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Suggestions for surveillance and radiation strategy in nasopharyngeal carcinoma treated with IMRT: Based on hazard-rate and patterns of recurrence

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ABSTRACT

Objective: The study was designed to appraise the locoregional recurrence patterns using conventional two-dimensional radiotherapy (2D-RT) and intensity modulated radiation therapy (IMRT) in nasopharyngeal carcinoma (NPC) in order to better establish the scenario of the modern radiotherapy and the duration of surveillance.

Materials and Methods: We reviewed the institutional database to identify patients with pathologically confirmed, non-metastatic NPC who completed radical 2D-RT or IMRT at our center from 2000 to 2011. We collected data on clinicopathologic features, treatments and outcomes. Statistical analyses were performed using SPSS 20.0 or STATASE 14.0.

Results: The median follow-up was 60.1 months. Of 2315 patients, 1289 (53%) were treated with 2D-RT and 1026 (47%) with IMRT. IMRT group achieved better locoregional control rate, with the 5-year locoregional relapse-free survival (LRRFS) were 84.9% and 87.7% among patients received 2D-RT and IMRT, respectively (P = 0.050). IMRT was superior to 2D technique in terms of local relapse-free survival (LRFS) (88.4% vs 91.1%, P = 0.047) and the advantage was only significant in T3-4 subgroup (81.6% vs 90.2%, P = 0.000). Similar neck control rates were observed using different RT techniques. And the recurrence time appeared to be postponed by IMRT, with peaks accounting for the year 1.5 and year 3–4 compared to which was predominant at the first two years using 2D-RT in nature.

Conclusions: IMRT provided an improved LRRFS in overall stage and LRFS in advanced T stage for NPC compared with 2D-RT. Annual hazard of recurrence also changed with RT techniques.

Introduction

Nasopharyngeal carcinoma (NPC) is highly radiochemosensitive and its locoregional control rate, which had been improved by the multidisciplinary approach, has approximated to 85% [1–3]. Once recurrence, salvage strategy should be administered [4–9] and the location and extent of the recurrent disease will determine the optimal therapy [10]. Nevertheless, the efficacies of evidence-based re-treatment are yet unsatisfactory for patients suffered recurrent diseases. It may partly due to the delayed diagnosis of recurrence to advanced stage, which made the re-treatment even harder, so it is essential to discover the recurrence in its infancy.

Currently, intensity modulated radiation therapy (IMRT), which uses complex modulated radiation beams to create sharper radiation dose gradients between tumor and critical organs than conventional two-dimensional radiotherapy (2D-RT), has been served as the standard initial treatment for any stage of NPC [1,11]. Its superiority over 2D-RT reflected mostly in locoregional control as well as toxicities reduction, however the standard dose and fractionation using simultaneous integrated boost (SIB) technique has not been determined [12,13].

Furthermore, the distinct patterns of locoregional recurrence between 2D and IMRT have historically been a relatively understudied area. The limited amount of clinical trial data assessing the patterns for locoregional recurrence changing with the RT techniques may in fact result in improper radiation dose, unnecessary follow ups for some, or conversely, a lack of consolidated treatment and effective recurrence surveillance for others.

In this retrospective study, we aimed to appraise the NPC long-term follow-up outcomes using two RT techniques in our institution and evaluate the different patterns of recurrence in a bid to improve our

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treatment strategies and surveillance protocols in the era of IMRT.

Materials and methods

Patient population and treatment delivery

Patients with histologically proven nasopharyngeal carcinoma, T1-4 disease, any nodal status, and no detectable distant metastatic disease were eligible. Completely documented patients treated with 2D-RT and IMRT were retrospectively enrolled from January 2000 to December 2003 and November 2008 to December 2011, respectively. Those who failed to complete the radiotherapy were excluded from the analyses. Pretreatment evaluation should consist of blood routine, biochemical profile, contrasted-MRI/CT of the nasopharynx and neck, chest CT, ultrasound of the abdomen, bone scan and/or PET/CT. Primary treatment included radiotherapy with or without chemotherapy. The diagnostic imaging of these patients were retrieved and reviewed; all diseases were re-staged according to the 6th AJCC (American Joint Commission on Cancer) staging system.

Conventional technique was used via laterally opposed faciocervical fields to treat the nasopharynx and upper neck in a single volume, followed by the shrinking-field technique to spare the spinal cord to a total prescription dose of approximate 70 Gy in 1.8–2.0 Gy/fraction. The curative dose to the positive lymph nodes was 62–68 Gy and prophylactic doses to the upper and lower neck drainage were 56–62 Gy and 50–54 Gy, respectively. Subsequently, a 4 Gy boost to the skull base and intracranial area in 2 fractions was delivered to the T3-4 primary. Brachytherapy of Ir-192 with 10–16 Gy/1–2 fractions every other week was used to boost the residual T1-2 tumor after external beam irradiation. Simultaneous integrated boost intensity-modulated radiotherapy (SIB-IMRT) plans were designed and optimized using the Pinnacle planning system as described in our previous manuscript [14]: 66–70.4 Gy in 2.2 Gy/fraction to the planning target volume (PTV) of primary gross tumor (66 Gy/30Fx to T1-2 and 70.4 Gy/32Fx to T3-4); 66–68 Gy/30-32fx to the PTV of nodal gross tumor (PTV-LN), 60 Gy to the PTV of high-risk CTV, and 54 Gy to the PTV of low-risk CTV. Residual diseases were boosted at the discretion of the physician.

Chemotherapy consisted of cisplatin mono-concurrent regimen and cisplatin-based, 5-Fu/docetaxel/gemcitabine-comprising induction/adjuvant chemotherapy.

We did follow-up every 3 months for the first and second year, every 6 months for year 3–5, then every year. Routine follow-up assessments included indirect nasopharyngoscope, neck palpation, contrasted-MRI/CT of the nasopharynx and neck and abdominal ultrasound. Plain CT scans of the chest were done every year; bone scan and/or PET/CT were performed whenever indicated. Any visibly intra-cavity recurrent lesion and neck lymph node relapse should be confirmed by pathology. Only recurrences with solitary skull base and/or intracranial invasion were allowed to use imaging diagnosis.

All data collection and statistical analysis of this observational study were conducted in accordance with the institutional Ethical Board of Fudan University Shanghai Cancer Center. Informed consent was obtained on each subject before treatment.

Statistical methods

Patient and tumor characteristics were compared with Student's t-tests, $\chi 2$ or Fisher exact test as appropriate. Locoregional relapse-free

Table 1
Demographic and clinical characteristics before and after PSM.

Characteristic	Before PSM			After PSM		
	2D-RT,% (n = 1289)	IMRT,% (n = 1026)	P	2D-RT,% (n = 951)	IMRT,% (n = 951)	P
Age			0.387			0.431
Median, years (range)	10–87 (48)	7–80 (48)		12–87 (48)	7–80 (48)	
≤50	743 (57.6)	573 (55.8)		550 (57.8)	533 (56.0)	
>50	546 (42.4)	453 (44.2)		401 (42.1)	418 (44.0)	
Sex			0.452			0.224
Male	986 (76.5)	771 (75.1)		720 (75.7)	697 (73.3)	
Female	303 (23.5)	255 (24.9)		231 (24.3)	254 (26.7)	
T stage			0.182			0.073
T1	238 (18.5)	220 (21.4)		193 (20.3)	220 (23.1)	
T2	504 (39.1)	366 (35.7)		385 (40.5)	334 (35.1)	
T3	340 (26.4)	283 (27.6)		245 (25.8)	273 (28.7)	
T4	207 (16.0)	157 (15.3)		128 (13.4)	124 (13.1)	
N stage			0.086			0.066
N0	259 (20.1)	188 (18.3)		210 (22.1)	178 (18.7)	
N1	348 (27.0)	291 (28.4)		231 (24.3)	268 (28.2)	
N2	545 (42.3)	407 (39.7)		396 (41.6)	374 (39.3)	
N3	137 (10.6)	140 (13.6)		114 (12.0)	131 (13.8)	
AJCC stage group			0.051			0.194
I	69 (5.4)	47 (4.6)		61 (6.5)	47 (4.9)	
II	301 (23.3)	195 (19.0)		221 (23.2)	195 (20.5)	
III	582 (45.2)	499 (48.6)		434 (45.6)	466 (49.0)	
IV	337 (26.1)	285 (27.8)		235 (24.7)	243 (25.6)	
Radiation dose, Gy			0.000			0.000
Median, range	70.3 (66.1–78.9)	70.0 (66.0–78.3)		70.3 (66.1–78.9)	69.0 (66.0–78.3)	
< 70	493 (38.2)	506 (49.3)		377 (39.6)	479 (50.4)	
≥70	796 (61.8)	520 (50.7)		574 (60.4)	472 (49.6)	
Combined chemotherapy			0.000			0.138
RT alone	541 (42.0)	224 (21.8)		252 (26.5)	224 (23.6)	
CRT	748 (58.0)	802 (78.2)		699 (73.5)	727 (76.4)	
Diagnostic imaging			0.000			0.000
CT	982 (76.2)	34 (3.3)		735 (77.3)	25 (2.6)	
MRI	307 (23.8)	992 (96.7)		216 (22.7)	926 (97.4)	

Abbreviations: PSM, Propensity score matching; 2D-RT, two-dimensional radiation therapy; AJCC, American Joint Commission on Cancer; IMRT, intensity modulated radiation therapy; N, clinical node stage; T, clinical tumor stage; CRT, chemoradiotherapy.
*P value from *t* test; otherwise, all other P values from $\chi 2$ test.