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CONCURRENT CHEMORADIOTHERAPY IN LOCALLY AND/OR REGIONALLY ADVANCED NASOPHARYNGEAL CARCINOMA

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A b s t r a c t: The aim of the study was to investigate the efficacy of concurrent chemoradiotherapy (CCRT) in patients with locally and/or regionally advanced nasopharyngeal carcinoma (NPC). Between February 2005 and November 2007, 27 patients with advanced NPC were included in a prospective study of CCRT at the Radiotherapy and Oncology Institute in Skopje. Radiotherapy was performed using a sophisticated three-dimensional conformal technique. A dose of 69.4–71.4 Gy (median, 69.4 Gy) was delivered to the primary tumour and to the positive neck nodes. Chemotherapy consisted of cisplatin 30 mg/m^2 given concomitantly with radiation on a weekly basis.

The median age was 49 years and 51.2% had stage IV disease. Eighty-eight percent received ≥ 5 cycles of concurrent cisplatin. Complete response rates three months after chemoradiotherapy completion were 81.5% (22 of 27) and 91.3% (21 of 23) at the primary site and in the neck, respectively. Only one patient had a locoregional relapse and four patients developed distant metastases. The most prevalent grade 3 acute effect was mucositis present in 63.0% of patients. The 2-year disease-free survival (DFS) rate was 42.6%, the 2-year locoregional relapse-free survival (LR-RFS) rate was 76.9%, and the 2-year distant metastases relapse-free survival (DM-RFS) rate was 63.6%.

Considering the preliminary results of our study which do not indicate that the therapeutic effects of CCRT evaluated are comparable with the results from the randomised phase III studies, we recommend an effort for the routine use of the new radiotherapy technique, intensity-modulated radiation therapy (IMRT), as well as an initiation of a phase III trial addressing the definition of the precise role of sequential chemotherapy in the management of patients with locally advanced NPC.

Key words: nasopharyngeal carcinoma, radiotherapy, three-dimensional conformal radiotherapy, concurrent chemoradiotherapy.

Introduction

NPC is a neoplasm of the head and neck that is rarely seen in Europe and the United States. It is much more common among Southeast Asian, North African, and Eskimo populations [1]. NPC differs from other HNC with regard to epidemiology, nodal presentation, histopathology, treatment strategies, response to radiation therapy and chemotherapy, incidence of systemic metastases, and overall survival [1, 2]. Nasopharyngeal carcinoma is usually present as a locally advanced (stage III or IV) disease [3]. Local recurrences following radiotherapy and high affinity for distant metastasis represent two major causes of treatment failure resulting in 5-year overall survival rates from 32% to 52% [4, 5].

NPC is both a radiosensitive and chemosensitive tumour [6, 7]. CCRT (CCRT) in the treatment of locoregionally advanced NPC has been investigated in six randomized controlled trials [8, 9, 10, 11, 12, 13]. The Intergroup Study (IGS) 0099 [8] and the study from Taiwan [9] have proved the greater effectiveness of CCRT compared with radiotherapy alone for advanced-stage NPC, demonstrating an improvement of both progression-free survival and overall survival. Two of the concurrent studies showed an improvement of locoregional control rate [9, 12] and in two other studies an improvement of distant metastasis control rate was observed [11, 13]. Although the results of the studies on the treatment of NPC by CCRT were not consistent, CCRT has proved its superiority to radiotherapy alone for the treatment of intermediate and advanced NPC [14, 15].

In this study we investigated a concurrent chemoradiation regimen with radiotherapy performed using a three-dimensional conformal technique and with concomitant chemotherapy consisting of cisplatin given on a weekly basis during external-beam radiotherapy in a cohort of patients with locally and/or regionally advanced NPC.

Material and methods

Between February 2005 and November 2007, 27 patients with advanced NPC were included in a prospective study of CCRT at the Radiotherapy and Oncology Institute in Skopje. The eligibility criteria were: [1] stage III or IV according to the American Joint Committee on Cancer (AJCC) 1997 Staging System [16] biopsy-proven NPC; [2] age ≥ 16 years; [3] performance status by the Eastern Cooperative Oncology Group (ECOG) system ≤ 1; [4] no distant metastases; [5] no severe liver or kidney dysfunction; and [6] no concurrent treatment for other malignant disease outside the upper aerodigestive tract. Pretreatment diagnostic work-up other than medical history and physical examination consisted of fiberoptic nasopharyngoscopy and biopsy to obtain the histo-

logical proof, blood chemistries, chest radiography, abdominal ultrasonography and bone scan. The disease evaluation also included a computed tomography scan (CT) or magnetic resonance imaging (MRI) from the base of the skull to the whole neck. Histological diagnosis was performed from biopsy material of the primary tumour and/or nodal excision tissue. Tumours were classified as squamous cell carcinomas or lymphoepithelioma.

Radiotherapy was performed on a Varian 23EX linear accelerator in accordance with a three-dimensional conformal radiotherapy (3DCRT) plan. A thermoplastic head mask was used for patients' immobilization. The treatment planning CT scans required to define gross target volume and clinical target volumes were carried out in the treatment position. The definition of volumes was in accordance with the ICRU Report 62 [17]. The gross tumour volume (GTV70), also known as CTV70, was defined as the extension of the nasopharyngeal tumour and the gross nodal disease revealed by physical examination and by imaging procedures. The high risk clinical target volume (CTV59.4) was defined as CTV70 plus a margin for the potential microscopic extension of the disease. This volume also included those lymph nodes considered to be at high risk such as: submanidibular lymph nodes; upper jugular lymph nodes; midjugular lymph nodes; posterior cervical lymph nodes, and retropharyngeal lymph nodes. The low risk clinical target volume (CTV50.4) referred to the lower jugular lymph nodes and supraclavicular lymph nodes. The planning target volumes were PTV70, PTV59.4, and PTV50.4. They provided a margin of 0.5 cm around the adequate CTV to compensate for the variabilities of treatment set-up and internal organ motions. Primary, subclinical PTV59.4 was treated with 6-MV photons through lateral fields to a total dose of 59.4 Gy (33 fractions of 1.8 Gy/fraction). An off-cord boost to the posterior neck was realized with 9-MeV electrons. Separate anterior and posterior fields with 6-MV and 15-MV photons were used for the low risk PTV50.4 to a total of 50.4 Gy (28 fractions of 1.8Gy/fraction). Arrangements with 4 to 7 fields in anterior, posterior, lateral, or oblique directions were used for the boost to the PTV70 up to a total of 69.4 to 71.4 Gy (5 to 6 fractions of 2 Gy/fraction). The maximum dose to the spinal cord did not exceed 50 Gy. Treatment was delivered once daily, 5 fractions per week.

Chemotherapy consisted of cisplatin 30 mg/m^2 in 0.5 L of normal saline over 1 hour given to the patients concomitantly with radiation on a weekly basis, starting on the first day of radiotherapy. The complete blood picture and biochemistry were checked weekly before chemotherapy.

Acute radiotherapy-related toxicities were assessed according to the Acute Radiation Morbidity Scoring Criteria of the Radiation Therapy Oncology Group (RTOG) [18] and chemotherapy-related toxicities by the World Health Organization (WHO) criteria [19]. All the toxicities were recorded on a weekly basis. According to our follow-up policy, the patients were seen for clinical

examination monthly during the first year after completion of treatment, every 2 months in the second year, and then every 3 to 6 months afterwards. The first assessment of tumour response was performed three months after completion of chemoradiotherapy by physical examination, fiberoptic nasopharyngoscopy and MRI of the nasopharynx and neck. The evaluation of response was also assisted by biopsy of any suspicious residual lesion. Complete response was defined as complete disappearance of locoregional disease. Partial response was defined as tumour shrinkage of ≥ 50% of the sum of the product of perpendicular diameters of all measurable lesions. Follow-up nasopharyngoscopy and MRI were performed every 6 months for the first 2 years and thereafter when clinically indicated.

Statistical analysis. The end-points examined were DFS, LR-RFS, and DM-RFS. The starting point for DFS was the date of commencement of treatment, and the terminating point was the date when a relapse first occurred or, in the case of persistent disease, the date of the first follow-up. Patients in whom there was no evidence of disease after treatment were censored at the date of last follow-up. LR-RFS and DM-RFS were also evaluated and calculated from the first day of treatment until the day of the first occurrence of primary, neck or distant relapse, or until the day of the last follow-up. Patients who did not achieve a complete response after treatment had the same starting and terminating points and were assigned a LR-RFS of 0 months. The DFS, LR-RFS and DM-RFS curves were constructed using the Kaplan-Meier method [20].

Results

Detailed patient and tumour characteristics are reported in Table 1. The male to female ratio was 2.3 : 1. Sixteen patients were aged 55 years or younger. Lymphoepithelioma was present in two thirds of the patients. Stage III and stage IV were almost equally presented.

The median total dose was 69.4 Gy (range, 69.4–71.4). The median duration of radiotherapy was 7.3 weeks (range, 7.1–9.4). Of 27 patients, 19 patients completed radiotherapy within 7.5 weeks, 7 patients between 7.6 and 9 weeks, and only 1 patient completed treatment after more than 9 weeks. Thirty percent of patients completed all 7 cycles, and 88.9% had ≥ 5 cycles of concurrent chemotherapy. The mean total dose of cisplatin given was 178 mg/m^2 ± 28.7 SD.

Acute toxicities are listed in Table 2. Acute radiation toxicity was as expected, with 63.0% patients experiencing grade 3 mucositis and 81.5% patients experiencing grade 2 skin toxicity (Table 2). The median duration of acute

mucositis RTOG grade ≥ 2 was 8 weeks (range, 5–12). The median weight loss at the end of chemoradiotherapy as a percentage of weight on commencing treatment was 9% (range, 6–18).

Table 1 – Табела 1

Baseline characteristics (total patients = 27)
Основни карактеристики (вкупно пациенти = 27)

Characteristics	
Patient characteristics	
Gender:	
male	19 (70.4%)
female	8 (29.6%)
Median age (years)	49 years (range, 17–70 years)
Age (years)	
< 40	6 (22.2%)
40–55	10 (37.1%)
> 55	11 (40.7%)
ECOG performance status:	
0	25 (92.6%)
1	2 (7.4%)
Tumour characteristics	
Histology:	
squamous cell carcinoma	9 (33.3%)
lymphoepithelioma	18 (66.7%)
T stage:	
T2	9 (33.3%)
T3	11 (40.7%)
T4	7 (26.0%)
N stage:	
N0	4 (14.8%)
N1	5 (18.6%)
N2	9 (33.3%)
N3	9 (33.3%)
Stage:	
III	13 (48.1%)
IV	14 (51.9%)

Table 2 – Табела 2

*Acute toxicity caused by concurrent chemoradiotherapy**
*Акутна токсичност предизвикана со конкурентната хеморадиотерапија**

Toxicity	Grade of WHO toxicity (% of 27 patients)			
	0	1	2	3
Nonhaematologic				
Mucositis†	0	0	37.0	63.0
Skin reaction†	0	7.4	81.5	11.1
Nausea	18.5	63.0	18.5	0
Vomiting	44.4	44.4	11.1	0
Weight loss	0	51.9	48.1	0
Haematologic				
Leucopenia	59.3	29.6	7.4	3.7
Anaemia	59.3	29.6	11.1	0
Thrombocytopenia	85.2	11.1	3.7	0

* Because of rounding, not all percentages total 100.

* Поради заокружувањето, збирот на сите проценти не изнесува секогаш 100.

† Toxicities assessed according to the Acute Radiation Morbidity Scoring Criteria of the Radiation Therapy Oncology Group (RTOG)

Three months after completion of chemoradiotherapy, 22 patients (81.5%) and five patients (18.5%) had a complete response or partial response, respectively, at the primary site, giving an overall response rate at the primary site of 100%. Similarly, the overall response rate at the neck region was 100%, with 91.3% of patients with a positive neck experiencing complete response, and the remaining 8.7% manifesting a partial response. When both the primary site and neck were considered together, the composite response rates were the same as those achieved at the primary site.

The median duration of follow-up was 12 months (range, 4–30). Only one patient (3.7%) initially staged as T4 developed local recurrence. Four patients (14.9%) developed distant metastases. All these patients had experienced a complete response following chemoradiotherapy. Three of them had metastases in the liver and one patient had lung metastases. Nineteen patients remained alive at the close-out date. Four patients died after developing distant metastases, three patients with a partial response following treatment died because of the progression of their persistent disease, and one patient, being in complete remission, died of an unknown cause.

The DFS rate at 2 years was 42.6% (Figure 1). The median duration of DFS was 9 months (range, 1.2–28). The LR-RFS rate at 2 years was 76.9% (Figure 1). The median duration of LR-RFS was 9 months (range, 0–32). The DM-RFS rate at 2 years was 63.6% (Figure 1). The median duration of DM-RFS was 13 months (range, 4–28).

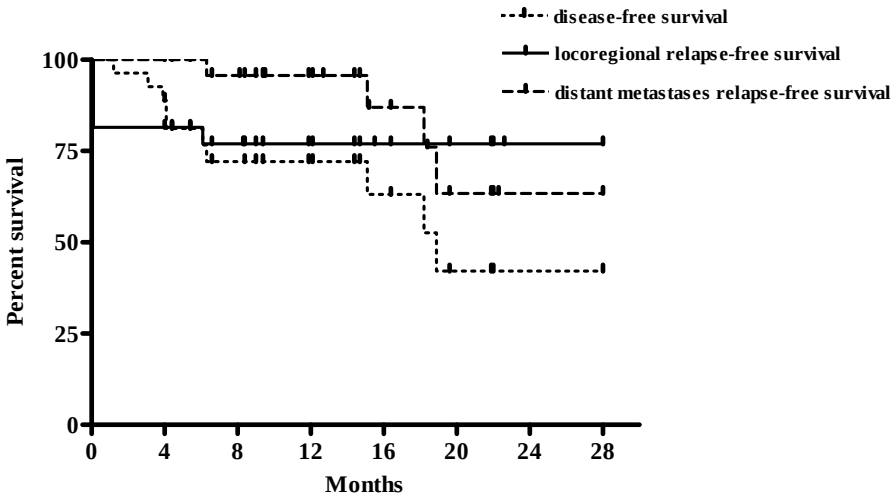

Figure 1 – Kaplan-Meier plots of survival
Слика 1 – Каѝлан-Маер криви на ѝреживување

Discussion

The results of extensive exploration of the effect of the addition of chemotherapy to radiotherapy for patients with advanced NPC during the last two decades has revealed survival benefits with CCRT compared with radiotherapy alone in several randomized trials [8, 9, 13, 14] and two meta-analyses [21, 22]. On the basis of these findings, CCRT is the current recommended treatment for patients with advanced-stage NPC. The principles of improved efficacy by CCRT are based on the following points: [1] up-regulated sensitivity to radiotherapy by chemotherapy; [2] the direct cell kill effect of chemotherapy; [3] the reduction of the repairing of sublethally injured tumour cells [23].

In this study we have investigated a concurrent chemoradiation regimen with concomitant chemotherapy consisting of cisplatin given on a weekly basis during radiotherapy performed using a sophisticated three-dimensional conformal technique. Two factors influenced our choice of treatment. Firstly, there were encouraging data on the use of a weekly moderate dose of cisplatin concurrent with

radiotherapy [10, 24]. The moderate dose of cisplatin at 30 mg/m^2 weekly was designed principally with the aim of improving local control, but also had an impact on the frequency of distant metastases. Secondly, using standard radiotherapy techniques, the nominal dose administered to patients with advanced NPC is often greater than the actual dose to parts of the PTV, because of technical limitations to radiation dose delivery. Using sophisticated treatment planning and delivery techniques, the specified tumour dose of 70 Gy was in fact received by a PTV encompassing all gross disease.

The composite complete response rate achieved in our study three months after completion of chemoradiotherapy was 81.5%. Data from the prospective randomized trials on CCRT in patients with locoregionally advanced NPC indicates moderate variation in the complete response rates – between 49 and 98% [8, 9, 10, 12, 13]. The overall response rate at the primary site of 100% in our study was 9% greater than the overall response rate in the chemoradiotherapy arm in the randomized trial conducted by Wee *et al*. [13].

In our study, the most common site of grade 3 acute reactions was the mucous membrane. Similar findings have been reported by other authors [8, 12, 13, 25].

Locoregional recurrence as a site of first progression following treatment was demonstrated in 3.7% of the patients in our study. This corresponds with the findings of Rischin [25], reporting locoregional relapse in only two patients (6%) in a study on 35 patients treated with three cycles of induction chemotherapy followed by CCRT of 60 Gy with cisplatin 20 mg/m2 daily for 5 days in weeks 1 and 6. Locoregional failure in 7% of the patients treated with chemoradiotherapy was reported by Chan *et al*. [10] in their analysis of a phase III randomized trial comparing concurrent cisplatin-radiotherapy with radiotherapy alone.

The present study showed 2-year rates of DFS, LR-RFS, and DM-RFS of 42.6%, 76.9%, and 63.6%, respectively. Cooper [26] reported on 35 patients treated with concurrent regimen, in which all but one received 70 Gy to the primary site by sophisticated three-dimensional techniques. Unfortunately, despite the similarities in the treatment approaches, the DFS rate of 42.6% at 2 years achieved in our study does not correspond with the projected 3 year DFS of 65% reported by Cooper.

The closer review of the phase III studies performed to compare CCRT versus radiotherapy alone for advanced NPC showed that the results concerning survival achieved in the arms treated with concurrent regimen are distinguished from the results obtained in our study. Namely, the IGS 0099, which demonstrated the superiority of chemoradiation followed by three cycles of adjuvant chemotherapy, reported a 3-year PFS rate of 69% [8]. In the study conducted in Hong Kong, a 2-year PFS rate of 76% for the group of patients treated with che-

moradiation was reported [10]. Analyzing the results of a phase III randomized trial conducted by the Taiwan group, Lin *et al*. [9] reported the 5-year PFS rate of 72% for the group treated with CCRT. These authors reported a 5-year nasopharynx disease-free survival rate of 89%, and a 5-year distant metastases disease-free survival rate of 79% in the same group of patients. In a factorial study, Kwong *et al*. [11], investigating the efficacy of CCRT and adjuvant chemotherapy in advanced NPC, reported a 3-year failure-free survival rate of 69% in the chemoradiotherapy group. In the same group of patients, the 3-year locoregional failure rate and distant metastases rate were 27% and 29%, respectively. Wee *et al*. [13], reporting the results of the Singapore trial, showed a 2-year DFS rate of 75% in the arm treated with concomitant chemotherapy and radiotherapy.

According to the results of our study with a short follow-up that are preliminary and do not clarify the relative importance of CCRT and more precise radiotherapy treatment, we assume that one area of concern regarding our treatment strategy must be the dose of cisplatin administered as concurrent chemotherapy that might have been inadequate to completely eradicate micrometastases. Given that the major cause of treatment failure in the CCRT was distant metastases [27], more should be done to improve on the efficacy of the adjunct chemotherapy that is administered. Although one can consider adding more cytotoxics in combination during the concurrent chemotherapy phase, the expected increased mucositis will limit both the number of cytotoxics and the dose that can be administered. On the other hand, sequential therapy (adding induction chemotherapy to CCRT) could be considered in the future as a recommendable treatment option for patients with advanced NPC leading to improvement of systemic control. Recent phase II studies using intensive induction chemotherapy followed by concurrent cisplatin-radiotherapy have shown encouraging toxicity profiles and disease control [28, 29].

Conclusion

Considering the results of our study which do not indicate that the therapeutic effects of evaluated CCRT are comparable with the results from the randomized phase III studies performed to compare CCRT versus radiotherapy alone for advanced nasopharyngeal carcinoma, we advocate the continuity of highly sophisticated 3DCRT as well as the initiation of a phase III trial addressing the definition of the precise role of sequential chemotherapy in the management of patients with locally advanced NPC. The use of novel radiotherapy technique (IMRT) in this patient category in the near future should be strongly encouraged and should also be a promising tool to achieve a higher rate of locoregional tumour control.

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Резиме

КОНКУРЕНТНА ХЕМОРАДИОТЕРАПИЈА КАЈ ЛОКАЛНО И/ИЛИ РЕГИОНАЛНО НАПРЕДНАТ НАЗОФАРИНГЕАЛЕН КАРЦИНОМ

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Целта на студијата беше да се проучи ефикасноста на конкурентната хеморадиотерапија (КХРТ) кај пациентите со локално и/или регионално напреднат назофарингеален карцином (НФК). Во периодот од февруари 2005 до ноември 2007 година, 27 пациенти со напреднат НФК беа вклучени во проспективна студија за конкурентна хеморадиотерапија во Институтот за радиотерапија и онкологија во Скопје. Радиотерапијата беше спроведувана со примена на софистицираната тридимензионална конформална техника. Остварената доза во подрачјето на примарниот тумор и на позитивните јазли на вратот беше 69,4–71,4 Gy (средно, 69,4 Gy). Хемотерапијата се состоеше од цисплатин 30 mg/m^2 администриран еднаш неделно конкомитантно со зрачењето.

Средната возраст беше 49 години и 51,2% од пациентите беа со болест во IV стадиум. Осумдесет и осум проценти имаа примено ≥ 5 циклуси на конкурентен цисплатин. Стапките на комплетниот одговор три месеци по завршувањето на хеморадиотерапијата беа 81,5% (22 од 27), и 91,3% (21 од 23) на местото на примарниот тумор, и во подрачјето на позитивните лимфни јазли на вратот, соодветно. Локорегионален релапс беше утврден само кај еден пациент, а далечни метастази беа манифестирани кај четири

пациенти. Најчесто застапен степен 3 на акутните реакции беше мукозитот, присутен кај 63,0% од пациентите. Стапката на двегодишното преживување без знаци на болест (ПББ) беше 42,6%, стапката на двегодишното преживување без локорегионален релапс (ПБЛРР) беше 76,9% и стапката на двегодишното преживување без далечни метастази (ПБДМ) изнесуваше 63,6%.

Земајќи ги предвид прелиминарните резултати од нашата студија кои не покажуваат дека терапевтските ефекти на евалуираната конкурентна хеморадиотерапија се компарабилни со резултатите од рандомизираните фаза III студии, се препорачува рутинско користење на новите радиотерапевтски техники како што е радиотерапијата со модулиран интензитет, како и започнување на фаза III клинички испитувања за дефинирање на прецизната улога на секвенцијалната хемотерапија во лекувањето на пациентите со локално напреднат НФК.

Клучни зборови: назофарингеален карцином, радиотерапија, тридимензионална конформална радиотерапија, конкурентна хеморадиотерапија.

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