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Two-Dimensional Conventional Radiotherapy Versus Intensity Modulated Radiotherapy for Nasopharyngeal Cancer Treatment: A Retrospective Study from Northeast Turkey

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Objective: This study aims to compare intensity-modulated radiotherapy (IMRT) and two-dimensional conventional radiotherapy (2DCRT) considering treatment response, treatment compliance, and toxicity in nasopharyngeal cancer (NPC) patients.

Materials and Methods: A total of 78 NPC patients admitted between January 1999–December 2013 were retrospectively evaluated for local control (LC), treatment compliance, and toxicity. Of these, 55 (70.5%) were treated with 2DCRT, and 23 (29.5%) were treated with IMRT.

Results: The median follow-up time was 34.1 months (range, 3.2–202.84). Xerostomia was the most common acute toxicity in both the 2DCRT (41, 77.4%) and IMRT (18, 78.3%) groups. The most common late toxicity occurred in 28 (51.9%) patients in the former was xerostomia, while that in the latter was soft tissue fibrosis in 13 (56.6%) patients. No differences between these treatments were observed considering acute or late toxicity. In the former, 23 patients (41.8%) interrupted the treatment, while in the latter only 4 patients (17.4%) interrupted it. This difference was statistically significant. Considering treatment response, no significant difference was noted.

Conclusion: IMRT was better than 2DCRT for treatment of NPC considering treatment compliance, toxicity, and tumor response; however, prospective studies with more patients are needed for confirmation.

Key Words: *IMRT, nasopharyngeal cancer, radiotherapy, treatment techniques*

Nazofarenks Kanseri Tedavisinde İki Boyutlu Konformal Radyoterapi ile Yoğunluk Ayarlı Radyoterapinin Karşılaştırılması: Türkiye'nin Kuzeyinde Retrospektif Bir Çalışma

Amaç: İki boyutlu konformal radyoterapi (2DCRT) ile yoğunluk ayarlı radyoterapinin (IMRT) tedavi cevabı, tedaviye uyum ve yan etkiler açısından retrospektif olarak kaşlılaştırılması amaçlanmıştır.

Gereç ve Yöntem: Ocak 1999–Aralık 2013 tarihleri arasında nazofarenks kanseri (NFC) tanısıyla başvuran 78 hasta, tedavi cevabı, tedaviye uyum ve yan etki açısından değerlendirilmeye alındı. 55'i (%70.5) 2DCRT ile 23'ü (%29.5) IMRT ile tedavi edilmiştir. Olguların E/K oranı 2.7 olup medyan ortalama yaş 46 (12-81)'dır. Olguların 5'i (%6.4) evre 1, 12'si (%15.4) evre 2, 39'u (%50) evre 3, 22 (%28.2) evre 4 tür.

Bulgular: Medyan izlem süresi 34.1 ay (3.2–202.84)'dır. Akut yan etki 2DCRT ve IMRT uygulananlarda en sık kserestomi olup sırası ile 41 (%77.4) ve 18 (%78.3) dir. Geç toksisite olarak 2DCRT uygulananlarda en sık 28 (%51.9) hastada kserestomi, IMRT uygulananlarda ise en sık 13 (%56.5) hastada yumuşak doku fibrosizi görülmüştür. RT tedavisi boyunca ve izlem süresince görülen akut ve kronik yan etkiler açısından 2DCRT ve IMRT arasında fark görülmemiş olup, sırasıyla P değerleri (P=0.398), (P=0.692) ve (P=0.332) şeklindedir 2DCRT tedavisi gören hastaların (23) %41.8'i tedaviye ara verirken, IMRT tedavisi alanların sadece (4) %17.4'ü tedaviye ara vermiştir ve bu istatistiksel olarak anlamlı bulunmuştur (P=0.039). Tedavi cevabı açısından iki grup arasında fark görülmemiştir (P=0.736).

Sonuç: Nazofarenks kanserinde 2DCRT ile IMRT kaşlılaştırıldığında tedaviye uyum, yan etkiler ve tümör cevabı için IMRT daha üstün görülmektedir

Anahtar Kelimeler: *IMRT, nazofarenks kanseri, radyoterapi, tedavi tekniği*

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Introduction

Diagnosis of nasopharyngeal cancer (NPC) is problematic due to the proximity of this anatomical region to other structures, such as the nasal cavity, paranasal sinuses, oral cavity, base of skull, and the orbit (1). Such proximity affects treatment planning and application as well. Protection and maintenance of functionality of the anatomical structures are as important as disease control. Thus, a multidisciplinary approach is essential for the treatment of NPC. Due to the associated high mortality and morbidity rates in NPC, surgery excision is limited with respect to diagnosis and salvage

treatments. Brachytherapy (BRT) can be used for local recurrence and residual tumors and can also be used in the adjuvant setting after external beam radiotherapy (EBRT) (2). For many years, only radiotherapy (RT) was used for NPC treatment; however, RT is insufficient for advanced stage cancers, mostly due to late treatment of the patient. Especially in this group of patients, chemotherapy (CTX) has been explored as an additional treatment in order to increase disease control and survival rates. In fact, some studies revealed that addition of CTX to RT increased survival rates in locally advanced NPC (3, 4). Three-dimensional conformal radiotherapy (3DCRT) was considered as the standard RT technique until intensity-modulated radiotherapy (IMRT) emerged as a technique that can adjust better dose around target volumes and better spare organs at risk. Because of a steep dose gradient and a high conformity index, the risk of missing the target with IMRT is higher than with conformal techniques. Furthermore, xerostomia is a common and disturbing late effect of conventional RT. Several studies have demonstrated the superiority of IMRT over 2DCRT or 3DCRT in sparing the parotid glands, and two randomized controlled trials have described a better salivary toxicity profile for IMRT (5, 6). In our study, 78 patients diagnosed with NPC between January 1999 and December 2013 were retrospectively evaluated in terms of local control (LC), compliance to treatment, toxicity, and prognostic factors related to LC.

Materials and Methods

Patients: Between January 1999 and December 2013, 107 patients diagnosed with NPC at the our clinic were evaluated retrospectively. A total of 29 of these 107 patients were excluded from the analysis because 15 failed to return for follow-ups, 2 did not complete the treatment, 8 experienced metastases, and 4 were intolerant of the treatment (grade 3 nausea and skin reaction). Survival evaluation was performed for 78 patients. The median age was 46 (20–81) years. Patient characteristics are shown in Table 1.

At diagnosis, all patients were evaluated with a complete physical examination and fiber-optic nasopharyngoscopy, magnetic resonance imaging (MRI) or computed tomography (CT) of the head and neck with contrast medium, chest CT or radiography, abdominal CT or a [18F]-fluoro-2-deoxy-D-glucose positron emission tomography-CT scan (18F-FDG PET-CT), and a complete blood count with a biochemical profile. The first radiologic evaluation was conducted using MRI in 34 patients (43.6%), CT in 29 patients (37.2%), and PET in 15 patients (19.2%).

Staging of the patients was performed according to the guidelines of the American Joint Committee on Cancer Staging System 2010. TNM staging and treatment complications were evaluated according to EORTC/RTOG criteria.

Table 1. Patients' characteristics

	Total	2DCRT	IMRT	P
The number of patients	78 (100%)	55 (70.5%)	23 (29.5%)	
Age (year)				
Median (range)	46 (12–81)	42 (12–78)	50 (14–81)	0.287
Gender (M/F)				
Male	57 (73.1%)	41 (74.5%)	16 (69.6%)	0.863
Female	21 (26.9%)	14 (25.5%)	7 (30.4%)	
Histology (WHO)				
I	5 (6.4%)	5 (9.1%)	–	
II	12 (15.4%)	9 (16.4%)	3 (13%)	0.281
III	57 (73.1%)	38 (69.1%)	19 (82.6%)	
Other	4 (5.1%)	3 (5.5%)	1 (4.3%)	
T stage				
T1	29 (37.2%)	18 (32.7%)	11 (47.8%)	
T2	22 (28.2%)	15 (27.3%)	7 (30.4%)	0.123
T3	11 (14.1%)	9 (16.4%)	2 (8.7%)	
T4	16 (20.5%)	13 (23.6%)	3 (13%)	
Node Status				
N0	18 (23.1%)	15 (27.3%)	3 (%13)	
N1	13 (16.7%)	11 (20)%	2 (8.7%)	0.204
N2	41 (52.6%)	23 (41.8%)	18 (78.3%)	
N3	6 (7.7%)	6 (10.9%)	–	
Stage				
I	5 (6.4%)	4 (7.3%)	1 (4.3%)	0.479
II	12 (15.4%)	10 (18.2%)	2 (8.7%)	
III	39 (50%)	22 (40%)	17 (73.9%)	
IVa	16 (20.5%)	13 (23.6%)	3 (13%)	
IVb	6 (7.7%)	6 (10.9%)	–	
Treatment				
RT	13 (16.7%)	12 (21.8%)	1 (4.3%)	
CRT	43 (55.1%)	21 (38.2%)	22 (95.7%)	
RT+BRT	6 (7.7%)	6 (10.9%)	–	
CRT+BRT	16 (20.5%)	16 (29.1%)	–	

Radiotherapy (RT): RT was performed on 55 patients using a two-dimensional planning system and delivered with a Co60 or linear accelerator (6–10 MV). In 23 patients, a three-dimensional planning system was used for treatment planning, and a linear accelerator (6 MV) was used for delivery of RT. All patients were stabilized with thermoplastic head and neck masks.

2DCRT: RT fields were determined in a conventional simulator device with the aid of patient CT and/or MRI images. Superior margins were determined to be the midline of the pituitary fossa in patients with no skull base involvement. In the presence of skull base involvement, the superior margin was defined as 1 cm above the pituitary fossa. The inferior margin was determined to be the inferior border of the sternoclavicular (SC) joint. Lateral borders were determined at the posterior of the vertebral processes, and the anterior borders were determined at the anterior border of the mandible. Shielding was determined according to lymph node involvement and tumor. An asymmetric field technique with two opposed parallel fields was used for the irradiation of the primary region and upper cervical region. One anterior field was used in lower cervical and supraclavicular (SCF) regions. Tumor dosage was calculated according to the midline in the treatment of lateral fields. Anterior field depth was calculated to be 3 cm. Daily fractional (fr) dose was 1.8 Gy and was applied 5 times per week. A linear accelerator with 6 MV energy was used for treatment. The lateral fields were modified to exclude medullaspinalis (MS) from the field when the total dose reached 45 Gy. In order to protect the temporomandibular joint, a dose of 10 MV energy was used, and a boost was delivered to the primary region when the total dose reached 56–60 Gy. Nasopharyngeal boost was provided with parallel opposed fields using 1.8 Gy/fr to attain a total dose of 70–72 Gy. Pathological cervical lymph nodes were irradiated with 1.8 Gy/fr to a total dose of 45 Gy, and then a 9 MeV electron boost was applied to the posterior neck region to reach a total dose of 56–60 Gy. For T1-T2 patients, BRT was performed 1 week after the completion of EBRT. Treatment was provided via high dose rate brachytherapy (HDR-BRT) using a nasopharyngeal probe at a depth of 0.5 cm. Dose delivery was achieved with 400 cGy for a total of 3 doses on alternate days.

IMRT: After patients are stabilized with thermoplastic masks, treatment planning was conducted using a CT simulator device with 2.5-mm slices. Gross Tumor Volume (GTV) was defined according to the extent of the tumor as evaluated by clinical examination, contrast-enhanced CT, MRI, and/or CT-PET. Clinical Target Volume (CTV72) was generated after a 5–10-mm expansion of the GTV. CTV59 included all lymph node levels at risk of subclinical disease (levels Ib, II, III, IV, upper part of V) and anatomic organ (petrous apex, ½ lower sphenoid body, ½ anterior clivus, 1/3 posterior maxillary sinus, nasal cavity, pterygoid fossa, parapharyngeal region). Planning Target Volume (PTV) was obtained with an isotropic expansion of 5 mm of the respective CTV. CTV56 was defined by uninvolved lymph node levels. Treatment plans were carried out based on the Radiation Therapy Oncology Group (RTOG) 0615 using a simultaneous integrated boost (SIB) with 2.12 Gy/fr in 33 days or 2 Gy/fr in 35 days. IMRT plans were delivered with a 6-MV LINAC. Organs at risk (OAR) were contoured as MS, parotid gland, optic nerves, optic chiasm, hypophysis,and brain stem. Dose restrictions were based on RTOG criteria.

Chemotherapy (CTX): Of the 78 patients in this study, 70 (89.7%) received CTX, while the remaining 8 (10.3%) did not (Table 2). Neoadjuvant CTX was given to 20 patients (25.6%), and 13 (16.7%) of these received cisplatin+5-florourasil (FU), 6 (7.7%) received Taxotere+cisplatin+5-FU, and 1 (1.3%) received cisplatin+epirubicine. In addition, 59 patients (75.6%) received concomitant CTX and RT. Of these, 41 patients (52.6%) received weekly cisplatin (40 mg/m2), and 18 patients (23.1%)received 100 mg/m^2 Cisplatin every 21 days (e.g., day 1, day 22, and day 43). Adjuvant CTX was given to 39 patients (50%). Of these, 34 (43.6%) received cisplatin+5-FU, and 5 (6.4%) received cisplatin+Taxotere.

Table 2. Chemotherapy times

	2DCRT	IMRT	Total
Neoadjuvant±concurrent	10 (18.2%)	2 (8.7%)	12 (15.4%)
Only concurrent	17 (30.9%)	2 (8.7%)	19 (24.3%)
Concurrent±adjuvant	21 (38.2%)	18 (78.3%)	39 (50%)
Absence of chemotherapy	7 (12.7%)	1 (4.3%)	8 (10.3%)
Total	55 (70.5%)	23 (29.5%)	78 (100%)

Follow-up: Patients underwent weekly examinations during treatment. The first follow-up evaluation occurred at 2 months post-treatment. Additional follow-ups occurred every 3–6 months during the first 2 years, every 6 months during years 3–5, and then annually with clinical examination, contrast-enhanced CT or MRI, chest radiograms, and thyroid function tests. Acute and late toxicity were scored according to the Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer (RTOC/EORTC) guidelines.

End Points: Response to treatment was defined according to RECIST criteria (complete, partial, or stabile). Survival without local recurrence was defined as the time from the date of diagnosis to local recurrence or local progression. Compliance to treatment was defined and calculated as the number of interruption days during RT.

Statistical Analysis: The end points were LC, acute toxicity, and late toxicity. Compatibility of the variables to normal distribution was investigated using visual (histogram and probability graphs) and analytical methods (Kolmogorov-Smirnov/Sharipo-Wilk tests). After examining the distribution of variables, the Student's t-test, which tests the significance of the difference between two means for parametric interval data, the Mann-Whitney U-test for non- parametric-interval data, the χ2-test (or Fisher's exact test for smaller samples) for ordinal/nominal data were used to compare the groups. Type 1 errors of less than 5% were accepted as statistically significant. All statistical analyses were performed using the SPSS version 13.

Results

Treatment Characteristics: RT doses were ≥72 Gy for 64 patients (82.1%) and ≤70 Gy for 14 patients (17.9%). In addition to EBRT treatment, 22 patients (28.2%) received BRT as well. During the follow-up (median 34.1 months, range, 3.2–202.84), 22 patients (28.2%) died. The other 56 patients (72.8 %) remained in follow-up until the completion of the study. In the 2DCRT arm, the median follow-up time was 59.04 months (range, 7.03–202.84), and in the IMRT arm, the median follow-up time was 14.8 months (range, 3.2–32.3). The difference in the duration of follow-up between the two groups was statistically significant (P<0.0001).

In the 2DCRT arm, 22 patients (40%) died. Among the 33 surviving patients, four (12.1%) continued follow-up evaluation without cure, and 29 (87.9%) continued follow-up evaluations with cure. While no deaths occurred in the IMRT arm, four of the patients (17.4%) continued follow-up evaluations without cure, and 19 patients (82.6%) continued follow-up with cure. No statistical differences between the two groups were detected when the treatment courses in the surviving patients of the 2DCRT and IMRT groups were compared (P=0.704).

In the first 3 months of evaluation after completion of RT and/or adjuvant CTX, 45 patients (57.7%) exhibited a complete response, 26 patients (33%) exhibited a partial response, and 7 patients (9%) exhibited stable disease. None of the patients experienced progression during treatment. In 3 patients (6.6%) who had a complete response, no recurrence in the nasopharyngeal region was noted during the median 6.4 months (range; 0.92–6.6) of follow-up. Upon evaluation of the treatment response in the 2DCRT arm, 5 patients (9.1%) experienced stable disease, 19 patients (34.5%) exhibited partial response, and 31 patients (56.4%) exhibited complete response.

In the IMRT arm, 2 patients (8.7%) experienced stable disease, 7 patients (26.9%) exhibited partial response, and 14 patients (31.1%) exhibited complete response (Table 3). In terms of treatment response, no statistically significant difference between 2DCRT and IMRT armswas detected (P=0.736). No statistically significant difference was observed for treatment response in terms of treatment interruption in patients treated with 2DCRT. When treatment responses were evaluated in terms of treatment interruption in patients in the IMRT arm, no statistically significant differences were observed (Table 5); however, subgroup analysis revealed that complete response rates were higher in the group without treatment interruption but that this difference is not statistically significant. This finding may be a result of the small sampling size of our study.In addition, local and distant progressions were observed in 23 patients (29.5%) in both groups.

During RT treatment, 27 patients (34.6%) interrupted their treatments due to acute toxicities, and the median treatment time before interruption was 3 days (range, 2–14). In the 2DCRT arm, the median time of treatment interruption was 3 days (range, 2–14), while in the IMRT arm, the median time of treatment interruption was 6.5 days (range, 3–10). Evaluation of the interruptions in terms of treatment time revealed that 23/55 patients (41.8%) in the 2DCRT group and 4/23 patients (17.4%) in the IMRT group interrupted their treatments. This difference is statistically significant (P=0.039). The median total time of RT treatment was 55.5 days (range, 22–82) in both groups. In the 2DCRT arm, the median treatment time was 58 days (range, 22–82), while in the IMRT group, the median treatment time was 48 days (range, 42–62). The difference in treatment times between the groups was statistically significant (P<0.0001). Local and distant progression were observed in a total of 23 (29.5%) patients from both groups, and RT was interrupted because of metastases in one patient during treatment.

Table 3. Treatment response in RT treatment arms

	2DCRT	IMRT	Total	P
Complete response	31 (56.4%)	14 (31.1%)	45 (57.7%)	0.908
Partial response	19 (34.5%)	7 (26.9%)	26 (33%)	0.930
Stable response	5 (9.1%)	2 (8.7%)	7 (9%)	1.0

Table 4. Treatment response in terms of treatment interruption in 2DCRT arm

	2DCRT			
	No interruption	Interruption	Total	P
Complete response	18 (56.3%)	13 (56.5%)	31 (56.4%)	1.0
Partial response	10 (31.3%)	9 (39.2%)	19 (34.5%)	0.750
Stable response	4 (12.4%)	1 (4.3%)	5 (9.1%)	0.387

Table 5. Treatment response in terms of treatment interruption in IMRT arm

	IMRT			
	No interruption	Interruption	Total	P
Complete response	13 (68.4%)	1 (25%)	14 (60.9%)	0.260
Partial response	4 (21.1%)	3 (75%)	7 (30.4%)	0.067
Stable response	2 (10.5%)	–	2 (8.7%)	1.0

Local control (LC): For all patients, the 2- and 5-year LC rates were 95.6% (standard error [S.E.)] ±0.025) and 93.6% (S.E., ±0.031), respectively. The 2-, 3-, and 5-year LC rates for 2DCRT and IMRT were 94.3% to 100%, 92% to 100%, and 92% to 100%, respectively (P=0.294; Figure 1). In univariate analysis, the prognostic factors that affect LC were identified as age (≤40 and >40), gender, histology (WHO I, II, III, others), T stage (T1-2 and T3-4), N stage (N0-1 and N2-3), stage (I-II and III-IV), RT (CRT and only RT), RT technique (2DCRT and IMRT), RT doses (<70 and ≥70), RT interruption (interruption or no interruption), and CTX method (neoadjuvant+concomitant, only concomitant,

and adjuvant+concomitant). No statistically significant prognostic factors that affect LC were identified.

The 1-, 2-, and 5-year LC rates in the RT group without treatment interruption were 97.8%, (S.E.±0.022), 95.3% (S.E.±0.033) and 95.3% (S.E.±0.033), respectively. In the group with treatment interruption, the 1-, 2-, and 5-year LC rates were 96.3% (S.E.±0.036), 96.3% (S.E.±0.036), and 91.5% (S.E.±0.058), respectively. Although a difference was noted for these LC rates between these two groups, the difference was not statistically significant (P=0.080; Figure 2). More specifically, the 1-, 2-, and 5-year LC rates in the 2DCRT group without treatment interruption were 96.7% (S.E.±0.033), 93.2% (S.E.±0.046), and 93.2% (S.E.±0.046), respectively. In the 2DCRT group with treatment interruption, the 1-, 2-, and 5-year LC rates were 95.7% (S.E.±0.043), 95.7% (S.E.±0.043), and 90.6% (S.E.±0.063), respectively. Although a difference was noted for the LC rates between these two groups, the difference was not statistically significant (P=0.117; Figure 3).

Toxicity: All toxicities that occurred during treatment were recorded as acute toxicities (most significant symptom within the first 3 months after completion of the treatment) and chronic toxicities (most significant symptom after 6 months of completion of the treatment). None of the patients experienced acute or chronic grade 4 toxicities. The most commonly occurring toxicity during RT treatment was mucositis, which occurred in 35 patients (63.6%) in the 2DCRT arm, and mucositis and skin toxicities in 11 patients (47.8%) in the IMRT arm. Xerostomia was the most common acute toxicity and occurred in 41 patients (77.4%) in the 2DCRT group and 18 patients (78.3%) in the IMRT group (Table 6). The difference in numbers of affected patients in each group was not statistically significant. In the 2DCRT arm, the most common chronic toxicity was xerostomia, which occurred in 28 patients (50.9%), and in the IMRT arm, the most common chronic toxicity was soft tissue fibrosis, which occurred in 13 patients (56.5%). No statistically significant difference between the chronic toxicities in the 2DCRT and IMRT arms was observed (Table 7).

Table 6. Acute toxicities in RT treatment arms

	Acute toxicities			
	2DCRT	**IMRT**	**Total**	**P**
Xerestomia	41 (74.6%)	18 (78.3%)	59 (75.6%)	1.0
Mucositis	4 (7.3%)	5 (21.7%)	9 (11.5%)	0.119
Hear loss	4 (7.3%)	-	4 (5.1%)	0.308
Tinnitus	2 (3.6%)	-	2 (2.6%)	1.0
Visiual loss	2 (3.6%)	-	2 (2.6%)	1.0

Table 7 Chronic toxicities in RT treatment arms

	Chronic toxicities			
	2DCRT	**IMRT**	**Total**	**P**
Xerestomia	28 (50.9%)	10 (43.5%)	38 (48.7%)	0.672
Soft tissue fibrosis	20 (36.4%)	13 (56.5%)	33 (42.3%)	0.184
Hear loss	5 (9.1%)	-	5 (6.4%)	0.314
Visual loss	1 (1.8%)	-	1 (1.3%)	1.0

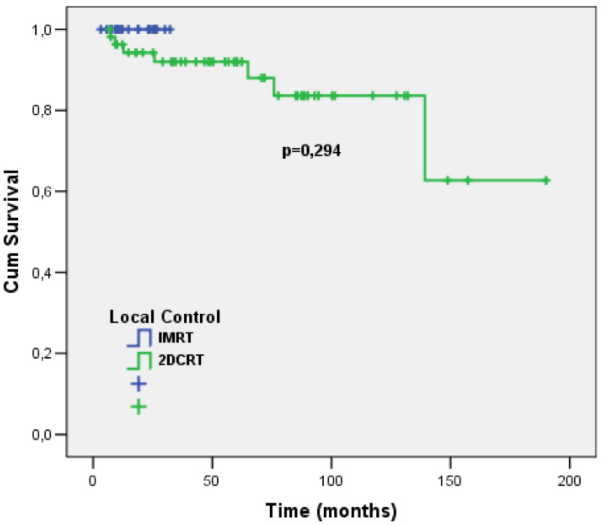

Figure 1. Local control rates in two treatment arms

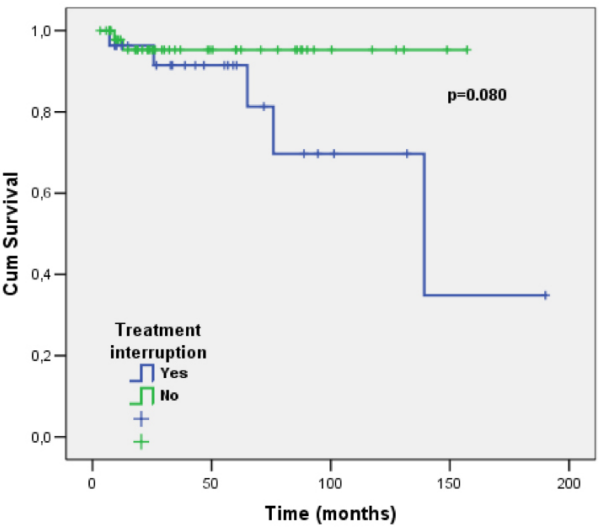

Figure 2. Local control rates in terms of treatment interruption

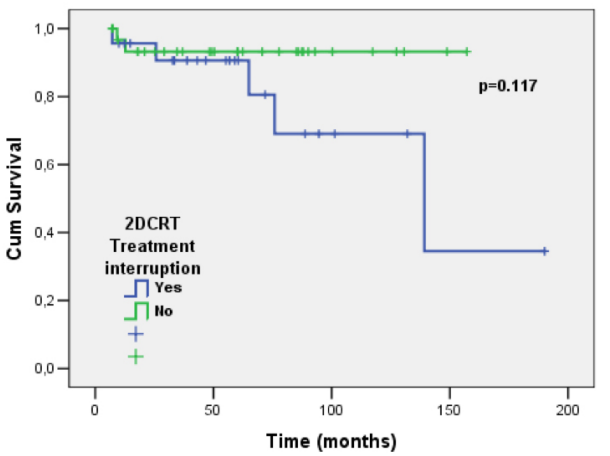

Figure 3. Local control rates in terms of treatment interruption in 2DCRT arm

Discussion

RT has been the mainstay of treatment for NPC for more than three decades. Until early 1990s, the use of 2DRT to deliver a "tumoricidal" dose (66–70 Gy, 2 Gy per fraction for 6.6–7 weeks) to the target via laterally opposed fields had been the standard treatment modality. This technique involved the manual projection of tumor volume and organs at risk (OARs) onto the orthogonal simulation films based on bony anatomy and the employment of nonconformal shielding blocks to protect the critical structures. The obvious drawbacks include normal tissues that lead to additional treatment complications and compromise of target coverage thus leading to local failures. (7, 8). LC rates of 71–93% for stage T1–2 and 40–68% for stage T3–4 disease have been reported for conventional RT techniques with or without concurrent chemotherapy (9-11) . In the current study, 2-, 3-, and 5-year LC rates in the 2DCRT patients were 94.3%, 92%, and 92%, respectively. LC may be improved with an increase in the radiation dose or with concurrent CTX (12, 13). However, the dose to the primary tumor is limited by the tolerance of the adjacent normal structures, especially when involvement of the base of the skull or intracranial spread is present. The incidence of severe and life-threatening toxicity of combined conventional RT and CTX was 55% for grade 3 and 21% for grade 4 in an intergroup trial for NPC[13] . Morretto et al. (14) demonstrated that rates of 8% for acute skin toxicity ≥G3, 23% for mucositis ≥G3, and 19% for dysphagia ≥G3 in the 2DCRT and 3DCRT arms. In our study, grade 4 toxicities were noted in patients treated with 2DCRT. The rate of acute xerostomia ≥G3 was 74.6%, and the rate of mucositis ≥G3 was 7.3% in the 2DCRT arm.

The transition from 2D-RT to 3DRT, in particular IMRT, represents a major step forward in the treatment of NPC. Unlike 2DCRT, IMRT CT planning exploits the spatial relationship between targets and OARs and allows for more comprehensive irradiation of the tumor and greater protection of critical structures. Although a number of dosimetric studies demonstrate an advantage of IMRT over 2DCRT in the treatment of NPC (15-18), further clinical data are still needed. Sultanem et al. (19) has achieved excellent LC with IMRT use in treatment of NPC in a study of 35 patients. IMRT delivers high doses to the tumor while protecting critical organs, such as salivary glands. Furthermore, previous studies demonstrated that IMRT leads to increased tumor doses and increased normal tissue protection compared to 3-D conformal planning (20, 21). A study of 86 patients (26% treated with IMRT) revealed a LC, and locoregional control LRC, and an OS or 96%, 93%, and 90%, respectively (22). Patients were stage III–IV in 75% of these cases, and 70% of patients were treated with induction plus concurrent CTX, while 20% were treated with concurrent CTX only. In the current study, the 2-, 3-, and 5-year LC rates for the patients treated with 2DCRT were 100%, 100%, and 100%, respectively.,

In a study by Morretto et al. (14), acute skin toxicity ≥G3 occurred in 15%, mucositis ≥G3 occurred in 31%, and dysphagia ≥G3 occurred in 31% of the patients treated with IMRT. In the study, life-threatening grade 4 toxicities were not observed in the patients treated with IMRT. In our study, rates of acute xerostomia ≥G3 were 78.3%, while mucositis ≥G3 occurred in 21.7% of patients in the IMRT arm.

The total radiation dose, as well as the fractionation and overall treatment time OTT, are decisive for local and regional tumor control for non-NPC head and neck patients (23, 24). With conventional fractionation, a break of about 1 week is associated with an absolute reduction of 10–12% in LC rates. A break of even 1 day could reduce the LC rate by about 1.4% regardless of the fractionation schedule or primary tumor site; however, this type of information is limited in NPC patients. Researchers from Hong Kong Queen Mary Hospital first reported an adverse effect of a treatment break for NPC on locoregional control and disease-free survival. Patients with prolonged OTT fared worse in terms of locoregional control, distant metastases-free survival, and disease-free survival. The negative effect of a treatment break was not offset by the use of an additional boost. (25) Xu et al. (26) suggested that treatment break is an independent prognostic factor associated with long-term survival in patients with NPC. In this study, 177 of 1706 cases (10.4%) had a treatment interruption of more than oneweek. Interruption of RT for more than 7 days is associated with an 18% reduction in 5-year survival rates (16).

In our study, a conventional fractionation schedule was used for almost all patients treated with 2DCRT, resulting in a median OTT of 58 days. On the other hand, a slightly hypofractionated accelerated schedule was chosen in most IMRT cases (median OTT 48 days). Treatment times in both groups were statistically significant. However, In our study, there was no statistically significant difference between 2DCRT and IMRT regimen, in terms of LC, acute and late toxicity. In our study, 27 patients (34.6%) interrupted their RT treatments due to acute toxicities, and median treatment time was 3 days (range, 2–14). In the 2D-RT arm specifically, the median treatment interruption time was 3 days (range, 2–14), while in the IMRT arm, the median treatment interruption time was 6.5 days (range, 3–10). When interruptions were evaluated in terms of treatment time in the 2DCRT arm, 23/55 patients (41.8%) interrupted their treatment, and in the IMRT arm, 4/23 patients (17.4%) interrupted their treatments. Although the patients in the IMRT arm appeared to be more compatible with the treatment than those in the 2DCRT arm, this difference was not statistically significant.

Xerostomia is the most common late-stage side effect of RT for head and neck cancer (27) and is the most common problem following RT for NPC. In astudy of 934 NPC patients treated with 2D RT alone, Chen et al (28) reported that the 5-year incidence rates for radiation- induced brain injuries, trismus, hearing loss, and xerostomia were 1.5%, 13.6%, 31.1%, and 38.7%, respectively. In contrast Wang et al. (29) reported that

incidence rates for radiation- induced brain injuries and trismus were only 0.8% and 1.1%, respectively.

In this study, the incidence rate of late xerostomia was 50.9% and was 2.7% for grade 3 late xerostomia in the 2DCRT arm. The rate of soft tissue fibrosis was 36.4% in 2DCRT arm. The use of IMRT has enabled sparing of the parotid glands, resulting in significant reduction of the incidence of xerostomia. Nancy et al. (30) revealed that the rates of G1 and G2 xerostomia in NPC patients 3 months after IMRT treatment were 35% and 65%, respectively, and at 12 months after the treatment, these rates changed to 50% and 0%, respectively. In our study, the rate of late xerostomia was 43.5% in the IMRT arm. Tissue fibrosis occurs in the neck region due to high doses of radiation. Sham and Chow (31) declared that tissue fibrosis occurred in 9% of the patients in their series. In our study, fibrosis occurred in 36.4% of the patients in the 2DCRT arm and in 56.5% of the patients in the IMRT arm. Overall, no statistically significant differences were detected between the 2DCRT and IMRT treatment arms in terms of chronic toxicities.

Many factors are associated with the results of NPC treatment. The following factors are generally thought to affect the results of RT treatment of NPC: gender, age, anemia, T stage, N stage, M stage, histopathology, RT dose, RT field, and inclusion of CTX (32-34). Regarding chemoradiation, optimal doses and sequencing (i.e., neoadjuvant, concurrent, and adjuvant approaches) remain controversial. In our study, the median age (46 years) and the male/female ratio (2.7/1) were the same as in most clinical trials (5). The proportion between early and locally advanced disease (78% of stage III–IVB) is similar to other previously published studies (22). In our study, no significant prognostic factors that have an effect on LC were identified.

Conclusions

In our study, no significant differences in terms of acute and late toxicities were detected between 2DCRT and IMRT which is consistent with other studies. Treatment compliance was higher in IMRT arm. Overall, though, treatment interruptions did not lead to a difference in treatment responses; however, subgroup analysis revealed that the complete response rates were higher in those without treatment interruption.

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