 doi:10.20944/preprints201903.0249.v1

Less is enough: outcome of bimodality definitive concurrent chemoradiation does not differ from that of trimodality upfront neck dissection followed by adjuvant treatment for >6 cm bulky lymph node (N3) head and neck cancer

Wan-Yu Chen M.D.[1,2,3], Tseng-Cheng Chen M.D., Ph.D.[4], Shih-Fan Lai M.D. [1,3], Tony Hsiang-Kuang Liang M.D. [1,3], Bing-Shen Huang M.D.[5], Chun-Wei Wang M.D., Ph.D.[1,3,6]*
*corresponding author

1 Division of Radiation Oncology, Department of Oncology, National Taiwan University Hospital, Taipei, Taiwan
2 Graduate Institute of Clinical Medicine, National Taiwan University College of Medicine, Taipei, Taiwan
3 Cancer Research Center, National Taiwan University College of Medicine, Taipei, Taiwan
4 Department of Otolaryngology, National Taiwan University Hospital and National Taiwan University, College of Medicine, Taipei, Taiwan
5 Department of Radiation Oncology, Chang Gung Memorial Hospital and Chang Gung University, Taoyuan, Taiwan
6 Department of Radiology, College of Medicine, National Taiwan University, Taipei, Taiwan

***Corresponding author:** Chun-Wei Wang M.D. Ph.D. Division of Radiation Oncology, Department of Oncology, National Taiwan University Hospital, No. 7, Chung-Shan South Road, Taipei 100, Taiwan.
cwwang@ntuh.gov.tw, TEL: 886-2-2312-3456 ext 66162, 62643
Running title: Outcome of N3 head and neck cancer

 doi:10.20944/preprints201903.0249.v1

Abstract

Currently, data regarding optimal treatment modality, response, and outcome specifically for N3 head and neck cancer are lacking. This study aimed to compare the treatment outcomes between definitive concurrent chemoradiotherapy (CCRT) to the neck and upfront neck dissection followed by adjuvant CCRT. 93 N3 squamous cell carcinoma head and neck cancer patients were included. Primary tumor treatment was divided to definitive CCRT (CCRT group) or curative surgery followed by adjuvant CCRT (surgery group). Neck treatment was also classified into two treatment modalities: definitive CCRT to the neck (CCRT group) or curative neck dissection followed by adjuvant CCRT (neck dissection group). Overall, the 2-year overall survival (OS), local recurrence-free survival (LRFS), regional recurrence-free survival (RRFS), and distant metastasis-free survival (DMFS) were 51.8%, 47.3%, 45.6%, and 43.6%, respectively. In both oropharyngeal cancer and nonoropharyngeal cancer patients, in terms of OS, LRFS, RRFS or DMFS no difference was noted regarding primary tumor treatment (CCRT vs. surgery) or neck treatment (CCRT vs. neck dissection). In summary, N3 neck patients treated with definitive CCRT can achieve similar outcomes to those treated with upfront neck dissection followed by adjuvant CCRT. Cautions should be made to avoid overtreatment for this group of patients.

 doi:10.20944/preprints201903.0249.v1

Key words: N3, head and neck cancer, radiation, upfront neck dissection, concurrent chemoradiotherapy

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 27 March 2019 doi:10.20944/preprints201903.0249.v1

Introduction

Currently, data regarding optimal treatment modality, response, and outcome specifically for N3 head and neck cancer are lacking. Most studies included a combination of N2 and N3 head and neck cancers, with only approximately 10–15% of N3 patients in prospective clinical trials[1-3] or retrospective studies[4, 5]. Planned neck dissection after definitive concurrent chemoradiotherapy (CCRT) can be omitted, and salvage post-RT neck dissection can be performed only in incomplete response to CCRT[3, 6]. However, some physicians choose neck dissection as primary treatment because of concerns for poor radiation response of bulky necrotic lymph nodes, anatomical change of bulky lymph nodes during radiation, and avoidance of postradiation neck dissection. For N3 head and neck cancer, whether direct neck dissection or definitive CCRT to the neck should be performed remains unsolved. This study aimed to compare the treatment outcomes between definitive CCRT to the neck and upfront neck dissection followed by adjuvant CCRT for N3 head and neck cancer patients.

Materials and Methods

Patients and treatments

The study protocol was approved by the Research Ethics Committee of National Taiwan University Hospital (NTUH: 201707061RINB). Between 2002 and 2015, 93 N3

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 27 March 2019 doi:10.20944/preprints201903.0249.v1

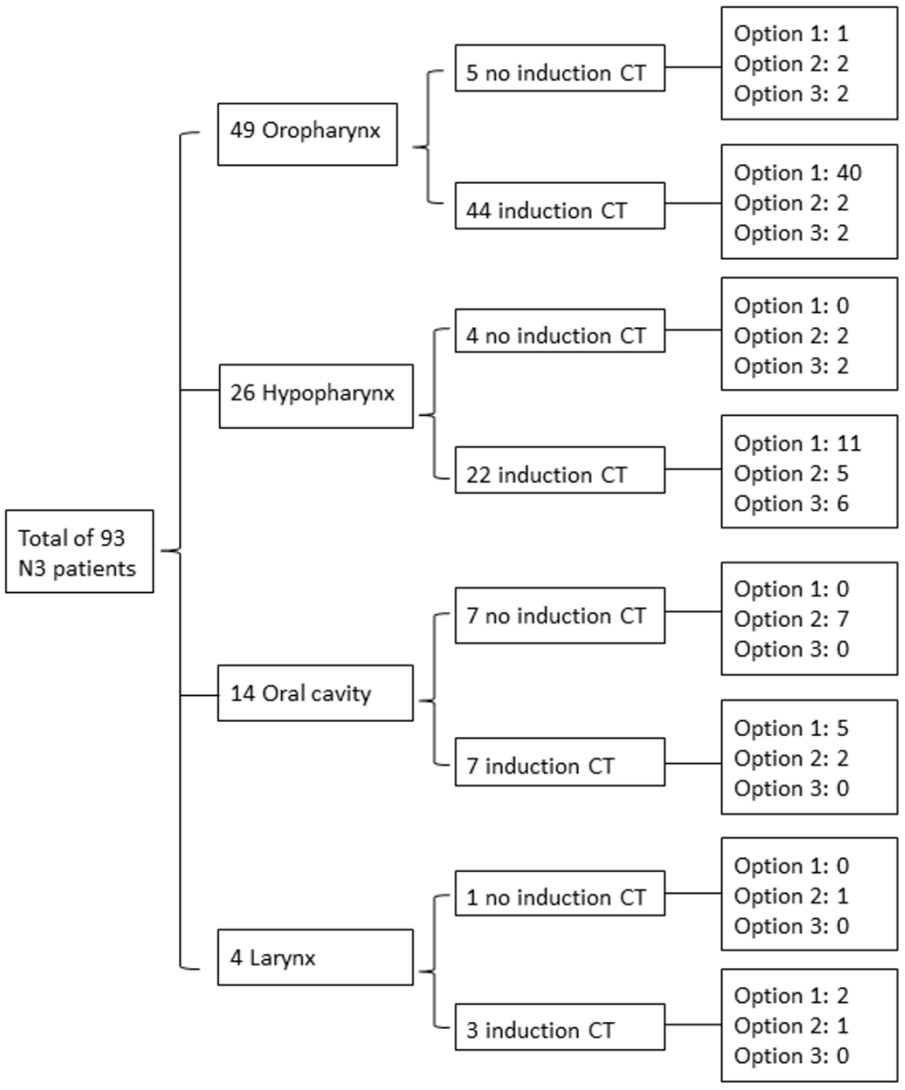
(>6 cm, American Joint Committee on Cancer 7th edition) squamous cell carcinoma head and neck cancer patients with no distant metastasis who received curative treatment at National Taiwan University Hospital were included in this study. Treatments for all the 93 patients are summarized in Figure 1. Among the 93 patients, 76 (81.7%) received induction chemotherapy, which included the following regimens: PF (cisplatin + 5-FU), EPF (Erbitux + PF), APF (Avastin + PF), TPF (Taxotere + PF), ATPF (Avastin + TPF), MEPFL (mitomycin, epirubicin, cisplatin, fluorouracil, and leucovorin)[7], intra-arterial (IA) MPA (mitomycin, cisplatin, Avastin), IA-MTPF (mitomycin, Taxotere, cisplatin, 5FU), IA-MATPF (MTPF + Avastin), or their combinations. For patients receiving induction chemotherapy, the median cycles received were 2 (range, 1–8).

After induction chemotherapy, curative treatments were categorized into options 1-3 as follows: 1) definitive CCRT to primary tumor and neck; 2) curative surgery for primary tumor and the neck followed by adjuvant CCRT; and 3) curative neck dissection followed by definitive CCRT for primary tumor and adjuvant CCRT for the neck (Figure 1). Curative surgery for primary tumor comprised of wide tumor excision with flap reconstruction if necessary. Curative neck dissection includes modified radical neck dissection for bulky neck nodes with or without contralateral neck dissection at the discretion of the treating physician. Definitive CCRT irradiation

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 27 March 2019 doi:10.20944/preprints201903.0249.v1

dose was 70 Gy in 33–35 fractions, which was delivered concurrently with weekly cisplatin or IA chemotherapy. Adjuvant RT dose was set to 60–66 Gy in 30–33 fractions.

Figure 1: Treatment for tumors with different primary sites.



Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 27 March 2019 doi:10.20944/preprints201903.0249.v1

Patients were routinely assessed 3–4 months after the completion of the treatment through clinical examination, chest X-ray, and head and neck magnetic resonance imaging. For patients who received definitive CCRT, neck dissection was not routinely performed. Salvage neck dissection or primary tumor excision was considered only if an incomplete response occurred.

Statistical analysis

The variables were compared using Chi-squared test, Fisher's exact test, or student's t-test. The following endpoints were used for assessment: overall survival (OS), local recurrence-free survival (LRFS), regional recurrence-free survival (RRFS), and distant metastasis-free survival (DMFS). These endpoints were measured from the day of diagnosis. Survival curves were estimated via the Kaplan-Meier method. Univariate and multivariate analyses were performed with log-rank test and Cox regression, respectively. A two-sided p value <0.05 was considered statistically significant. Statistical analysis was performed with SPSS 19.0.

Results

Table 1 shows the patients characteristics. The primary tumor sites included the oropharynx (n=49) and nonoropharynx (n=44; 26 hypopharynx, 14 oral cavity, and 4 larynx). Patients with oropharyngeal malignancy were associated with more T1/T2 tumors (p=0.030). Primary tumor treatment was divided to definitive CCRT (CCRT

 doi:10.20944/preprints201903.0249.v1

group; treatment options 1+3) or curative surgery followed by adjuvant CCRT (surgery group; treatment option 2). The oropharyngeal group had more patients receiving definitive CCRT to primary tumor sites (p=0.030). Neck treatment was also classified into two treatment modalities: definitive CCRT to the neck (CCRT group; treatment option 1) or curative neck dissection followed by adjuvant CCRT (neck dissection group; treatment option 2+3). The oropharyngeal group had more patients receiving definitive CCRT to the neck (p=0.000).

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 27 March 2019 doi:10.20944/preprints201903.0249.v1

Table 1: Patient characteristics

Characteristics	All patients No. (%) (N=93)	Oropharynx No. (%) (N=49)	Non-Oropharynx No. (%) (N=44)	P value
Gender				
Male	89 (95.7)	48 (98.0)	41 (93.2)	
Female	4 (4.3)	1 (2.0)	3 (6.8)	0.341
Age (years old) (median, range)	52 (34-78)	53 (34-78)	51.5 (35-78)	0.870
T classification				
T1/T2	32 (34.4)	22 (44.9)	10 (22.7)	
T3/T4	61 (65.6)	27 (55.1)	34 (77.3)	0.030
Primary tumor treatment				
CCRT	71 (76.3)	45 (91.8)	26 (59.1)	
Surgery	22 (23.7)	4 (8.2)	18 (40.9)	0.000
Neck treatment				
CCRT	59 (63.4)	41 (83.7)	18 (40.9)	
Neck dissection	34 (36.6)	8 (16.3)	26 (59.1)	0.000
Radiotherapy				
Definitive to both primary and neck (option 1)	59 (63.4)	41 (83.7)	18 (40.9)	
Adjuvant (option 2)	22 (23.7)	4 (8.2)	18 (40.9)	
Definitive to primary and adjuvant to neck (option 3)	12 (12.9)	4 (8.2)	8 (18.2)	0.000
Induction chemotherapy				
No	17 (18.3)	5 (10.2)	12 (27.3)	
Yes	76 (81.7)	44 (89.8)	32 (72.7)	0.058

Abbreviation: CCRT= concurrent chemoradiation

 doi:10.20944/preprints201903.0249.v1

Among patients who received definitive CCRT to primary tumor sites, oropharyngeal cancer patients had higher complete response (CR) rate than non oropharyngeal cancer patients. A total of 37 (82.2%) and 19 (73.1%) patients had oropharyngeal and nonoropharyngeal cancer, respectively. The number (rate) of patients who achieved partial response (PR) was 8 (17.8%) and 7 (26.9%) in those with oropharyngeal and nonoropharyngeal cancer, respectively (p=0.000). For patients who received definitive CCRT to the neck, the number of patients with oropharyngeal and nonoropharyngeal cancer who achieved CR were 31 (75.6%) and 12 (66.7%), respectively, and those who achieved PR were 10 (24.4%) and 6 (33.3%), respectively (p=0.000). A total of 7 (22.6%) and 3 (25%) patients with oropharyngeal cancer and nonoropharyngeal cancer developed regional recurrence after CR was achieved post definitive neck CCRT, respectively.

The median follow-up time for all patients was 21.1 months (range, 6.9–105.4 months). Overall, the 2-year OS, LRFS, RRFS, and DMFS were 51.8%, 47.3%, 45.6%, and 43.6%, respectively.

Univariate and multivariate analyses for survival rate in oropharyngeal cancer patients are summarized in Table 2. In oropharyngeal cancer patients, in terms of OS, no difference was noted regarding primary tumor treatment (CCRT vs. surgery) (HR: 0.607; 95% CI: 0.123–3.000; p=0.540) or neck treatment (CCRT vs. neck dissection)

 doi:10.20944/preprints201903.0249.v1

(HR: 2.199; 95% CI: 0.522–9.256; p=0.283). Advanced T3/T4 stage was associated with worse OS (HR: 3.337; 95% CI: 1.312–8.488; p=0.011). The 2-year OS rate for definitive CCRT to the neck (CCRT group) or curative neck dissection followed by adjuvant CCRT (neck dissection group) was 57.4% and 37.5%, respectively (Fig. 2a). For LRFS, no difference was noted in terms of primary tumor treatment (CCRT vs. surgery) (HR: 0.446; 95% CI: 0.079–2.536; p=0.363) or neck treatment (CCRT vs. neck dissection) (HR: 2.689; 95% CI: 0.448–16.145; p=0.280). The 2-year LRFS rate for definitive CCRT to the neck (CCRT group) or curative neck dissection followed by adjuvant CCRT (neck dissection group) was 53.9% and 37.5%, respectively (Fig. 2b). For RRFS, no difference was noted in terms of neck treatment (CCRT vs. neck dissection) (HR: 1.284; 95% CI: 0.270–6.115; p=0.754). The 2-year RRFS for definitive CCRT to the neck (CCRT group) or curative neck dissection followed by adjuvant CCRT (neck dissection group) were 50.6% and 37.5%, respectively (Fig. 2c). For DMFS, no difference was noted in terms of primary tumor treatment (CCRT vs. surgery) (HR: 0.706; 95% CI: 0.150–3.322; p=0.660) or neck treatment (CCRT vs. neck dissection) (HR: 1.962, 95% CI: 0.503–7.660; p=0.322). Advanced T3/T4 stage was associated with worse DMFS (HR: 3.307; 95% CI: 1.289–7.157; p=0.011). The 2-year DMFS rate for definitive CCRT to the neck (CCRT group) and curative neck dissection followed by adjuvant CCRT (neck dissection group) was 56.3% and 37.5%, respectively (Fig. 2d). In

 doi:10.20944/preprints201903.0249.v1

summary, for N3 oropharyngeal cancer, bimodality definitive CCRT to the neck (CCRT group) did not differ from trimodality curative neck dissection followed by adjuvant CCRT (neck dissection group) in terms of survival outcome.

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 27 March 2019 doi:10.20944/preprints201903.0249.v1

Table 2 Univariate and multivariate analysis for survival in oropharyngeal cancer patients

	Univariate			Multivariate		
Characteristics	HR	95% CI	P value	HR	95% CI	P value
OS						
Gender (male vs. female)	0.047	0.000-1069.263	0.550	0.000	0.000-	0.980
T classification (T1/T2 vs. T3/T4)	2.391	1.043-5.482	0.039	3.337	1.312-8.488	0.011
Primary tumor treatment (CCRT vs. Surgery)	1.689	0.504-5.664	0.391	0.607	0.123-3.000	0.540
Neck treatment (CCRT vs. Neck dissection)	2.085	0.869-5.000	0.100	2.199	0.522-9.256	0.283
Induction chemotherapy (No vs. Yes)	0.514	0.192-1.373	0.184	0.557	0.128-2.242	0.410
LRFS						
Gender (male vs. female)	0.047	0.000-824.709	0.540	0.000	0.000-	0.980
T classification (T1/T2 vs. T3/T4)	2.131	0.969-4.689	0.060	3.054	1.242-7.509	0.015
Primary tumor treatment (CCRT vs. Surgery)	1.486	0.446-4.947	0.519	0.446	0.079-2.536	0.363
Neck treatment (CCRT vs. Neck dissection)	1.971	0.832-5.671	0.123	2.689	0.448-16.145	0.280
Induction chemotherapy (No vs. Yes)	0.448	0.169-1.186	0.106	0.629	0.124-3.185	0.575
RRFS						
Gender (male vs. female)	0.047	0.000-563.595	0.524	0.000	0.000-	0.978
T classification (T1/T2 vs. T3/T4)	1.873	0.878-3.993	0.104	2.354	1.037-5.342	0.041
Primary tumor treatment (CCRT vs. Surgery)	1.196	0.361-3.963	0.770	0.588	0.120-2.884	0.513
Neck treatment (CCRT vs. Neck dissection)	1.522	0.648-3.573	0.335	1.284	0.270-6.115	0.754
Induction chemotherapy (No vs. Yes)	0.508	0.193-1.335	0.169	0.457	0.098-2.132	0.319
DMFS						
Gender (male vs. female)	0.047	0.000-785.047	0.538	0.000	0.000-	0.979
T classification (T1/T2 vs. T3/T4)	2.389	1.080-5.287	0.032	3.307	1.289-7.157	0.011
Primary tumor treatment (CCRT vs. Surgery)	1.710	0.513-5.697	0.382	0.706	0.150-3.322	0.660
Neck treatment (CCRT vs. Neck dissection)	1.940	0.819-4.597	0.132	1.962	0.503-7.660	0.322
Induction chemotherapy (No vs. Yes)	0.572	0.216-1.515	0.261	0.643	0.167-2.485	0.522

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 27 March 2019 doi:10.20944/preprints201903.0249.v1

For nonoropharyngeal cancer patients, univariate and multivariate analyses for survival are summarized in Table 3. With regard to primary tumor treatment, (CCRT vs. surgery) no difference was noted in terms of OS (HR: 0.940; 95% CI: 0.247–3.571; p=0.927), LRFS (HR: 0.780; 95% CI: 0.227–2.675; p=0.693), RRFS (HR: 1.033; 95% CI: 0.281–3.802; p=0.961) or DMFS (HR: 0.665; 95% CI: 0.207–2.135; p=0.493). Neck treatment (CCRT vs. neck dissection) did not affect OS (HR: 0.444; 95% CI: 0.127–1.549; p=0.203), LRFS (HR: 0.473; 95% CI: 0.149–1.503; p=0.204), RRFS (HR: 0.364; 95% CI: 0.101–1.274; p=0.114) or DMFS (HR: 0.717; 95% CI: 0.248–2.077; p=0.540). The 2-year survival outcome in terms of OS, LRFS, RRFS, and DMFS for definitive CCRT to the neck (CCRT group) or curative neck dissection followed by adjuvant CCRT (neck dissection group) were 37.0% and 45.6% (Fig. 2e), 27.8% and 45.2% (Fig. 2f), 33.3% and 45.6% (Fig. 2g), and 33.3% and 32.8% (Fig. 2h), respectively. Similarly, for N3 nonoropharyngeal cancer, the OS, LRFS, RRFS, and DMFS of bimodality definitive CCRT to the neck (CCRT group) did not differ from that of trimodality curative neck dissection followed by adjuvant CCRT (neck dissection group).

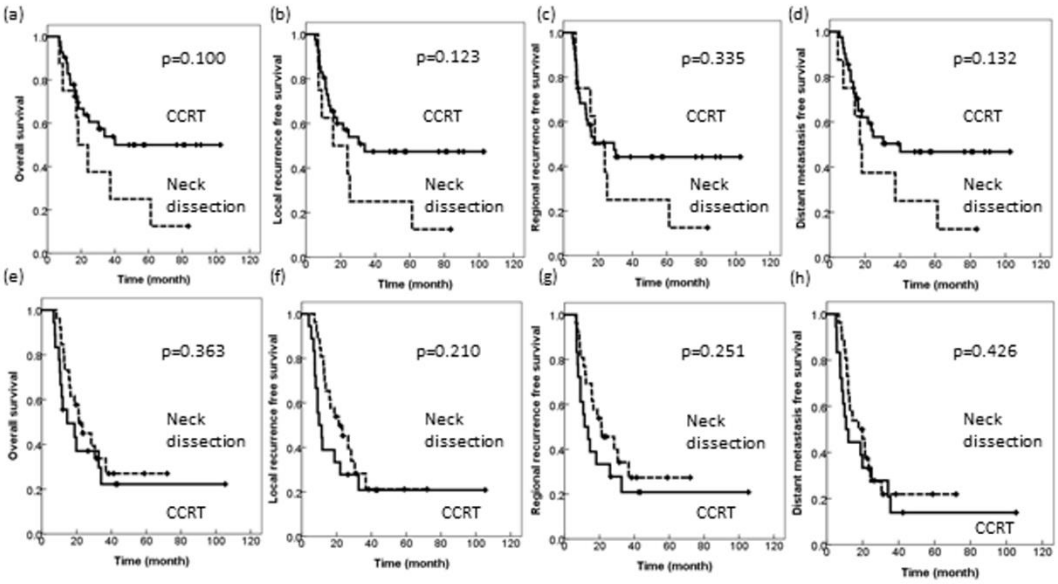
Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 27 March 2019 doi:10.20944/preprints201903.0249.v1

Table 3 Univariate and multivariate analysis for survival in non-oropharyngeal cancer patients

	Univariate			Multivariate		
Characteristics	HR	95% CI	P value	HR	95% CI	P value
OS						
Gender (male vs. female)	0.989	0.234-4.177	0.988	0.621	9,142-2.725	0.528
T classification (T1/T2 vs. T3/T4)	2.466	0.853-7.132	0.096	2.899	0.862-9.746	0.085
Primary tumor treatment (CCRT vs. Surgery)	1.139	0.548-2.368	0.727	0.940	0.247-3.571	0.927
Neck treatment (CCRT vs. Neck dissection)	0.714	0.346-1.475	0.363	0.444	0.127-1.549	0.203
Induction chemotherapy (No vs. Yes)	0.602	0.286-1.269	0.182	0.306	0.100-0.932	0.037
LRFS						
Gender (male vs. female)	0.816	0.194-3.429	0.781	0.491	0.112-2.140	0.343
T classification (T1/T2 vs. T3/T4)	2.218	0.844-5.828	0.106	2.675	0.869-8.227	0.086
Primary tumor treatment (CCRT vs. Surgery)	0.950	0.466-1.933	0.087	0.780	0.227-2.675	0.693
Neck treatment (CCRT vs. Neck dissection)	0.638	0.316-1.289	0.210	0.473	0.149-1.503	0.204
Induction chemotherapy (No vs. Yes)	0.710	0.341-1.475	0.358	0.351	0.122-1.004	0.051
RRFS						
Gender (male vs. female)	0.958	0.227-4.037	0.954	0.626	0.143-2.751	0.535
T classification (T1/T2 vs. T3/T4)	1.745	0.662-4.603	0.261	1.927	0.640-5.085	0.244
Primary tumor treatment (CCRT vs. Surgery)	1.022	0.497-2.101	0.954	1.033	0.281-3.802	0.961
Neck treatment (CCRT vs. Neck dissection)	0.660	0.324-1.342	0.251	0.364	0.101-1.274	0.114
Induction chemotherapy (No vs. Yes)	0.602	0.288-1.259	0.178	0.307	0.103-0.915	0.034
DMFS						
Gender (male vs. female)	0.814	0.194-3.415	0.778	0.582	0.134-2.525	0.470
T classification (T1/T2 vs. T3/T4)	1.700	0.699-4.136	0.242	2.044	0.735-5.687	0.171
Primary tumor treatment (CCRT vs. Surgery)	0.896	0.447-1.797	0.758	0.665	0.207-2.135	0.493
Neck treatment (CCRT vs. Neck dissection)	0.758	0.383-1.500	0.426	0.717	0.248-2.077	0.540
Induction chemotherapy (No vs. Yes)	0.769	0.372-1.591	0.479	0.440	0.155-1.245	0.122

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 27 March 2019 doi:10.20944/preprints201903.0249.v1

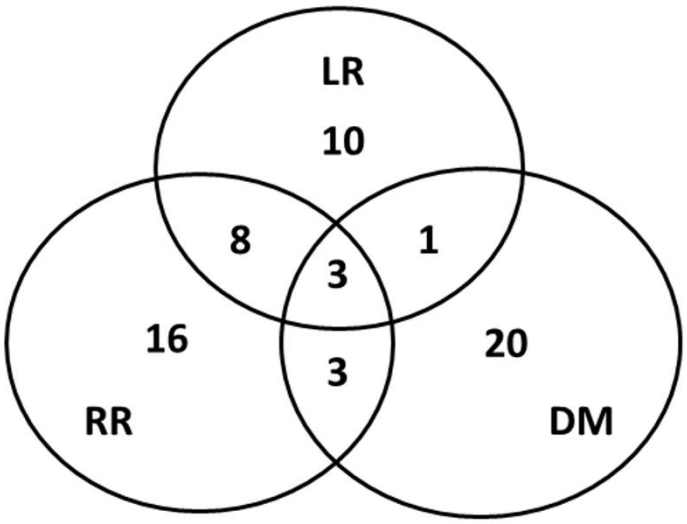
Figure 2: Survival curve. (a) OS, (b) LRFS, (c) RRFS, and (d) DMFS for oropharyngeal cancer patients. (e) OS, (f) LRFS, (g) RRFS, (h) and DMFS for nonoropharyngeal patients.



Among the 93 patients, 32 (34.4%) had disease-free recurrence at last follow-up. The first failure sites are summarized in Figure 3. In total, 30 out of the 61 patients experiencing recurrence had regional recurrence, whereas 27 had distant metastasis. Local recurrence occurred in 22 of the 61 patients.

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 27 March 2019 doi:10.20944/preprints201903.0249.v1

Figure 3: Pattern of first failure sites with numbers of patients. LR, local recurrence; RR, regional recurrence; DM, distant metastasis.



Discussion

Studies focusing on the management of N3 head and neck patients are limited. The results of previous and current studies are summarized in Table 4. Adams et al.[8] reported outcomes for 33 N3 head and neck cancer patients treated with definitive CCRT and PET-guided neck management. Their patient cohort consisted of 25 (76%) cases of oropharyngeal; 4 (12%), nasopharyngeal; 1 (3%), laryngeal; and 1 (3%) hypopharyngeal malignancy. Overall PET CR rate was 64.5%, and subsequent nodal failure rate after PET CR was 10% (2 patients). The 3-year nodal control rate and metastasis-free survival rate for all patients were 68.6% and 59.5%, respectively. For the patients with oropharyngeal cancer, the 3-year nodal control rate and metastasis-free survival were 64.8% and 59.1%, respectively.

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 27 March 2019 doi:10.20944/preprints201903.0249.v1

Table 4 Summary of outcomes for N3 neck cancer patients in the literature

Study	Igidbashian et al. [10]	Karakaya et al. [9]	Adams et al. [8]	Zenga et al. [11]	Chen et al. (current study)
Study period	1998–2006	2004–2010	2005–2012	1998–2013	2002–2015
No. of patients	70	40	33	39	93
Primary tumor site	56 (80%) oropharynx, 8 (11.4%) unknown, 2 (2.9%) larynx, 2 (2.9%) oral cavity, and 2 (2.9%) hypopharynx	24 (60%) oropharynx, 4 (10%) larynx, 2 (2.9%), 6 (15%) hypopharynx, 2 (5%) oral cavity, and 4 (10%) unknown	25 (76%) oropharynx, 4 (12%) nasopharynx, 1 (3%) larynx, and 1 (3%) hypopharynx	16 (41%) base of tongue, 22 (56%) tonsil, and 1 (3%) unknown	49 (52.7%) oropharynx, 26 (27.9%) hypopharynx, 14 (15%) oral cavity, and 4 larynx (4.3%)
Neck management	Definitive CCRT with neck dissection only for those with incomplete response	Definitive CCRT without planned neck dissection	Definitive CCRT with PET-guided management at 12 weeks	Neck dissection with or without adjuvant therapy	Definitive CCRT without planned neck dissection or upfront neck dissection followed by adjuvant therapy
Overall survival	2-year at 63.0% for cCR and 79.4% and cPR-ND	3-year at 51.4%	3-year at 48.4%	5-year at 87%	Oropharynx: 2-year at 57.4% for definitive CCRT and 37.5% for neck dissection. Non-oropharynx: 2-year at 37.0% for definitive CCRT and

 doi:10.20944/preprints201903.0249.v1

					45.6% for neck dissection
Neck control	2-year regional relapse-free survival at 87.8% for cCR patients	3-year at 69.3%	3-year nodal control rate at 68.6%	Isolated regional disease recurrence or persistence in two (5%) patients	Oropharynx: 2-year at 50.6% for definitive CCRT and 37.5% for neck dissection. Nonoropharynx: 2-year at 33.3% for definitive CCRT and 45.6% for neck dissection
Distant failure	2-year distant disease-free survival at 67.1 for cCR and 92.6% for cPR-ND	NA	3-year metastasis-free survival at 59.5%	NA	Oropharynx: 2-year at 56.3% for definitive CCRT and 37.5% for neck dissection. Nonoropharynx: 2-year at 33.3% for definitive CCRT and 32.8% for neck dissection

Abbreviations: cCR, clinically complete response; cPR-ND, neck dissection after achieving cCR at the primary site and clinically partial response in the neck; NA, not available; CCRT, concurrent chemoradiotherapy

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 27 March 2019 doi:10.20944/preprints201903.0249.v1

Karakaya et al. [9] reported on 40 N3 head and neck cancer patients treated with definitive CCRT. Of them, 24 (60%), 4 (10%), 6 (15%), 2 (5%), and 4 (10%) had oropharyngeal, laryngeal, hypopharyngeal, oral cavity, and unknown primary cancer, respectively. Twenty-seven (67.5%) patients achieved CR with subsequent nodal failure rate of 3/27 (11%). The 3-year overall survival and regional control in the whole cohort were 51.4% and 69.3%, respectively. Igidbashian et al.[10] reported on 70 N3 patients treated with definitive CCRT with neck dissection only for those with incomplete response. Oropharyngeal patients comprised 56 (80.0%) of the cohort. The CR rate was 26/70 (37.1%), and the 2-year regional relapse-free survival was 87.8% for patients who achieved clinical CR. Our data showed that CR rate in the neck in patients with oropharyngeal and nonoropharyngeal cancer were 31/41 (75.6%) and 12/18 (66.7%), respectively. A total of 7/31 (22.6%) patients with oropharyngeal cancer and 3/12 (25%) patients with nonoropharyngeal cancer who achieved CR in the neck after definitive CCRT had subsequent regional recurrence. In our definitive CCRT to the neck cohort, the overall 2-year RRFS rate was 45.2%, while it was 50.6% and 27.8% in patients with oropharyngeal and nonoropharyngeal cancer, respectively.

Meanwhile, Zenga et al.[11] reported the outcomes of upfront neck dissection for 39 patients with N3 human papillomavirus (HPV)-related oropharyngeal cancers.

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 27 March 2019 doi:10.20944/preprints201903.0249.v1

Thirty-six (90%) underwent adjuvant therapy, with 69% of them receiving adjuvant CCRT. Isolated regional disease recurrence or persistence was found in two (5%) patients. Five-year OS, disease-specific survival, and disease-free survival were 87%, 89%, and 84%, respectively. In our study, oropharyngeal cancer patients who received upfront neck dissection followed by adjuvant CCRT had 2-year OS and RRFS of 37.5% and 37.5%, respectively. The result probably reflects the effects of the combination of HPV-positive and HPV-negative oropharyngeal cancer in our cohort. In the current study, the 2-year survival outcome in terms of OS and RRFS for definitive CCRT to neck (CCRT group) or curative neck dissection followed by adjuvant CCRT (neck dissection group) was 45.6% and 45.6%, respectively.

Our study showed that the survival outcomes in terms of OS, LRFS, RRFS, or DMFS for N3 oropharyngeal and nonoropharyngeal cancer patients treated with bimodality definitive CCRT to the neck did not differ from those treated with trimodality curative neck dissection followed by adjuvant CCRT. The present study showed that even for bulky N3 neck, bimodality definitive CCRT to the neck without planned neck dissection can be the treatment of choice. However, this study has some limitations. First, during the study period, PET-CT was not routinely performed in our institution. With more widespread PET-CT implementation in head and neck cancer, a more accurate staging, target definition, and treatment response evaluation

 doi:10.20944/preprints201903.0249.v1

can be achieved[12]. Second, our cohort lacked HPV-related biomarkers. HPV-related oropharyngeal cancer has better radiation response and survival outcome [13-15]. Whether outcomes of definitive CCRT or upfront neck dissection for N3 neck will differ according to HPV status should be further investigated.

Conclusion

In summary, N3 neck patients treated with definitive CCRT can achieve similar outcomes to those treated with upfront neck dissection followed by adjuvant CCRT. Bimodality definitive CCRT can be the primary treatment of choice for this group of patients with poor prognosis. Cautions should be made to avoid overtreatment for this group of patients.

 doi:10.20944/preprints201903.0249.v1

List of abbreviations

APF: Avastin + cisplatin + 5-FU; ATPF: Avastin + Taxotere + cisplatin + 5-FU; CCRT: chemoradiotherapy; CR: complete response; DMFS: distant metastasis-free survival; EPF: Erbitux + cisplatin + 5-FU; IA: intra-arterial; LRFS: local recurrence-free survival; MATPF: mitomycin, Taxotere, cisplatin, 5FU + Avastin; MEPFL: mitomycin, epirubicin, cisplatin, fluorouracil, and leucovorin; MPA: mitomycin, cisplatin, Avastin; MTPF: mitomycin, Taxotere, cisplatin, 5FU; OS: overall survival; PET: positron emission tomography; PF: cisplatin + 5-FU; PR: partial response; RRFS: regional recurrence-free survival; TPF: Taxotere + cisplatin + 5-FU;

 doi:10.20944/preprints201903.0249.v1

Declarations

Acknowledgements: This study was supported by research grants NTUH 104-M2861, NTUH 105-N3224 and NTUH 106-N3609 from National Taiwan University Hospital.

Authors' contributions: WYC and TCC analyzed the data and wrote the manuscript. WYC, TCC, SFL, THL, BSH and CWW participated in the draft of manuscript. TCC, BSH and CWW supervised and study design and manuscript writing.

Conflicts of interests: The authors declare no conflicts of interests

Ethics approval and consent to participate: The study protocol was approved by the Research Ethics Committee of National Taiwan University Hospital (NTUH: 201707061RINB).

 doi:10.20944/preprints201903.0249.v1

Figure legends

Figure 1: Treatment for tumors with different primary sites.

Figure 2: Survival curve. (a) OS, (b) LRFS, (c) RRFS, and (d) DMFS for oropharyngeal cancer patients. (e) OS, (f) LRFS, (g) RRFS, (h) and DMFS for nonoropharyngeal patients.

Figure 3: Pattern of first failure sites with numbers of patients. LR, local recurrence; RR, regional recurrence; DM, distant metastasis.

 doi:10.20944/preprints201903.0249.v1

Reference

1. Cohen, E.E., et al., *Phase III randomized trial of induction chemotherapy in patients with N2 or N3 locally advanced head and neck cancer.* J Clin Oncol, 2014. **32**(25): p. 2735-43.
2. Haddad, R., et al., *Induction chemotherapy followed by concurrent chemoradiotherapy (sequential chemoradiotherapy) versus concurrent chemoradiotherapy alone in locally advanced head and neck cancer (PARADIGM): a randomised phase 3 trial.* Lancet Oncol, 2013. **14**(3): p. 257-64.
3. Mehanna, H., et al., *PET-CT Surveillance versus Neck Dissection in Advanced Head and Neck Cancer.* N Engl J Med, 2016. **374**(15): p. 1444-54.
4. Huang, S.H., et al., *Temporal nodal regression and regional control after primary radiation therapy for N2-N3 head-and-neck cancer stratified by HPV status.* Int J Radiat Oncol Biol Phys, 2013. **87**(5): p. 1078-85.
5. Lorch, J.H., et al., *Induction chemotherapy with cisplatin and fluorouracil alone or in combination with docetaxel in locally advanced squamous-cell cancer of the head and neck: long-term results of the TAX 324 randomised phase 3 trial.* Lancet Oncol, 2011. **12**(2): p. 153-9.
6. Hamoir, M., et al., *The role of neck dissection in the setting of chemoradiation therapy for head and neck squamous cell carcinoma with advanced neck disease.* Oral Oncol, 2012. **48**(3): p. 203-10.
7. Hong, R.L., et al., *Induction chemotherapy with mitomycin, epirubicin, cisplatin, fluorouracil, and leucovorin followed by radiotherapy in the treatment of locoregionally advanced nasopharyngeal carcinoma.* J Clin Oncol, 2001. **19**(23): p. 4305-13.
8. Adams, G., et al., *Outcomes after primary chemoradiotherapy for N3 (>6 cm) head and neck squamous cell carcinoma after an FDG-PET--guided neck management policy.* Head Neck, 2014. **36**(8): p. 1200-6.
9. Karakaya, E., et al., *Outcomes following chemoradiotherapy for N3 head and neck squamous cell carcinoma without a planned neck dissection.* Oral Oncol, 2013. **49**(1): p. 55-9.
10. Igidbashian, L., et al., *Outcome with neck dissection after chemoradiation for N3 head-and-neck squamous cell carcinoma.* Int J Radiat Oncol Biol Phys, 2010. **77**(2): p. 414-20.
11. Zenga, J., et al., *Outcomes of surgically treated human papillomavirus-related oropharyngeal squamous cell carcinoma with N3 disease.* Laryngoscope, 2016.

 doi:10.20944/preprints201903.0249.v1

12. Cacicedo, J., et al., *Role of fluorine-18 fluorodeoxyglucose PET/CT in head and neck oncology: the point of view of the radiation oncologist.* Br J Radiol, 2016. **89**(1067): p. 20160217.
13. Rischin, D., et al., *Prognostic significance of p16INK4A and human papillomavirus in patients with oropharyngeal cancer treated on TROG 02.02 phase III trial.* J Clin Oncol, 2010. **28**(27): p. 4142-8.
14. Ang, K.K., et al., *Human papillomavirus and survival of patients with oropharyngeal cancer.* N Engl J Med, 2010. **363**(1): p. 24-35.
15. Rosenthal, D.I., et al., *Association of Human Papillomavirus and p16 Status With Outcomes in the IMCL-9815 Phase III Registration Trial for Patients With Locoregionally Advanced Oropharyngeal Squamous Cell Carcinoma of the Head and Neck Treated With Radiotherapy With or Without Cetuximab.* J Clin Oncol, 2016. **34**(12): p. 1300-8.