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ORIGINAL ARTICLE

Toxicity and feasibility analysis for cisplatin-based concomitant chemoradiotherapy in locally advanced nasopharyngeal carcinoma

B.M. Atasoy[1], F. Dane[2], P.F. Yumuk[2], Z. Akgün[1], N.S. Turhal[2], U. Abacioğlu[1], M. Şengöz[3]

[1]Department of Radiation Oncology and [2]Department of Internal Medicine, Division of Medical Oncology, Marmara University Medical School, Istanbul; [3]Acibadem Kozyatagi Hospital, Radiotherapy Centre, Istanbul, Turkey

Summary

Purpose: *To assess the side effects of cisplatin-based concurrent chemoradiotherapy (CRT) for locally advanced nasopharyngeal carcinoma (NPC).*

Patients and methods: *From 2001 through 2007, 34 (27 males; 7 females) patients received a median of 70 Gy curative radiotherapy (RT) with conventional fractionation. Twenty-one (62%) patients received induction chemotherapy (CT): 8 of them received 2 courses of cisplatin (75 mg/m^2, day 1) and 5-fluorouracil (5-FU) (750 mg/m^2, days 1-5) every 3 weeks and 13 patients received 3 courses of cisplatin (75 mg/m^2, day 1) and docetaxel (75 mg/m^2, day 1) every 3 weeks. Concomitant cisplatin was administered either 40 mg/m^2 weekly (n=8) or 75-80 mg/m^2 every 3 weeks (n=26) during RT. Median Karnofsky performance status (KPS) prior to RT was 80 (range 70-90). Patient, disease and treatment-related factors were analysed in relation to termination of concurrent CT.*

Results: *Concurrent CT was administered to 13 (38.2%) patients without cisplatin termination, whereas 10 (29.4%) patients received 2 cycles of the 3-weekly schedule. Grade 3 oral mucositis (47.1%), grade 2-3 weight loss (44.2%) and grade 2 fatigue (44.1%) were the most frequently dose-limiting side effects during concurrent therapy. The rate of receiving cisplatin cycles as planned was 85% for patients with KPS >80, whilst it was 15% only for patients with KPS ≤ 80 (p=0.006). None of the patients suffering of grade 2 fatigue could complete all cycles compared to 68% of patients with < grade 2 fatigue who completed all cycles (p <0.001). The severity of mucositis was significantly related to initial haemoglobin level (p=0.02) and weight loss during RT (p=0.04).*

Median follow-up was 20 months (range 5-65). Three-year locoregional relapse free (LRRFS), disease free (DFS) and overall survival (OS) rates were 79.3%, 68.8% and 79.2%, respectively.

Conclusion: *Concurrent administration of CT during RT reveals better outcome but requires careful consideration for toxicity. Initial performance status prior to CRT might be a predictor for unplanned CT stopping due to side effects.*

Key words: cisplatin, concurrent chemoradiotherapy, nasopharyngeal cancer, toxicity

Introduction

Nasopharyngeal carcinoma is a radiosensitive tumor, and single-modality RT had been the traditional treatment for non-metastatic disease until recently. Combining RT with CT reduces the rate of distant metastases and improves local control as well as survival [1-7]. The Intergroup Study INT 0099 randomly assigned 147 patients with locally advanced NPC to concomitant chemoradiotherapy (CRT) followed by adjuvant CT or the same dose of RT alone [2]. Patients in the CT arm received cisplatin (100 mg/m^2) on days 1, 22, and 43 of standard RT followed by adjuvant cisplatin (80 mg/m^2 on day 1) and 5-fluorouracil (5-FU; 1000 mg/m^2 daily, days 1 through 4), given every 4 weeks for 3 cycles. The study was terminated early due to a highly significant 3-year survival advantage for CRT (76 vs. 46%), a finding that was supported with

Correspondence to: Beste M. Atasoy, MD, MSc. Department of Radiation Oncology, Marmara University Hospital, Tophanelioğlu cad. No: 13/15 Altunizade, Istanbul 34660, Turkey. Tel & fax: +90 216 3276956, E-mail: bmatasoy@yahoo.com

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5-year follow-up data (67 vs. 37%) [3]. However, only 63% of patients received all 3 cycles of concurrent CT with RT, whereas 13 (16.6%) patients went off study permanently due to toxicity. The sum of grade 3 and 4 of any kind of toxicity during the concomitant schedule was 59% (grade 3: 43%, and grade 4: 16%).

Other studies were performed with similar regimens used in previous trials in Asian patients [4-7]. CRT with/without adjuvant CT showed significantly better local control, disease free and overall survival, and the 2-year cumulative incidence of distant metastases was decreased. However, significantly higher incidence of toxicity with CRT was reported in these previous trials. Particularly, the incidence of non-haematological toxicity (oro-pharyngeal mucositis, anorexia and emesis) was significantly higher in the CRT arm during the initial phase of treatment. As for haematological toxicity the incidence of severe neutropenia was significantly higher in CRT than RT alone.

There are several published data from different countries which demonstrates the toxicity profile and efficacy of cisplatin-based concurrent CRT. Adoption of recommended concurrent protocols for locoregionally advanced NPC should be cautious due to reported toxicity profiles in previous studies.

In the present retrospective analysis, we aimed to report our experience in a number of Turkish patients treated with concurrent CRT for locally advanced NPC.

Patients and methods

Between 2001 and 2007, 34 locally advanced (UICC/AJCC 1997 IIB-IVB), histologically proven NPC patients who received curative RT with concurrent cisplatin in our department were enrolled into this analysis. Patient characteristics are shown in Table 1. The median KPS was 80 (range 70-100); median haemoglobin level was 11.7 g/dl (range 11.1-13.4) in females and 13.9 g/dl (range 8.7-16.2) in males. Median body mass index (BMI) was 26.5 (range 16.6-35.7).

Pre-treatment work-up consisted of history, physical and panendoscopic examination, magnetic resonance imaging and/or computerized tomography of the nasopharynx and neck, chest X-ray and/or thoracic computerized tomography. Abdomen was evaluated with either ultrasonography or computerized tomography. Complete blood count, liver and kidney function tests were required prior to RT and every 3 weeks during CT. For weekly administrations of cisplatin complete blood count was required weekly whereas liver and kidney functions tests were done every other week.

Table 1. Patient characteristics

Characteristic	*n (%)*
Age (years)	
Median	49
Range	18-73
Gender	
Male	27 (79.4)
Female	7 (20.6)
UICC stage	
IIB	5 (14.7)
III	14 (41.1)
IVA	10 (29.5)
IVB	5 (14.7)
AJCC T stage	
T1	2 (5.8)
T2	13 (38.2)
T3	7 (20.5)
T4	12 (35.5)
AJCC N stage	
N0	5 (14.7)
N1	5 (14.7)
N2	19 (55.9)
N3	5 (14.7)
Pathology (WHO classification)	
Type I	1 (3)
Type II	5 (14.4)
Type III	28 (82.3)
KPS*	
Median	80
70	2 (5.8)
80	17 (50)
90	15 (44.2)
Haemoglobin (g/dl)	
Males	
Median	13.9
Range	8.7-16.2
Females	
Median	11.7
Range	11.1-13.4

*Karnofsky performance status

Radiotherapy

For patients who had received induction CT, RT began 3-4 weeks after the last cycle of CT. Individual thermoplastic mask was used for immobilisation. Irradiation was performed with 6 MV and 18 MV photons and appropriate electron beams using a linear accelerator. Two-phase treatment was used. The phase 1 treatment portal consisted of two parallel opposed fields comprising the primary tumor bed and all bilateral cervical lymphatic nodal areas and a single adjacent anterior field for supraclavicular regions and lower neck. For phase 2 treatment the portal field was planned to spare the spinal cord and primary tumor site of the nasopharynx and clinical and/or radiological metastatic lymphatic regions were comprised separately. Computed tomography-based planning was done in 19 (55.8%) patients. Meanwhile, individual cerrobend blocks were used for appropriate shielding

for all patients. A daily dose of 1.8-2 Gy was given in a single daily fraction, 5 fractions per week.

Chemotherapy

Twenty-one patients received one of 2 induction CT regimens. Eight patients who were treated between 2000 and 2004 received 2 courses of induction cisplatin (75 mg/m^2, day 1) and 5-FU (750 mg/m^2, days 1-5) every 3 weeks. Three courses of cisplatin (75 mg/m^2, day 1) and docetaxel (75 mg/m^2, day 1) every 3 weeks were administered as induction CT to 13 (38.2%) patients treated since 2004. Concurrent cisplatin was given either 40 mg/m^2 weekly (n=8, 23.5%) for 7 weeks or 75-80 mg/m^2 (n=26, 76.5%) on days 1, 22 and 43 of RT. All patients received intravenous dexamethasone and serotonin antagonist as routine antiemetic prophylaxis prior to CT. Some patients who could not tolerate oral fluid intake were given intravenous hydration continued for 3 or more days after CT administration.

A 20% CT dose reduction was planned if grade 2 toxicity was seen. CT was discontinued if any grade 3 toxicity occurred or grade 2 toxicity persisted even from the previous dose reduction.

Toxicity evaluation criteria

Acute toxicities were considered those occurring within the first 90 days of the concurrent CRT and were graded according to National Cancer Institute Common Toxicity Criteria (NCI-CTC), version 2.0. Late toxicities were defined those occurring after 90 days and RTOG/EORTC Late Morbidity Scoring Scale was used for their grading. Toxicity evaluation was done by physicians and recording was performed weekly during CRT, and then during each follow-up visit.

Survival definitions

LRRFS was defined as the time period from pathological diagnosis to locoregional tumor progression, whereas DFS was the period from histological diagnosis to first appearance of disease relapse, progression or death of any cause. OS was defined as the time period from the date of diagnosis to the date of death from any cause or last follow-up visit.

Statistical analysis

Patient-related factors like gender, age, KPS prior to RT, BMI, treatment-related factors like phase 1 RT portal volume, and tumor-related factors like T-classification and N-classification were analysed for termination of concurrent CT. Correlations among these factors for CT termination were assessed using the chi-square test. P-values less than 0.05 were considered statistically significant. LRFS, DFS and OS rates were calculated using Kaplan-Meier product limit method [8]. Survival differences for treatment were analysed using the log-rank test.

Results

All patients completed RT as scheduled but one female patient suffered neutropenic sepsis and died at the 5th week of RT. However, she was included in the analyses. RT was completed in a median of 7 weeks (range 6-9) or 52 days (range 36-67). The median radiation doses for phase 1 were 46 Gy (range 45-50.4) and 70 Gy (range 50-73) for phase 2 with daily fractions of 1.8-2 Gy. The median treatment volume of phase 1 was 5278 cm^3 (range 3530-6800). RT was only interrupted for 2-6 days in 2 patients due to acute pneumonitis.

A total of 111 CT cycles were given and this was 86% of the expected 129 cycles of weekly and 3-weekly schedules. Thirteen (38.2%) patients completed 3 cycles of concomitant cisplatin-RT with or without dose reduction. Concurrent cisplatin was given without any dose reduction only in 6 (17.6%) patients, whereas 10 (29.4%) patients received 2 cycles and 3 (8.8%) patients had only 1 cycle of the 3 weekly CT schedule. Median dose of cisplatin for each course was 75 mg/m^2. For weekly administration cisplatin was planned to be given for 7 courses during radiotherapy and none of the 8 patients managed to complete this planned concurrent CRT. Therefore, cisplatin was stopped during the last course in 2 patients, the last 2 courses in 2 patients, the last 3 courses in 3 patients and the last 6 courses in 1 patient.

Twenty-one (61.7%) patients received induction CT prior to concurrent treatment. The median cisplatin dose that included both induction and concurrent CT was 304 mg/m^2 (range 150-466) and median cisplatin dose administered only concurrently was 225 mg/m^2 (range 80-296).

Toxicity evaluation and analyses

Acute and late toxicity profiles are shown in Table 2. The main acute non-haematological toxicities were oral mucositis, taste alteration, fatigue, weight loss and radiation-related pharyngeal dysphagia. Two patients who had received induction CT developed grade 4 febrile neutropenia during CRT and cisplatin was withdrawn in these patients. One died due to neutropenic sepsis and the other was successfully treated with intra-

Table 2. Proportion and intensity of side effects of concurrent chemoradiotherapy (n=34)

Toxicity	*Grade 1 n (%)*	*Grade 2 n (%)*	*Grade 3 n (%)*	*Grade 4 n (%)*
Acute*				
Fatigue	19 (55.9)	15 (44.1)	–	–
Oral mucositis	–	18 (52.9)	16 (47.1)	–
Pharyngeal dysphagia	1 (2.9)	28 (82.4)	5 (14.7)	–
Taste alteration	10 (29.4)	24 (70.6)		
Weight loss	14 (41.2)	11 (32.4)	4 (11.8)	–
Radiation dermatitis	1 (2.9)	32 (94.1)	1 (2.9)	–
Nausea/vomiting	18 (52.9)	14 (41.2)	2 (5.9)	–
Serum creatinine	4 (11.8)	1 (2.9)		
Neutropenia	–	–	1 (2.9)	2 (5.9)
Late†				
Xerostomia	11 (32.4)	21 (61.8)	2 (5.9)	–
Subcutaneous tissue	15 (44.1)	2 (5.9)	–	–
Larynx	3 (8.8)	1 (2.9)	1 (2.9)	–
Hypothyroidism	2 (5.9)	5 (14.7)	–	–
Serum creatinine	2 (5.9)	–	–	–

*According to the NCI/CTC v.2.0 †According to RTOG/EORTC Late Morbidity Scoring Scale

venous antibiotics for pneumonia, after which she completed her therapy.

Among patients who received 3 cycles of the 3-weekly schedule of cisplatin, dose reduction was necessary because of grade 3 weight loss for 1 patient and grade 3 mucositis for 5 patients. Three patients refused to continue CT following the 1st or 2nd cycle as they had grade 1 fatigue, grade 1 weight loss and grade 2 mucositis. None of the patients suffering of grade 2 fatigue could complete all cycles compared to 68% of patients with < grade 2 fatigue who completed all cycles ($p < 0.001$). Grade 2-3 nausea/vomiting were more frequently observed in CT cancelled patients ($p = 0.01$).

Only 17% of patients with KPS ≤ 80 completed the total concomitant CRT schedule whilst for KPS >80 patients this ratio was 63% ($p < 0.006$). Other parameters (age, gender, BMI, RT portal volume, T- and N-classification) showed no significant correlation with toxicity (Table 3).

Symptomatic hypothyroidism was observed in 5 (14.7 %) patients; all these cases had received induction CT. Most common late toxicity was xerostomia (grade 2, 62%; grade 3, 6%) (Table 2).

Mucositis in patients with haemoglobin level lower than the median (13.9 g/dl for men and 11.7 g/dl for women) was significantly more intense than in those with higher haemoglobin level (75 vs. 29%, $p=0.02$). The cumulative dose of cisplatin affected the severity of mucositis. Grade 3 mucositis was increasingly observed in patients who received more than the median cumulative dose of cisplatin (61 vs. 31%, $p=0.08$). The intensity of mucositis was also affected by weight loss (Table 4; $p=0.04$).

Table 3. Analysed factors regarding CT completeness

	Concurrent chemoradiotherapy		
	Completed n (%)	*Cancelled n (%)*	*p-value*
Age (years)			
< 50	4 (23.5)	13 (76.5)	
≥ 50	9 (52.9)	8 (47.1)	0.07
Gender			
Male	12 (44.4)	15 (55.6)	
Female	1 (14.2)	6 (85.8)	NS
KPS*			
≤ 80	3 (16.6)	15 (83.4)	
≥ 90	10 (62.5)	6 (37.5)	<0.006
Haemoglobin (g/dl)**			
< median	10 (62.5)	6 (37.5)	
≥ median	2 (11.7)	15 (88.3)	0.002
BMI§			
< 26.5	6 (40)	9 (60)	
≥ 26.5	7 (36.8)	12 (63.2)	NS
RT† Phase 1 volume (cm^3)			
< 5278	5 (26.3)	12 (73.7)	
≥ 5278	8 (47.1)	9 (52.9)	NS
Induction CT††			
(+)	5 (38.4)	8 (61.6)	
(–)	8 (38)	13 (62)	NS
T stage			
T1	1 (50)	1 (50)	
T2	5 (35.7)	9 (64.3)	
T3	1 (16.6)	5 (83.4)	
T4	6 (50)	6 (50)	NS
N stage			
N0	1 (2)	3 (75)	
N1	2 (33.3)	4 (66.7)	
N2	9 (47.3)	10 (52.7)	
N3	1 (20)	4 (80)	NS

*Karnofsky performance status, **median haemoglobin was 11.7 g/dl in females and 13.9 g/dl in males, NS: not significant, §body mass index, †radiotherapy, ††chemotherapy

Table 4. Correlations between haemoglobin levels, weight loss, cumulative cisplatin dose and T stage with treatment-related mucositis

	Mucositis		
	Grade 2 n (%)	*Grade 3 n (%)*	*p-value*
Haemoglobin (g/dl)			
< median	5 (26.3)	12 (73.7)	
> median	12 (73.7)	5 (26.3)	0.02
Weight loss (grade)			
0	4 (80)	1 (20)	
1	9 (64.2)	5 (35.8)	
2	5 (45.4)	6 (54.6)	
3	–	4 (100)	0.04
Cumulative cisplatin dose (mg/m^2)			
< 305	11 (68.7)	5 (31.3)	
≥ 305	7 (38.8)	11 (61.2)	0.08
T stage			
T1	2 (100)	–	
T2	9 (64.2)	5 (35.8)	
T3	3 (50)	3 (50)	
T4	4 (33.3)	8 (66.7)	NS

NS: not significant

Local control and survival

Median follow-up was 20 months (range 5-65). Five (15%) patients showed local progression. Three patients with local relapse were treated by stereotactic radiosurgery. Two patients relapsed in the neck and received CT. Five (14.7%) patients developed distant metastases and 3 of them died with systemic disease [bone and lung (2), and bone and liver (1)] without any locoregional progression. One disease free patient died while abroad, possibly due to thromboembolic event after 14 hours bus ride. Three-year LRRFS was 79.3%, whilst DFS was 68.8% and OS 79.2% (Figure 1).

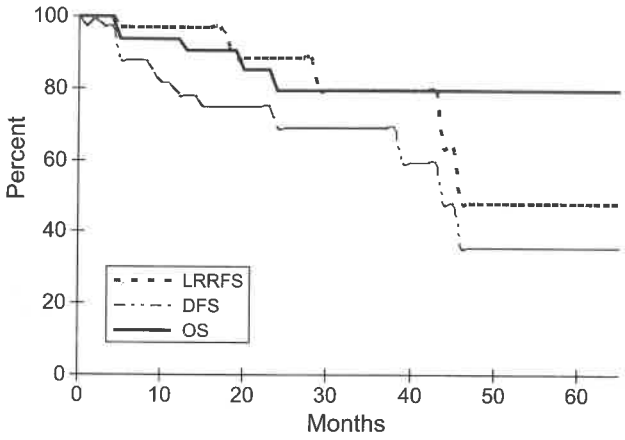


Figure 1. Locoregional relapse free survival (LRRFS), disease free survival (DFS) and overall survival (OS) for all patients.

Discussion

NPC is a highly sensitive tumor to both RT and CT, and concomitant administration of these two modalities for locally advanced disease lead to better local and systemic control [1-7]. Toxicity still remains the major limiting factor of this more effective but highly aggressive concurrent CRT. However, applicability of planned schedules may be interrupted due to intolerable side effects. Still, investigators in many clinical trials generally consider toxicity of the combined approach tolerable. In fact, there are no published standards or further recommendations for acceptable maximum risk levels for normal tissues and organs. Notwithstanding reported advantages concerning local and distant failures, the optimum concurrent CT dose and regimen has not been established yet [9].

We aimed to analyse the outcomes of our patients who received concurrent CRT since not only reports from different therapeutic centers are conflicting but also discrepancies exist between countries or nations [10,11]. We also aimed to define factors that might explain side effects and their severity. Some of our patients who were treated prior to this study received concurrent cisplatin with 100 mg/m^2 every 3 weeks, but tolerability was very low and continuation of therapy was very poor. Therefore, we preferred to administer 75-80 mg/m^2 of cisplatin every 3 weeks.

An important result of our study was that there was statistically significant association between CT termination ratio and initial KPS. Hence, we think this data might help anticipate patients who will need a better supportive care prior to and during CRT in order to complete the treatment schedule.

We did not observe any grade 4 mucositis. Grade 3 mucositis in our study (47.1%) was comparable with previous reports by Al-Sarraf et al. (37%), Lee et al. (61%), Chan et al. (48.9%), and Wee et al. (48%) [2, 5-7]. None of our patients who suffered mucositis was hospitalised; still, according to literature data 6% of patients treated with CRT were hospitalised due to mucositis [12]. Although not statistically significant, we observed more severe mucositis in advanced T stages (Table 4). Although we did not measure the tumor volume, severe mucositis might be secondary to RT portal volumes. We believe that relieving serious side effects and completing therapy might be more crucial for patients with advanced T stage, as T stage status negatively affects DFS [13].

Our data revealed a high incidence of grade 2-3

weight loss (44.2%). Al-Sarrat et al. reported weight loss in 6.4% of their patients, Chan et al. in 74%, Lee et al. in 32% and Wee et al. in 12% [2,5-7]. Mean weight loss was 8.1 kg (range 0-20) whereas 15 (44.2%) patients lost more than 10 kg during RT. We offered feeding tube for maintaining nutritional status to all of our patients before treatment but none of them accepted this procedure. Mangar et al. reported that feeding tube and enteral feeding requirements are significantly more frequent in patients with advanced stages and low performance status [14]. Cheng et al. reported 88% of completeness of concurrent CT in their study [15]. They reported 25% grade 2 and no grade 3 weight loss and attributed this result to immediate intervention with nasogastric tube feeding when patients developed 5% weight loss or grade 3 mucositis. We observed that our patients did not want to be fed via feeding tube and did not want to consume any nutritional supplements. Patients reported that the thought of having a feeding tube or receiving high caloric nutritional supplements increased their psychological stress. This was also observed by our nutritional home support team.

We did not find any significant difference in severity and frequency of mucositis regarding to RT-related factors as phase 1 portal volume. A probable reason might be that all patients received relatively uniform doses from similar RT field.

We compared our results with the current literature, particularly the INT 0099 study (Table 5) [2]. Although the percentage of patients receiving 3 courses of CT during RT was less in our patients, a similar percentage of patients received 2-3 courses in both studies. Among similar total RT doses and patient characteristics of these 2 studies, patients' refusal was more frequent in INT 0099 (23 vs. 28.5%). Furthermore, analysis of CT cancellations in our study regarding age revealed that the younger the patients (< 50 years) the more cancellations were observed (76.4 vs. 47%, p= 0.07).

The most common late side effect was xerostomia and in over 60% of the cases it was of moderate grade. No significant correlation between severity of xerostomia and the analysed factors was seen, however we believe that the number of patients in this study was small to detect a possible chemo-adding effect.

Turkey as a Mediterranean country is an endemic area for NPC and most (82.3%) of the diagnosed NPC belong to the undifferentiated type [16-18]. However, the INT 0099 study included less WHO type III tumors (41%) and a real benefit for concurrent CRT for WHO type III pathology is still debated [19]. Our patients displayed pathological characteristics similar to patients in Asian studies; still, our results were also slightly inferior compared to the literature.

Table 5. Toxicity comparison of our patients and INT 0099 study [2]

	INT 0099 Study n (%)	*Our experience* n (%)*
Patients, n	78	26
Median age, years (range)	50 (16-79)	49 (18-69)
Gender		
Male	52 (67)	20 (77)
Female	26 (33)	6 (23)
Stage		
IIB	–	3 (11.5)
III	7 (9)	12 (46.1)
IV	71 (91)	11 (42.3)
Performance status		
	72 (92)-ECOG 0-1	26 (100)-KPS 80-90
	6 (8)-ECOG 2	–
Total dose to primary tumor (Gy)	70	70 (median)
Cisplatin dose (mg/m^2, days 1,22,43)	100	75 (median)
Compliance to chemotherapy		
3 courses	49 (63)	13 (50)
2 courses	18 (23)	10 (38.4)
1 course	9 (14)	3 (11.6)
Reasons off treatment		
Toxicity	13 (62)	7 (54)
Refusal	6 (28.5)	3 (23)
Physician's decision	–	3 (23)

*Only data from patients treated with the 3-weekly schedule was included in this comparison

Lin et al. described a high risk group of locally advanced NPC in their analysis [20]. In that study, any of the following criteria was enough to allocate patients into high risk categories: nodal size >6 cm, supraclavicular nodal metastases, 1992 AJCC stage T4N2, and multiple nodal metastases with 1 node >4 cm in the neck. When we did the same analysis we found that our patients who had one of these high risk factors showed poor outcome regarding 3-year DFS (83.6 vs. 53.3%, p=0.01) and OS (93.7 vs. 59.4%, p=0.08) (Figure 2a and 2b). In our study 63% of high risk patients had KPS ≤ 80. Therefore, it might be concluded that performance status may be useful not only in predicting the probability of completeness of concurrent CRT but also in determining the risk of patients.

Conclusions

Concurrent CRT has advantages but must be carefully considered in terms of toxicity [21]. Our study showed that severity of fatigue, mucositis and weight loss during treatment are the major risks for stopping concurrent CRT. Initial performance status prior to

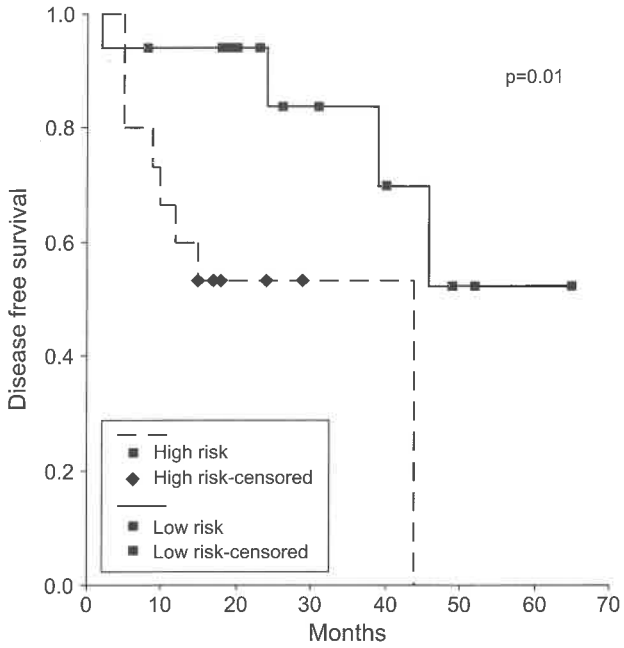


Figure 2a. Disease free survival of high and low risk patients.

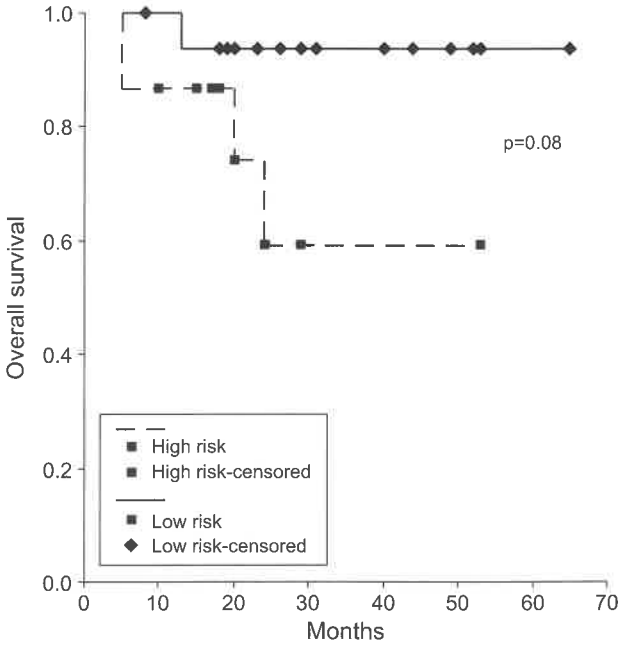


Figure 2b. Overall survival of high and low risk patients.

CRT might be a reliable predictor for patients whether they are "fit to complete" therapy. However, further prospectively designed studies with larger numbers of patients are needed to reveal and define all other factors before deciding the appropriate treatment regimen and schedule.

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