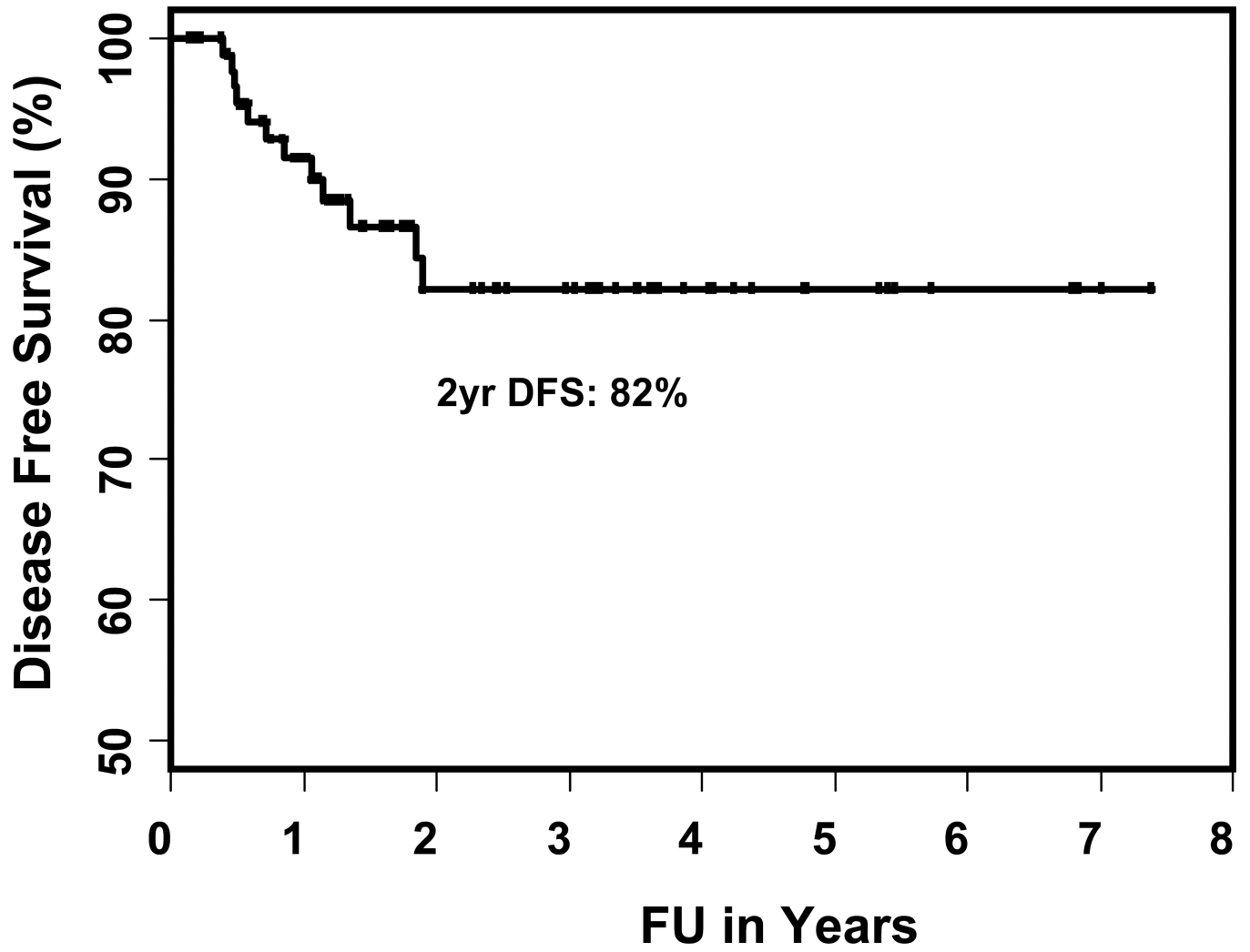
Figure 1.
The DFS rates for total cohort treated with IMRT
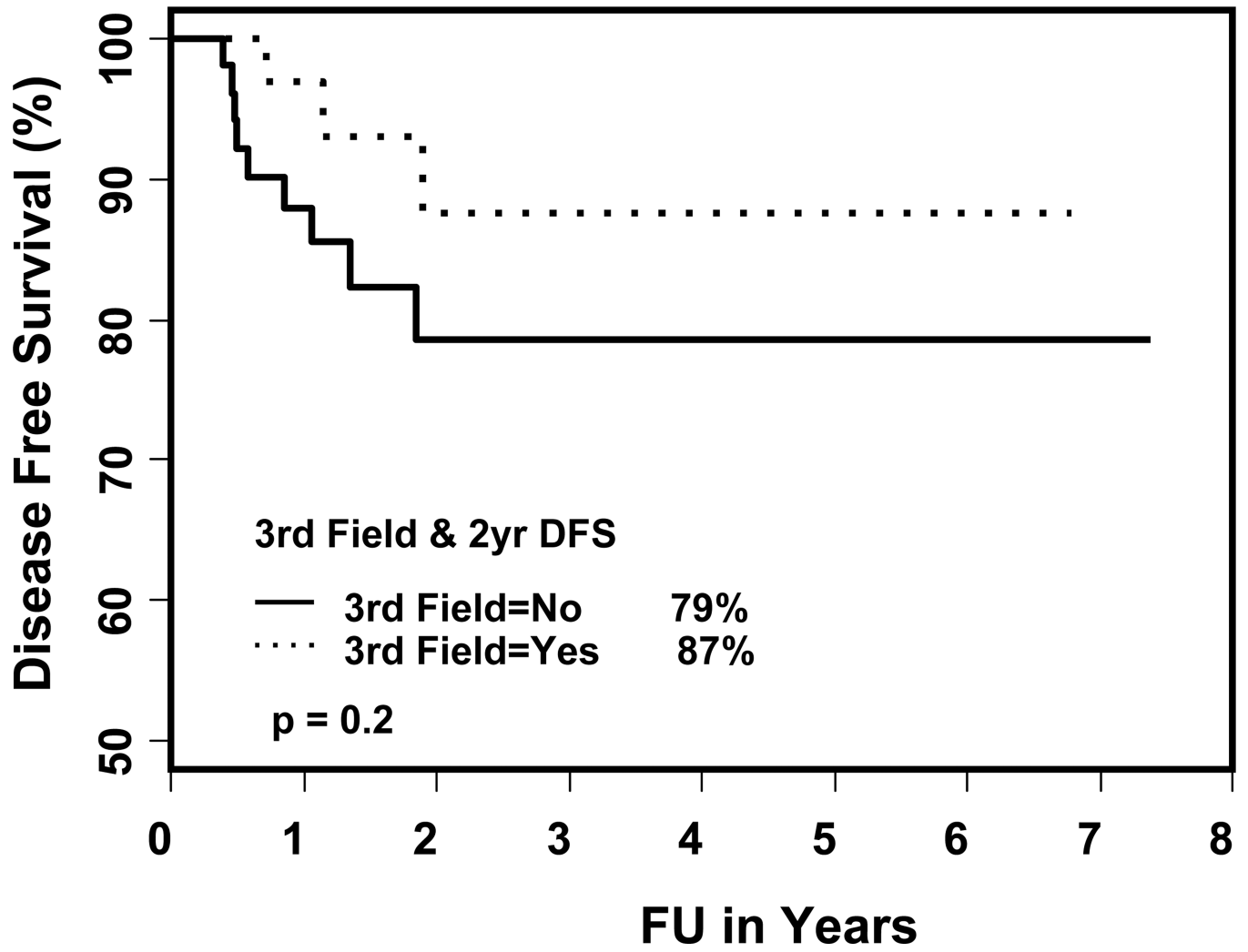
Figure 2.
The DFS rates in patients with and without LNF
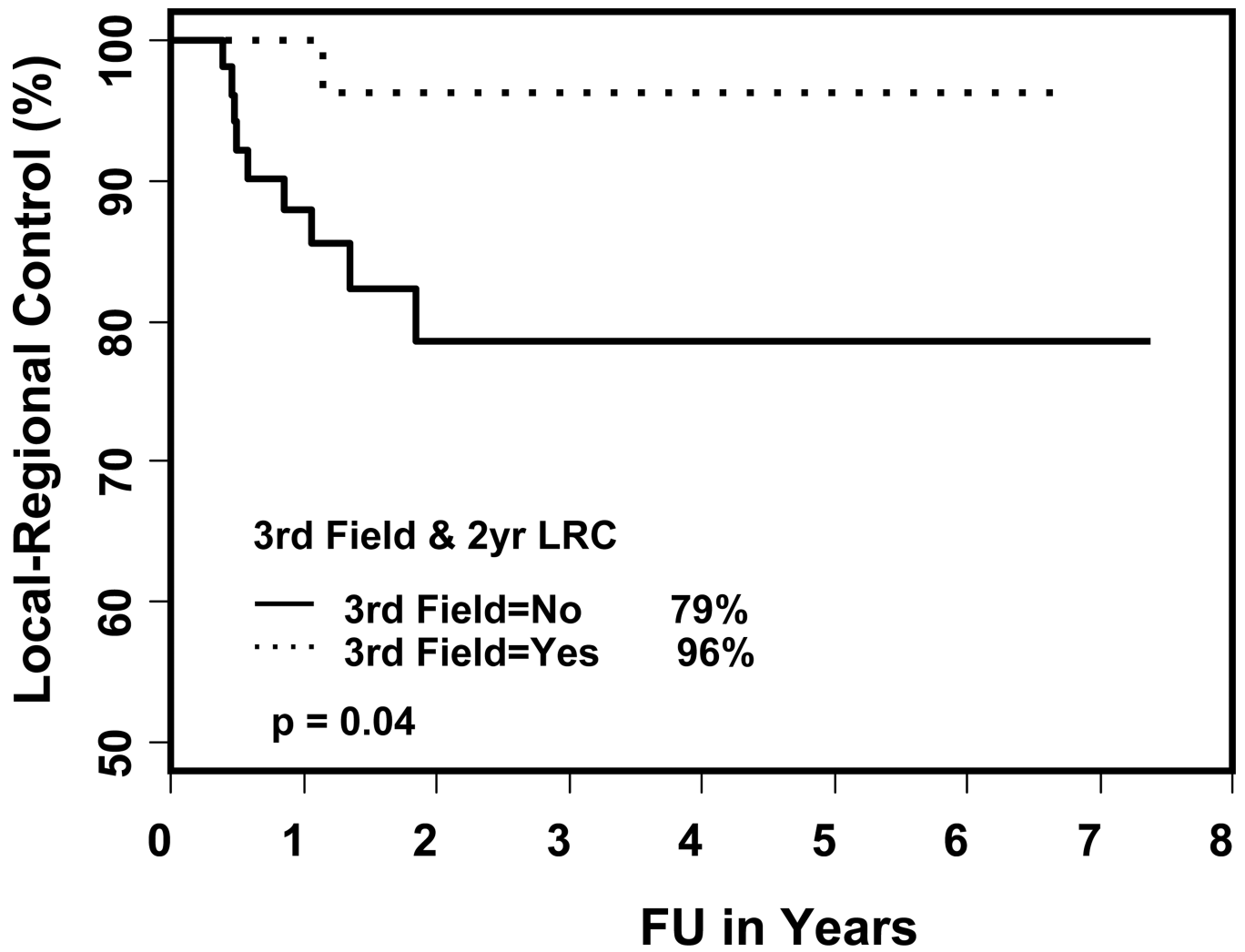
Figure 3.
The loco-regional control rates with and without LNF

Table 1

Patient- related characteristics with and without LNF (n = 91)

Variable	Without LNF No. of. patients (%)	With LNF No. of. patients (%)	p* value
Age, median in years	63 (28–85)	57 (30–88)	0.3
Gender			0.3
Male	39 (72)	30 (81)	
Smoking			
Yes	42 (78)	29 (78)	1.00
Alcohol intake			
Yes	42 (81)	28 (76)	0.61
Race			
White	51 (94)	37 (100)	0.71
African-American	2 (4)	0 (0)	
Asian	1 (2)	0 (0)	

Abbreviations: LNF= low neck field.

*p < 0.05 considered statistically significant.

Table 2

Tumor and treatment- related characteristics (n = 91)

Variable	Without LNF No. of. patients (%)	With LNF No. of. patients (%)	p* value
Primary site			0.16
Nasopharynx	1 (2)	5 (13)	
Oropharynx	24 (44)	20 (54)	
Oral cavity	14 (26)	8 (22)	
Hypopharynx	1 (2)	1 (3)	
Larynx	5 (9)	1 (3)	
PNS & Nasal cavity	7 (13)	2 (5)	
Others	2 (4)	0 (0)	
T stage			0.16
T1	12 (24)	12 (33)	
T2	15 (29)	13 (36)	
T3	16 (31)	4 (11)	
T4	8 (16)	7 (20)	
Missing	3	1	
N stage			0.009
N0	24 (45)	10 (27)	
N1	9 (17)	18 (49)	
N2	19 (36)	9 (24)	
N3	1 (2)	0 (0)	
Missing	1	0	
Overall stage			0.21
I	3 (6)	3 (8)	
II	9 (17)	3 (8)	
III	14 (26)	17 (46)	
IVA/B	27 (51)	14 (38)	
Missing	1	0	
Type of treatment			0.24
Definitive RT	35 (65)	30 (81)	
RT alone	9 (17)	9 (24)	
Concurrent CRT	26 (48)	21 (57)	
Postoperative RT	19 (35)	7 (19)	
RT alone	17 (31)	5 (14)	
Concurrent CRT	2 (4)	2 (5)	
Chemotherapy			0.28
Yes	28 (52)	24 (65)	
Neck dissection			0.13

Variable	Without LNF No. of. patients (%)	With LNF No. of. patients (%)	p* value
Yes	27 (50)	12 (32)	
PEG tube use			0.82
Yes	18 (33)	11 (30)	

Abbreviations: PNS= Para nasal sinuses, T= tumor, N= nodal stage, PEG= percutaneous endoscopic gastrostomy, RT= radiation therapy, CRT= definitive chemoradiotherapy.

*
p < 0.05 considered statistically significant.

Table 3

RTOG Acute toxicity with and without LNF

	Grade 2, N (%)		Grade 3, N (%)		Grade 4, N (%)		p * value
	Without LNF (N=54)	With LNF (N=37)	Without LNF (N=54)	With LNF (N=37)	Without LNF (N=54)	With LNF (N=37)	
Skin	23 (43)	20 (54)	2 (4)	0 (0)	0	0	0.56
Mucosa	28 (52)	17 (46)	17 (32)	15 (41)	0	0	0.54
Pharynx/Esophagitis	29 (54)	20 (54)	9 (17)	5 (14)	0	1 (3)	0.21
Larynx	4 (7)	1 (3)	1 (2)	0	0	0	0.43
Taste changes	37 (69)	29 (78)	4 (7)	1 (3)	0	1 (3)	0.43
Xerostomia	34 (63)	27 (73)	1 (2)	2 (5)	0	0	0.38
Hematological	5 (9)	6 (16)	1 (2)	0	0	0	0.58

Abbreviations: N= number of patients.

*
p < 0.05 considered statistically significant.

Table 4

RTOG Late toxicity with and without LNF

	Grade 2, N (%)		Grade 3, N (%)		Grade 4, N (%)		p* value
	Without LNF (N=54)	With LNF (N=37)	Without LNF (N=54)	With LNF (N=37)	Without LNF (N=54)	With LNF (N=37)	
Skin	4 (8)	2 (6)	0	0	0	0	0.52
Mucosa	0	0	0	0	0	0	0.56
Pharynx/Esophagitis	4 (8)	1 (3)	0	0	0	0	0.84
Larynx	2 (4)	0	0	0	0	0	0.41
Xerostomia	42 (81)	29 (88)	0	0	0	0	0.55
Hematological	1 (2)	2 (6)	0	0	0	0	0.56

*
p < 0.05 considered statistically significant.

Table 5

Local control and survival rates with and without LNF

Type of treatment	Local control rate			Loco-regional control rate			Overall Survival		
	2 year	3 year	p value	2 year	3 year	p value	2 year	3 year	p* value
Total group	94%	94%		86%	86%		80%	71%	
Without LNF	89%	89%	0.06	79%	79%	**0.04**	81%	73%	0.98
With LNF	100%	100%		96%	96%		78%	68%	

Abbreviations: CRT= concurrent chemoradiation; RT= definitive radiation therapy; PORT+CT= postoperative concurrent chemoradiation.

*
p < 0.05 considered statistically significant.

Table 6

Failure patterns with and without LNF

Variable	Without LNF No. of. Patients (%)	With LNF No. of. Patients (%)	p* value
Total (n = 12)	9 (17)	3 (8)	0.35
Local only	5 (9)	0 (0)	0.08
Loco-regional	9 (17)	1 (3)	**0.04**
Regional	2 (4)	0 (0)	0.5
Distant	1 (2)	3 (8)	0.3

*
p < 0.05 considered statistically significant.

Table 7

Factors associated with locoregional failures (LRF) and disease free survival (DFS)

Variable	LRF p* value	DFS p* value
Type of treatment (definitive CRT versus Postop CRT)	0.2	**0.004**
Type of treatment (definitive RT versus PORT)	0.1	0.07
Smoking (yes versus no)	0.67	0.99
Alcohol intake (yes versus no)	0.69	0.5
T stage (T1, 2 versus T3, 4)	0.8	0.8
N stage (N0,1 versus N2, 3)	0.6	0.8
Overall stage (I, II, III versus IV)	**0.02**	**0.05**
Location of primary (oral cavity versus other sites)	**0.01**	**0.008**
Chemotherapy (yes versus no)	**0.04**	0.07
Neck dissection (yes versus no)	0.1	0.04
PEG tube use (yes versus no)	0.5	0.3
Amifostine (yes versus no)	0.1	0.2
Third field use (yes versus no)	**0.04**	0.2
RT duration (< 46 days versus > 46 days)	0.7	0.5

Abbreviations: LRF= loco-regional failure, DFS= disease-free survival, others as in the above tables.

*
p value < 0.05 considered statistically significant.