Factors Associated with Late Toxicity in Nasopharyngeal Carcinoma Patients Treated with Radio-Chemotherapy

Radyo-Kemoterapiyle Tedavi Edilen Nazofarinks Karsinomlu Hastalarda Geç Toksisiteyi Belirleyen Etkenler

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ABSTRACT Objective: To quantify late toxicity in patients treated with intensive chemotherapy (ChT) and radiotherapy (RT) for nasopharyngeal carcinoma (NPC) and to investigate factors associated with it. **Material and Methods:** We retrospectively reviewed the treatment outcome in terms of moderate-severe late toxicity (MSLT) in 44 NPC patients diagnosed between 2001 and 2007. All the patients were treated with conformal RT and cisplatin containing ChT. Twenty-eight (63.6%) patients among 44 received only multidrug neoadjuvant ChT, while the remaining 16 (36.4%) patients received additional concomitant cisplatin during RT. MSLT was evaluated according to RTOG/EORTC scoring system and defined as grade 3-5 late toxicity. The median follow-up of these 44 patients was 38 months (range, 12-84 months). Statistical analyses were performed with Kaplan-Meier method and a multiple Cox's regression model. **Results:** The hazard probability of developing MSLT at 5 years was 49%. In univariate analyses; gender, age, histopathology, T stage, N stage and ChT schema did not have significant impact on treatment outcome in terms of MSLT. Total radiation dose to the neck, which appeared to have a paradoxical effect on late toxicity in univariate analysis turned to be insignificant in multivariate analysis. Treatment response was found to be the only prognostic factor in multiple Cox's regression analysis, which had an impact on MSLT in NPC patients. Probability of MSLT among the 12 NPC patients with less than complete response to the treatment was higher than 32 patients with complete response to the treatment (85.7% and 35.2% at 5 years, respectively; p= 0.0254). **Conclusion:** Late toxicity in NPC patients is treatment related. Poor tumour control can be a triggering factor for development of late toxicity. Long lasting residual disease following treatment is an interesting phenomenon in NPC patients, which appears to be related with MSLT and has to be further investigated in prospective studies.

Key Words: Adverse effects; chemotherapy, adjuvant; nasopharyngeal neoplasms; radiotherapy

ÖZET Amaç: Nazofarinks karsinomu (NFK) nedeniyle yoğun kemoterapi (KT) ve radyoterapi (RT) ile tedavi edilen hastalarda geç toksisitenin derecesini ve geç toksisite ile ilişkili etkenleri belirlemektir. **Gereç ve Yöntemler:** Nazofarinks karsinomu tanısıyla 2001-2007 yılları arasında tedavi edilen 44 hastada, orta-ağır geç toksisite (OAGT) retrospektif araştırılmaktadır. Tüm hastalar konformal RT ve sisplatinli KT ile tedavi edilmiştir. Kırk dört hastanın 28'ine (%63.6) yalnız çok ilaçlı neoadjuvan KT uygulanırken, kalan 16 (%36.4) hastaya neoadjuvan KT'den sonra RT ile eş zamanlı sisplatin de verildi. OAGT'nin tanımı RTOG/EORTC skorlama sistemine göre grade 3-5 geç toksisitedir. Kırk dört hastanın ortanca izlem süresi 38 aydır (dağılım, 12-84 ay). İstatistiksel analizler Kaplan-Meier yöntemi ve çok değişkenli Cox regresyon modeliyle yapılmıştır. **Bulgular:** Beş yılda OAGT gelişme olasılığı %49'dur. Tek değişkenli analizlerde; cinsiyet, yaş, histopatoloji, T evresi, N evresi ve ChT şemasının OAGT için tedavi sonuçlarına anlamlı etkisi saptanmamıştır. Boyun lenf nodu bölgelerine toplam radyasyon dozunun geç toksisiteye tek değişkenli analizde paradoksal olan etkisi çok değişkenli analizde kaybolmaktadır. Çok değişkenli analizde, NFK'lu hastalarımızda OAGT'yi belirleyen tek prognostik faktörün tedaviye alınan yanıt olduğu bulunmuştur. On iki tedaviye tam yanıt vermeyen NFK'lu hastada 5 yılda OAGT saptanma olasılığı, tedaviye tam yanıt veren 32 hastadan yüksektir (sırasıyla, %85.7 ve %35.2; p= 0.0254). **Sonuçlar:** NFK'lu hastalarda geç toksisite tedaviyle ilişkilidir. Yetersiz tümör kontrolü geç toksisitenin oluşmasını uyarabilmektedir. NFK'lu hastalarda tedaviden sonra uzun süreli rezidüel hastalık varlığının geç toksisiteyle ilişkisi prospektif çalışmalarla araştırılması gereken bir olgudur.

Anahtar Kelimeler: Yan etkiler; kemoterapi, adjuvant; nazofarinks neoplazileri; radyoterapi

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Intensive treatment to nasopharyngeal carcinoma (NPC) patients results in high cure rates. Neoadjuvant and concomitant chemotherapy (ChT) with radiotherapy (RT) to large volumes proved to be effective in this highly invasive tumour. Recently, 4-6% survival advantage with adjunctive ChT to RT compared with RT alone was reported in the metaanalysis of randomised trials.[1] Although longer survival can be achieved in NPC patients with RT and ChT, the probability of treatment-related moderate-severe late toxicity (MSLT) may increase and cause important decline in quality of life.[2-5] Toxic deaths may occur and morbidity may be so much that the patients may regret to be cured of their disease.[6]

The most frequently diagnosed late side effects in patients treated for NPC are soft tissue fibrosis, lymph edema, xerostomy, growth retardation, teeth carries, micrognathy, hearing loss, temporomandibular joint dysfunction, swallowing disorder, chronic sinus disease, laryngeal edema, cognitive dysfunction and radiation induced cancer.[3,7-10] Cancer patients may have late side effects related with characteristics of their disease, the way they are treated or their intrinsic sensitivity to the treatment. Intrinsic sensitivity plays the biggest role on patient-to-patient variability in late toxicity of cancer treatments.[11,12]

The late side effects are irreversible and progressive. Therefore, they determine the treatment choice and the dose. The tolerance doses of critical organs and tissues should not be exceeded. Appearance of late effects of RT shows a typical latent period after treatment.[13] They do not recover and gradually become worse. Patients must be closely monitored during follow-up for late side effects.

Quantification, analyzing and reporting of late side effects is another problem, which is very important for comparison of data from different institutes. The Radiation Therapy Oncology Group / European Organisation for the Research and Treatment of Cancer (RTOG/EORTC) grading system has been advocated for quantification and categorization of late side effects.[14] Statistical analyses are subject to further discussion. However, survival analyses such as Kaplan-Meier are generally preferred as they give a more realistic impression of the risk of the treatment.[15]

This study investigates late toxicity in NPC patients to determine associated factors with MSLT. The role of treatment related factors, particularly the total radiation dose and response to treatment was evaluated.

MATERIAL AND METHODS

Forty-four NPC patients diagnosed between 2001 and 2007 were retrospectively reviewed for the clinical findings, treatment choice and outcomes. Our main concern was to decide the incidence and timing of MSLT and find reasons for it. All of the patients exhibited various forms of squamous cell carcinoma. Tumours were staged according to the American Joint Committee on Cancer (AJCC) 6th edition criteria.[16]

Prescribed therapy included RT (66 Gy to 70 Gy to the primary tumour and the clinically positive cervical nodes; and 46 to 50 Gy to all of the cervical lymphatics with 2 Gy daily fractions during weekdays) and three courses of platinum-based ChT in a neoadjuvant schema for 28 of 44 (63.4%) patients. Sixteen of 44 (36.4%) patients also received concomitant cisplatin ChT with RT following neoadjuvant cisplatin containing multidrug ChT. Conformal RT was performed with computed tomography (CT) simulation, and treatment was delivered with 6-18 MV photons and 9-12 MeV electrons from multileaf collimator shaped treatment portals. Follow-up was performed bimonthly and quarterly during the first and second years, respectively; biannually during years 3 to 5; and annually during succeeding years. Magnetic resonance imaging (MRI) or CT scans were obtained in the second and fourth months of the first year and annually in the following years. Treatment outcomes were progression-free survival (PFS), overall survival (OS) and MSLT. Moderate-severe late toxicity is defined as grade 3 or 4 late toxicity (no toxic death has been recorded, which is grade 5).

Late toxicity of treatment was evaluated for skin, subcutaneous tissue, oral and pharyngeal mucosa, salivary glands, mandible, teeth, pituitary-thyroid axis, bones, paranasal sinuses, cranial

nerves, larynx, oesophagus, ears, eyes, and pulmonary, cardiac, gastrointestinal, urinary and central nervous systems according to the RTOG/EORTC scoring system.[14] The median follow-up of these 44 patients was 38 months (range, 12-84 months).

Patient characteristics were described with frequency tables. Overall survival and PFS analyses were performed with the Kaplan-Meier method and cumulative crude incidence of MSLT in time was plotted on a Cartesian graphic. The hazard probability of MSLT was decided with Kaplan-Meier method (one minus survival). Time was calculated from the diagnosis of NPC to the development of MSLT. Univariate analyses were performed with factors: Gender (female vs. male), age (<43 vs. = >43), histopathology (WHO1-2 vs. WHO 3), T (X-2 vs. 3-4) and N (0-1 vs. 2-3) stages, ChT schema (neoadjuvant vs. neoadjuvant + concomitant), total radiation dose to the cervical nodal regions (≥66 Gy vs. ≤60 Gy) and treatment response (complete response (CR) vs. less than complete response (LTCR). Complete response is defined as no evidence of disease with MRI evaluation within four months following treatment. Less than complete response is defined as long term residual disease or disease progression with MRI longer than four months following treatment. Total radiation dose to the nasopharynx was not included in the analyses as all the patients received homogenous doses (≥66 Gy) to the primary tumour site. Univariate analyses were performed with the Kaplan-Meier method and the difference of probability curves was tested with the Log-Rank test. Multiple Cox's regression analysis with forward-LR method was applied to decide the pre-treatment and treatment related factors causing MSLT in patients with NPC. The proportionality assumption was confirmed in SPSS by the similar shape of the plotted baseline hazard functions for each category of each covariate analysed.

RESULTS

Seventeen (39%) of 44 NPC patients were found to have MSLT during their follow-up. However, with the Kaplan-Meier survival analysis the hazard probability (one minus cumulative survival) of MSLT was calculated 49% at five years (Figure 1). Patient characteristics are presented in Table 1. In univariate analyses; gender, age, histopathology, T stage, N stage and ChT schema did not influence MSLT. Thirty four patients who received total radiation dose ≥66 Gy to the cervical nodal regions paradoxically had lower risk of developing MSLT compared to the 10 patients who received ≤60 Gy to the cervical nodal regions (p= 0.01). The 5-year hazard probability of MSLT among the 32 NPC patients with CR to the treatment was significantly less than the 12 patients with LTCR to the treatment (35.2% and 85.7%, respectively; p= 0.0005) (Table 2, Figure 2).

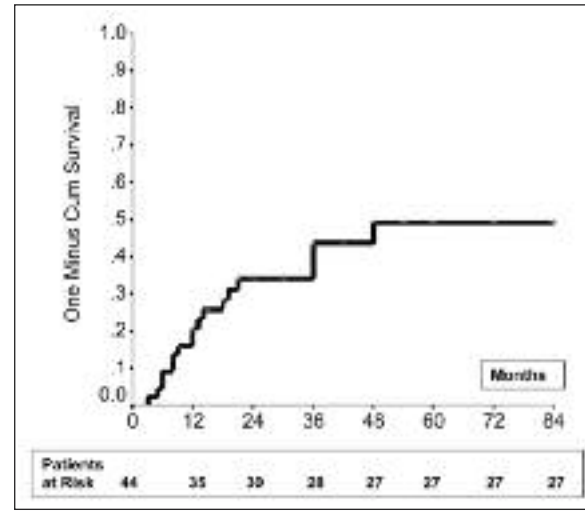

FIGURE 1: The probability of moderate-severe late toxicity (grade 3-4) in 44 nasopharyngeal carcinoma patients was calculated 49% at 5 years with the Kaplan-Meier method.

The only grade 4 late toxicity observed was formation of a fistula after infection in necrotic subdermal tissues of the cheek. The remaining 16 patients experienced grade 3 late toxicity (Table 3). MSLT was diagnosed starting from 4 months to 48 months (median 12 months) post treatment.

Overall survival and PFS of 44 patients with NPC was found 84% and 66% at 5 years, respectively (Figure 3, 4).

The results of multiple Cox's regression analysis revealed that the only significant factor associated with MSLT was the treatment response (p = 0.0254) (Table 4, Figure 5). The total radiation dose to the involved neck nodes was not a significant

TABLE 1: Characteristics of 44 nasopharyngeal carcinoma patients.

Characteristics	Patients	
	n	(%)
Age, years		
Median 43 (range; 11-79)		
Gender		
Female	15	(34%)
Male	29	(66%)
Histopathology (WHO*)		
WHO 1	2	(5%)
WHO 2	14	(32%)
WHO 3	28	(63%)
T Stage#		
T0	2	(5%)
T2a	6	(13%)
T2b	21	(48%)
T3	13	(29%)
T4	2	(5%)
N Stage		
N0	7	(16%)
N1	8	(18%)
N2	19	(43%)
N3a	6	(13%)
N3b	4	(10%)
Stage		
IIA	3	(7%)
IIB	5	(11%)
III	25	(57%)
IVA	4	(10%)
IVB	7	(15%)
Type of chemotherapy		
Neoadjuvant only	28	(64%)
Neoadjuvant and concomitant with radiotherapy	16	(36%)
Total radiation dose to the nasopharynx		
66 Gy-72 Gy	40	(91%)
126 Gy-130 Gy (after reirradiation for locoregional recurrences)	4	(9%)
Total radiation dose to the neck		
46 Gy-50 Gy	6	(13%)
56 Gy-60 Gy	4	(10%)
66 Gy-72 Gy	31	(70%)
96 Gy-110 Gy (after reirradiation for locoregional recurrences)	3	(7%)
Current status		
Alive with no evidence of disease	33	(75%)
Alive with disease	5	(11%)
Dead with disease progression	6	(14%)

* WHO, World Health Organisation. #Patients are staged according to the American Joint Committee on Cancer (AJCC) 6th edition criteria.[16]

factor associated with MSLT in multivariate analysis. This was a paradoxical association between total dose to the involved neck node regions and the MSLT, as lower dose to the neck resulted in less toxicity compared with higher dose to the neck. MSLT developed in 7 of 10 patients who were given ≤60 Gy to the neck. However, more than half (4/7) of these patients had involved neck nodes and they could not get the prescribed dose to the neck due to severe acute toxicity.

DISCUSSION

No toxic death (RTOG grade 5) was observed among 44 patients with NPC. One patient with soft tissue necrosis and fistula (RTOG grade 4) during follow-up consisted the 5-year actuarial incidence of RTOG grade 4-5 late complication (2%) in this patient group. Although the treatment for NPC became more intensive with neoadjuvant and concomitant ChT, this low actuarial incidence of severe late toxicity might be taken as a reflection of improved treatment technology in sparing normal tissues. Our results have shown a further improvement in treatment of NPC in terms of side effects compared with the reports from 1954-1971 (10 year actuarial incidence of 14% with a 3% mortality) and 1983-1992 (10 year actuarial incidence of 5%).[3,17] In NPC patients treated only with RT, 10-year cumulative incidence of MSLT was reported 16% by Sanguinetti, et al.[17] They also reported total radiation dose >60 Gy to the nasopharynx did not have an impact on the development of MSLT. Five-year cumulative incidence of MSLT among our 44 patients with NPC was much higher (17/44; 39%), and 5-year hazard probability of MSLT was estimated 49%. How to analyse late toxicity of cancer treatment is subject to further discussion. However, survival analyses such as Kaplan-Meier are generally preferred as they give a more realistic impression of the risk of the treatment.[15] The crude incidence leads to overestimate the safety of treatment due to the latent period for late side effects. Some of the patients with cancer will die before the late side effects can be diagnosed. On the contrary, survival analysis may overestimate treatment toxi-

TABLE 2: Characteristics of nasopharyngeal carcinoma patients with grade 0-2 and grade 3-4 (moderate-severe) late toxicity and univariate analyses with the Kaplan-Meier method and the log-rank test.

Characteristic	Grade 0-2 Late Toxicity (n= 27) n (%)	Grade 3-4 (Moderate-Severe) Late Toxicity (n= 17) n (%)	5-year Actuarial Probability of MSLT[#]	Log-Rank p
Age, years				
Median	42	44		
Range	12-79	11-68		
= <43	14 (52%)	8 (47%)	50.7%	
> 43	13 (48%)	9(53%)	56.2%	0.82
Gender				
Female	11 (41%)	4 (24%)	43%	
Male	16 (59%)	13 (76%)	51%	0.18
Histopathology (WHO*)				
1-2	10 (37%)	6 (35%)	36.2%	
3	17 (63%)	11 (11%)	44.5%	0.54
T stage				
1-2	17 (63%)	12 (71%)	52%	
3-4	10 (37%)	5 (29%)	36.4%	0.91
N stage				
0-1	9 (33%)	6 (35%)	42.7%	
2-3	18 (67%)	11 (65%)	49.2%	0.69
Chemotherapy				
Neoadjuvant	15 (56%)	13 (77%)	52.9%	
Neoadjuvant + Concomitant	12 (44%)	4 (23%)	25.5%	0.51
Total radiation dose to the neck				
≤60 Gy	3 (11%)	7 (41%)	81.3%	
≥66 Gy	24 (89%)	10 (59%)	38.4%	0.01
Treatment response				
CR[a]	24 (89%)	8 (47%)	35.2%	
LTCR[b]	3 (11%)	9 (53%)	85.7%	0.0005

[#] MSLT, Moderate-Severe Late Toxicity. * WHO, World Health Organisation. [a]CR, Complete Response. [b]LTCR, Less Than Complete Response.

city, as all patients may not express late side effects eventually. For this reason survival analysis may not estimate late toxicity as they successfully do estimate overall survival.[18,19] The tumour of some patients can be controlled with acceptable late toxicity. On the other hand, some patients with uncontrolled tumours with very little or no late toxicity may make us suspicious about the aimed dose given to the patient. The response of the patients to the same treatment may also vary because of intrinsic radiosensitivity of individual patient. All these are the short comings of hazard estimates of late side effects though it provides a more relevant estimate of treatment toxicity.[13,20]

Univariate analysis revealed that one of the significant contributing factors was the total radiation dose to the involved neck nodes (Table 2). However, this contribution to the development of MSLT in patients with NPC was in a paradoxical way. Contrary to our expectation total neck radiation dose ≤60 Gy was related with higher probability of MSLT compared with total neck radiation dose ≥66 Gy (81% and 38%, respectively; p= 0.01). In an analysis of 230 patients with head-and-neck cancer from RTOG trials 5-year hazard probability of MSLT was found 43%.[21] They found older age, advanced T stage, laryngeal or hypopharyngeal localization and post treatment neck dissection as

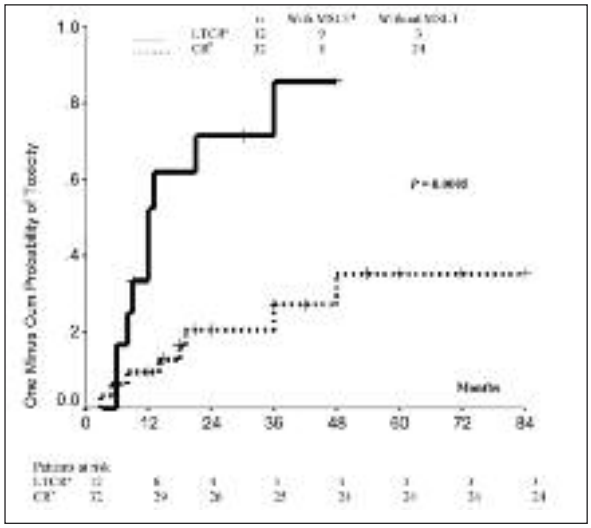

FIGURE 2: Hazard probability of MSLT* among the 12 patients with nasopharyngeal carcinoma who had less than complete response to treatment (for longer than 4 months following treatment) compared with 32 patients who had complete response was 85.7% and 35.2% at 5 years, respectively with Kaplan-Meier method (Log-Rank p= 0.0005).

*MSLT: Moderate-Severe Late Toxicity. [a]LTCR: Less Than Complete Response (>4 months). [b]CR: Complete Response.

TABLE 3: Types of late toxicity observed in patients treated for nasopharyngeal carcinoma (n = 44).

Late Toxicity	n	%
No severe late toxicity	27 (Grade 1-2)	62
Severe Late Toxicity	17 (Grade 3-4)	38
Soft tissue necrosis and fistula	1 (Grade 4)	2
Trismus	3 (Grade 3)	7
Growth retardation and trismus	1 (Grade 3)	2
Mucosal dryness (xerostomy)	2 (Grade 3)	5
Soft tissue fibrosis	2 (Grade 3)	5
Chronic sinus disease	2 (Grade 3)	5
Weakness of left limbs	1 (Grade 3)	2
12th Cranial nerve injury	1 (Grade 3)	2
Cervical lymph oedema	1 (Gade 3)	2
Cervical atrophy	1 (Grade 3)	2
Teeth carries	1* (Grade 3)	2
Serous otitis	1 (Grade 3)	2

* One patient was diagnosed with teeth carries in more than 50% of his teeth, which was scored as grade 3.

contributing factors to the development of MSLT. No ChT or RT factors were found significantly contributing to the late toxicity in multivariate analysis. However, in univariate analysis a paradoxical negative association between total radiation dose and MSLT was found similar to our study. They thought selection bias could lead to this association as patients with larger volume neck disease would undergo neck dissection and receive lower doses of radiation to the neck, although they would have more tumour and surgery related damage to the normal tissues.[21] However, in our 44 patients with NPC, surgery was consisted of an incisional biopsy. Reevaluation of our treatment records did not reveal systematic planning or dosimetry errors that would result in higher doses than prescribed. An interesting finding was that four out of seven patients developing MSLT after total radiation dose ≤60 Gy to the neck nodes were patients who were planned to be given total radiation dose ≥66 Gy to the neck nodes as they had involved neck nodes. These four patients could not be given the prescribed high total dose to the neck because of severe dermal and mucosal acute toxicity. Among the 44 patients with NPC there was no correlation between acute grade 3-4 toxicity and MSLT (data not shown). Many studies have shown that late radiation effects are often not consequential to acute radiation effects.[22-24] A severe late toxicity does not have to follow severe acute toxicity or does not have to start just after the treatment.

From the multiple Cox's regression analysis we know that neoadjuvant and concomitant ChT together was not different than only neoadjuvant

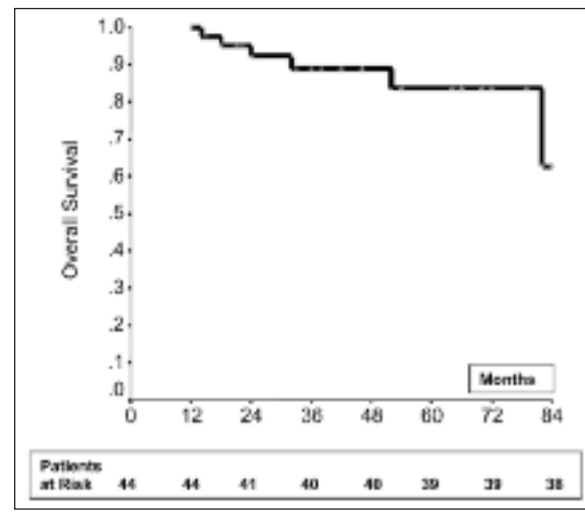

FIGURE 3: Overall Survival of 44 nasopharyngeal carcinoma patients (5 years overall survival is 83.62%; mean 75 months, SE 4, 95%CI 68-82).

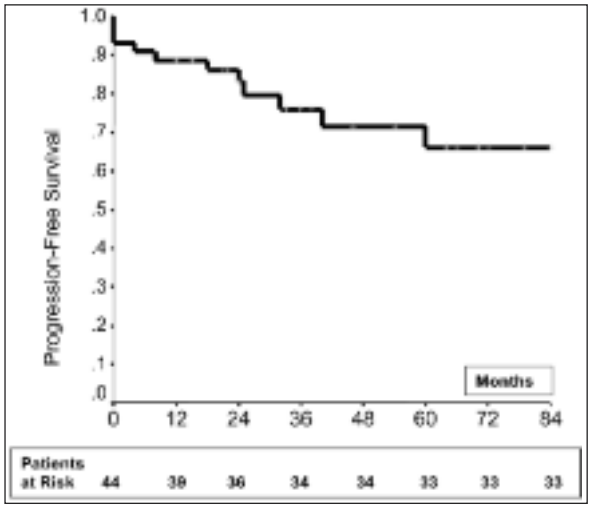

FIGURE 4: Progression-Free Survival of 44 nasopharyngeal carcinoma patients (66.02% at 5-years; mean 64 months, SE 5, 95%CI 54-74).

ChT in terms of probability of MSLT. However, a very interesting finding in these 4 patients with MSLT and lower dose than intended to the neck was the long lasting residual tumour, which eventually disappeared leaving a MSLT. If we remember the new interpretation to the pathophysiology of late radiation effects, a defective healing response was accepted as the reason for late radiation toxicity and it was the only explanation for their appearance after a lag time.[25] When the recovery response is induced, for example if recurrence occurs, then the late effect will also develop. If we interpret for the soft tissues; infection, trauma or directly tumor progression causes rapid progression of fibrosis of subdermal tissues to necrosis and

TABLE 4: Multiple cox's regression analysis with Forward-LR method to identify covariates that are associated with moderate-severe late toxicity in 44 nasopharyngeal carcinoma patients.

Covariate		B[1]	P	RR[2]	95% CI[3]
Gender		-.6007	.3370	.5485	.1609-1.8690
	(r.4) Female (n= 15)				
	Male (n= 29)				
Age		.1484	.7944	1.1599	.3800-3.5408
	(r.) ≤43 (n= 22)				
	>43 (n= 22)				
Histopathology		-.4146	.4923	.6606	.2023-2.1572
	(r.) WHO[5] 1-2 (n= 16)				
	WHO 3 (n= 28)				
T Stage		.6836	.3704	1.9810	.4439-8.8402
	(r.) T_{0-2} (n= 29)				
	T_{3-4} (n= 15)				
N Stage		.0234	.9711	1.0237	.2884-3.6337
	(r.) N0-1 (n= 15)				
	N2-3 (n= 29)				
Chemotherapy schema		-.1168	.8713	.8897	.2165-3.6566
	(r.) Neoadjuvant (n= 28)				
	Neoadjuvant +Concomitant (n= 16)				
Total dose to the involved neck nodes		.6062	.3655	1.8335	.4932-6.8158
	(r.) ≤60 Gy (n= 10)				
	≥66 Gy (n= 34)				
Treatment response		-1.5432	.0254	.2137	.0552-.8267
	(r.) CR[a] (n= 32)				
	LTCR[b] (n= 12)				

[1] B: Regression Coefficient. [2] RR: Risk Ratio. [3] CI: Confidence Interval. [4] r: reference. [5] WHO: World Health Organisation. [a] CR: Complete Response. [b] LTCR: Less Than Complete Response (>4 months).

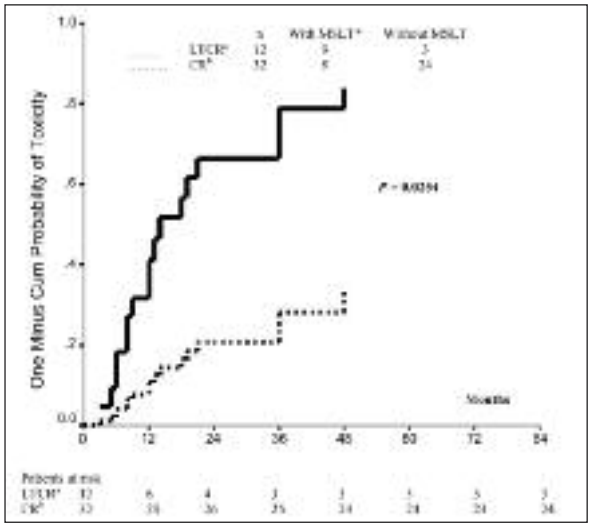

FIGURE 5: Hazard probability of MSLT* among the 12 patients with nasopharyngeal carcinoma who had less than complete response to treatment (for longer than 4 months following treatment) compared with 32 patients who had complete response was 85.7% and 35.2% at 5 years, respectively with multiple Cox's regression analysis (B^1= -1.5432; P= 0.0254; RR^2= 0.2137; 95% CI^3= 0.0552 - 0.8267).

*MSLT: Moderate-Severe Late Toxicity. [a]LTCR: Less Than Complete Response (> 4 months). [b]CR: Complete Response. [1]B: Regression Coefficient. [2]RR: Risk Ratio. [3]CI: Confidence Interval.

ulceration or fistula can develop. This new interpretation of late side effects makes it clear that the treated tissues must be closely monitored during follow-up to prevent late side effects from becoming worse. Treatment related late toxic events would continue to appear life long often after a lag time.

A similar interpretation of appearance of late radiation toxicity and defective healing response of irradiated tissues was reported for patients with head and neck cancer.[21,26] An association was found between neck dissection for residual neck nodes after RT and MSLT.[21] Another explanation can be high intrinsic radiosensitivity of these four patients. Most inter-patient radiation response variability is due to differences in intrinsic radiosensitivity.[11,12] Several studies report a significant association between intrinsic radiosensitivity of cells and the severity of late effects of RT.[27-29] All of these studies have shown that total radiation dose has to be tailored due to intrinsic radiosensitivity to achieve the highest tumour control with the least late toxicity.

Although the univariate analyses revealed radiation dose to the neck as a siginificant factor to decide late treatment toxicity in NPC patients, the recorded MSLT's such as trismus, chronic sinus disease and teeht carries (one patient was diagnosed with carries in all his teeth, which is scored as grade 3) could have been related with total radiation dose to the nasopharynx rather than radiation dose to the neck. However, total radiation dose to the nasopharynx was more homogenous among the patients not allowing comparisons (Table 1). The level of total radiation dose to the neck was chosen as a covariate in the analysis as it reflects the level of intensity of the treatment to control the disease in NPC patients.

The high probability of lymph node metastases (75%) in patients with NPC,[3] and the high incidence of nodal recurrence (5-year actuarial 30%)[9] makes it unavoidable to treat the neck in these patients from large volumes with high total radiation doses. In our 44 patients the nodal involvement was 84% (37/44) and 5-year actuarial nodal recurrence rate was 9% (4/44). Logically the probability of MSLT will increase with the dose given to the normal tissues.[30,31] However, when the necessary dose to control the disease can not be given the long lasting residual disease may have the potential to trigger MSLT by causing a defective healing response, which is accepted to be the main reason of developing late normal tissue toxicity. These paradoxical findings of less radiation dose with more MSLT must not be interpreted, as higher doses of radiation are safer than lower doses for head and neck cancer, and in our study NPC. What must be interpreted from our findings is that suboptimal RT for a disease with a propensity to metastasise to the neck nodes may increase the probability of late toxicity by poor disease control. In addition, residual disease or early recurrences would make aggressive surgical treatments (neck dissections) or second choice ChT and RT necessary with more treatment toxicity. This makes sense and the relation between higher dose and higher incidence of late toxicity in a particular way may not be valid in this setting. However, in multivariate analysis total radiation dose to the neck was not a significant prognostic factor of MSLT.

In our 44 NPC patients the only prognostic factor for MSLT was found to be treatment response in multiple Cox's regression analysis (Table 4). Five-year hazard probability of MSLT among 12 NPC patients with LTCR to treatment was higher than 32 NPC patients with CR to treatment (85.7% vs. 35.2%, p= 0.0254). Nine patients among 12 NPC patients with LTCR were diagnosed with MSLT and seven of them had residual disease without progression with MRI. Although, they were long term survivors, they suffered MSLT's due to long lasting residual disease.

Aggressive multimodality treatment for patients with NPC is associated with increased probability of MSLT. However, this increase in MSLT to a certain extent can be associated with poor tumour control related with less compliance to treatment. The residual disease appears to be the triggering factor for defective healing response of normal tissues, and by this means late toxicity. If supportive care of the patients with NPC during treatment can be improved to be able to apply the planned treatment, it is probable to increase cure rates even with less toxicity.

Although, no association was found between ChT sequencing and MSLT, compliance to concomitant ChT was generally poor. While all the patients could be given the neoadjuvant three courses of ChT, only five patients among 16 (31%) patients with NPC who also received concomitant ChT with RT could be given the planned treatment. Safe administration of concomitant ChT must be further evaluated in the Turkish society. Social and cultural factors may be associated with poor compliance to concomitant ChT.[32] Cisplatin is the agent given to all our patients together with RT in a neoadjuvant, concomitant setting or both. The incidence of sensorineural hearing loss has been reported to be increased with this treatment approach.[33] However, we did not diagnose any severe hearing loss in our patients that can be related with cisplatin ChT. Four children were treated with bleomycin containing ChT and grade 3 neck fibrosis developed in two of them. This finding supports that bleomycin containing ChT regimen can frequently result in neck fibrosis.[34]

The only patient who would prefer not to be treated for her cancer was the only patient among 44 (2.2%) NPC patients who suffered grade 4 toxicity. Eleven patients among the 16 (69%) patients who suffered grade 3 toxicity were happy for their cancer to be controlled. The remaining three patients have died because of NPC and two suffered recurrent disease; one with lung metastases and the other with local recurrence. We are already studying with questionnaires how the late toxicity of treatment translates into quality of life in NPC patients. The results will be published later.

We diagnosed no second primary or radiation induced cancers in our 44 NPC patients up to the study time. However, an increase in second primary radiation induced cancers have been reported in NPC patients.[35,36]

One of the challenges of treating NPC is tolerability of RT and ChT. The side effects must be monitored and supportive treatments must be given adequately.[37] The clear benefit of aggressive multimodality treatment of NPC patients in terms of survival can be further improved by this way and the price paid for cure will be less.

CONCLUSION

Late toxicity in NPC patients is treatment related. Poor tumour control can be a triggering factor for development of late toxicity. Long lasting residual disease following treatment is an interesting phenomenon in NPC patients, which appears to be related with severe late toxicity and has to be further investigated. Less than optimal radiation dose to the involved neck nodes may have an impact on late toxicity through long lasting residual neck nodes. Supportive care during intensive treatments is important to give the patients prescribed doses necessary to reach higher survival rates. How the late toxicity translates to quality of life must be further studied.

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