ORIGINAL PAPERS

POORLY DIFFERENTIATED LOCO-REGIONALLY ADVANCED NASO - AND OROPHARYNGEAL CARCINOMA: RESULTS OF NEOADJUVANT CHEMOTHERAPY FOLLOWED BY RADIOTHERAPY

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ABSTRACT

Over the years 1986-1997, at the Centre of Oncology in Kraków, 82 patients (28 women, 54 men; mean age: 50.8 years) with poorly differentiatied naso- and oropharyngeal carcinoma with metastases to regional nodes (stage III and IV) received neoadjuvant chemotherapy followed by teleradiotherapy. The primary tumour was located in the nasopharynx in 57 patients (69.5%), in the tonsil - in 24 (29.3%), and in the base of the tongue (one patient). Chemotherapy cycles consisted of cisplatin in a dose of 100 mg/m^2 administered intravenously on the first day, and 5-fluorouracil in a dose of 1000 mg/m^2 over days 1 to 5. Forty-seven (57.3%) patients received 3 cycles, 25 (30.5%) patients – 2 cycles, 8 (9.8%) patients – 1 cycle. After chemotherapy, patients received conventionally fractionated (200 cGy 5x a week) radiotherapy to the primary tumour (50-65 Gy) and regional nodes (50-70 Gy). The therapy was generally well tolerated, however two patients developed fatal late complications. Improvement in therapy results was observed when comparised with a historical group. Five-year overall survival was 52%. The degree of regression (PR + CR), following neoadjuvant chemotherapy, which appeared to depend on the number of chemotherapy cycles, is the main prognostic factor for this group of patients.

Poorly differentiated cancer (lymphoepithelioma, undifferentiated carcinoma) is commonly found in the naso- and oropharynx, although its general incidence in non-endemic areas is rather low (Chan et al.,1998; Reddy et al., 1995). In patients with poorly differentiated cancer of naso- and oropharynx (PDCNO), even with a locally advanced disease and regional node involvement, it is relatively easy to obtain loco-regional control of the disease with adequate dose and tumour coverage. About 20-30% of patients with a loco-regionally controlled disease will eventually die of distant metastases (Teo et al., 1996). Thus, many authors recommend adjuvant chemotherapy in node-positive patients with PDCNO (Al-Sarraf and McLaughlin, 1995; Chan et al., 1998; Garden et al., 1996; Geara et al., 1997; Munro, 1995; Wong, 1998).

In the mid 'eighties, patients with PDCNO were treated at the Oncology Centre in Kraków (Poland) by radiotherapy alone (years 1970 - 1980), or by radiotherapy combined with neoadjuvant monochemotherapy using methotrexate (years 1981 - 1985). Review of the results of these treatments indicated that the clinical status of the cervical nodes is an independent prognostic factor. In the group of patients with negative nodes (N0 according to TNM UICC classification, 1987), 3-year disease-free survival was achieved in 86% of the patients, while the respective ratios in patients with nodal metastases N1, N2 and N3 were 57%, 21% and 3% (Reinfuss et al., 1991; Reinfuss, 1981).

Our observations are in accord with those of other authors (Chan et al., 1998; Cheng et al., 1998; Lee et al., 1992; Teo et al., 1996). We have also found that distant metastases were the cause of failure in 90% of our patients. The use of methotrexate in adjuvant therapy neither improved the results of the treatment nor changed the distribution of the causes of radiotherapy failures. Therefore, in positive - node PDCNO patients a study of radiotherapy combined with neoadjuvant chemotherapy (cisplatin and 5-fluorouracil) began in 1986 (Radkowski et al., 1997). In this paper we present the updated results of this study.

MATERIAL AND METHODS

Over the years 1986 - 1997, eighty-two patients (28 women and 54 men) with PDCNO with metastases to the cervical nodes were treated for the first time at the Oncology Centre in Kraków. Their median age was 50.8 years (14 - 76 years). Fifty-seven (69.5%) patients had cancer of the nasopharynx, 25 (30.5%) - of the oropharynx (in 24 patients the palatine tonsil, in 1 patient the base of the tongue were involved). The performance status of the patients, on Karnofsky's scale, ranged between 60 and 100 (median 80).

Twelve (14.6%) patients had stage T1 PDCNO, 33 (40.2%) patients - T2, 19 (23.2%) patients - T3 and 19 (22.0%) patients -T4. All patients had metastatic cervical nodes, of the diameter ranging between 1 cm and 15 cm (median 5.5 cm). In 10 (12.2%) of these patients the diameter of the involved nodes did not exceed 3 cm (N1), in 22 (26.8%) patients it ranged between 3 cm and 6 cm (N2), and in 50 (60.0%) patients it exceeded 6 cm (N3). The detailed clinical staging of our patients is presented in table 1.

Primary Tumour / Nodes	T 1	T 2	T 3	T 4	Total
N 1	1	2	2	5	10 (12.2%)
N 2	4	10	8	0	22 (26.8%)
N 3	7	21	9	13	50 (61.0%)
Total	12 (14.6%)	33 (40.2%)	19 (23.2%)	18 (22.0%)	82 (100%)

Table 1. Stage of disease in 82 patients with PDCNO treated by chemo- and radiotherapy.

Chemotherapy consisted of cisplatin in a dose of 100 mg/m^2 administered intravenously on day 1, and 5-fluorouracil in a dose of 1000 mg/m^2 over days 1 through 5. Fluorouracil was administered by intravenous infusion for at least 10 hours a day. Prior to each cycle of chemotherapy, complete blood count, and biochemical tests of the liver and kidney efficiency were performed. The cycles of chemotherapy were applied with 3-week intervals.

We initially planned to administer 2-3 cycles of chemotherapy depending on the degree of tumour remission and treatment tolerance. Forty-seven (57.3%) patients received three complete cycles of chemotherapy, 25 (30.5%) patients - 2 cycles, 8 (9.8%) patients - only one cycle. Four (50%) of the patients had partial remission after only one cycle. After two cycles of chemotherapy we observed partial remission in 16 patients (64%) and in 6 patients (24%) complete remission. In 9 of 33 patients (27.3%) we stopped chemotherapy after1or 2 cycles because of the toxicity G3-4. Two (2.4%) patients received 4 and 6 cycles due to extended delay in commencing radiotherapy.

Radiotherapy was initiated 3 - 4 weeks after completion of chemotherapy. In the first phase, the whole pharynx was irradiated for five weeks with 50 Gy in 25 fractions by two opposed cobalt-60 beams. Cervical nodes with the larynx shielded were irradiated with 50 Gy in 25 fractions by one anterior cobalt-60 beam. In 69 (84.2%) patients the bed of primary tumour was further irradiated to a total dose of 60 - 65 Gy. The involved cervical nodes were irradiated by an additional dose of 10 - 20 Gy using electron beams of 11 - 15 MeV.

The overall survival rate was calculated from the first day of chemotherapy until the date of death or last follow-up examination (censored observation). Disease-free survival rate was calculated from the day of complete regression of the disease evaluated by clinical examination until the first evidence of disease relapse, distant metastases, or last follow-up examination. For graphic presentation of the

survival rate, the Kaplan-Meier method was used, for calculations - the Statsoft Statistica programme. The accepted level of statistical significance was $P \leq 0.05$.

RESULTS

At the end of our observation period, of the 82 patients treated, 53 patients were alive, including 45 disease-free; 29 patients died, 6 without cancer (2 patients died of necrosis of the posterior pharyngeal wall, one patient of prostate carcinoma, one patient of malignant lymphoma, and two patients of circulatory insufficiency). The median observation time was 21 months, observation time ranging from 5 months to 105 months). Figure 1 shows the follow-up of all 82 patients qualified for treatment and figure 2 shows the overall and disease-free survival curves of our patients. Fifty-two percent of overall and forty-seven percent of disease-free 5-year survival were obtained.

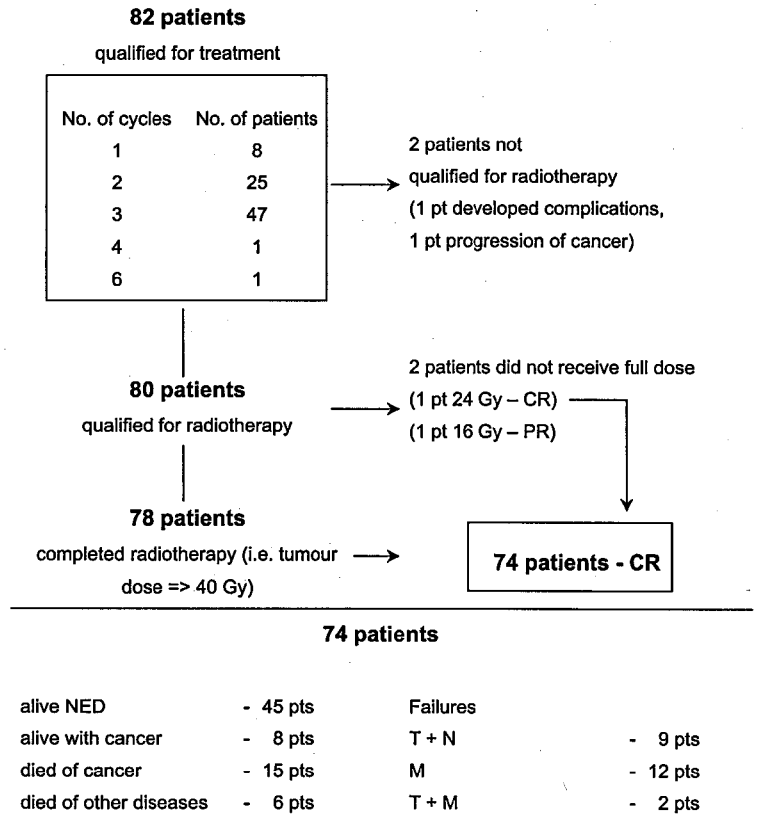

Fig. 1. Follow-up of 82 patients with PDCNO treated with chemo - and radiotherapy.

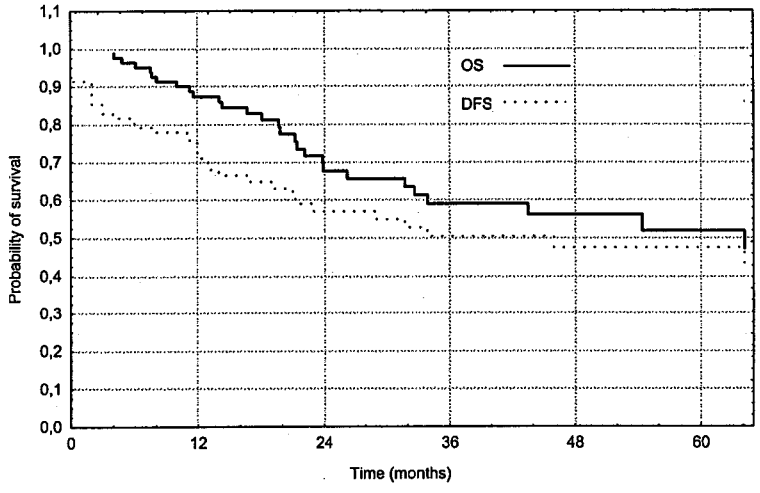

Fig. 2. Overall survival and disease-free survival in a group of 82 patients with PDCNO.

The effectiveness of neoadjuvant chemotherapy was high: in 18 (21.9%) patients complete remission of disease (CR), in 50 (61.0%) patients partial remission (PR), and in 11 (13.4%) patients disease stabilisation (MR + NC) were observed. In three (3.7%) patients the disease progressed during chemotherapy. In 68 (82.9%) patients with significant response to chemotherapy (PR + CR), there appeared to be a relation between the percentage of responses and the number of chemotherapy cycles. After one cycle only 4.9% of partial remissions were observed, while 19.5% and 35.4% of partial remission were seen after two and three cycles, respectively. Complete remission of disease was obtained in 7.3% of patients after two cycles, and in 14.6% of patients after three cycles of chemotherapy (Figure 3).

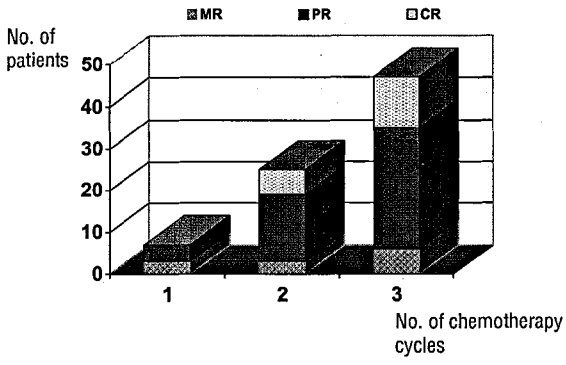

Fig. 3. Relation between number chemotherapy cycles and regression of tumour after chemotherapy.

Toxicity	N	%
Vomiting (G3-4)*	4	4.9
Trombocytopenia (<100 x10^9/l)	6	7.3
Leucopenia (<2.0 x10^9/l)	3	3.7
Infection (treated with antibiotics)	4	4.9
Anaemia (transfusions)	3	3.7
Renal insufficiency	2	2.4
Exacerbation of circulatory insufficiency	3	3.7
Increase of hepatic transaminase activity	1	1.2

* - toxicity scale according to WHO.

Table 3. Toxicity of induction chemotherapy in 82 patients with PDCNO, leading to cessation of treatment or extension of the interval between chemotherapy cycles.

Most patients tolerated chemotherapy well. Only three patients had exacerbation of circulation insufficiency, causing a deterioration of their general condition. Further treatment of two of these patients was discontinued. Detailed information on the toxicity causing cessation of treatment or extension of intervals between chemotherapy cycles is shown in table 3. The overall percentage of serious complications following chemotherapy was 25.6%.

Seventy-eight (95.1%) patients received minimum combined therapy: at least one cycle of chemotherapy and radiotherapy dose 40 Gy for primary tumour and cervical nodes. During the course of teleradiotherapy 26 (31.7%) patients developed cutaneous or mucosal reaction G3, according to WHO intensity classification (Beretta). In one patient, irradiation was discontinued after a dose of 40 Gy, due to hepatic metastases. The median value of the total dose to the primary tumour was 60 Gy (mean: 60,2 Gy) and to the lymph nodes - 58 Gy (mean: 58,5 Gy). Thirty-five (44.9%) patients maintained the same body weight during the course of treatment, 36

(46.1%) patients lost weight within 5% and 7 (9.0%) - within 5% and 10%. Two patients died of necrosis of the posterior pharyngeal wall, 10 and 30 months after radiotherapy, respectively.

After the full course of therapy, 74 patients had complete locoregional remission (CR) (figure 1). Out of 74 complete responders 19 (25.7%) patients developed locoregional recurrence: 13 (17.6%) of these in cervical lymph nodes, 4 (5.4%) at the primary site and two (2.7%) both in the primary site and cervical lymph nodes. Of 13 patients with recurrence in cervical lymph nodes, 10 patients were successfully treated with rescue surgery, surgery and re-irradiation, or re-induction and surgery. In 15 of 82 patients distant metastases were diagnosed, i.e. in 14 of 74 patients with CR, and in one patient of 8 without CR. The metastases occurred in: bones (31.8%), liver (22.7%), central nervous system (9.0%), peripheral lymph nodes (9.0%), and lungs (4.6%).

In single - or multi-variable analysis, we investigated the influence on the overall survival of: sex, age, Karnofsky's performance status, site of the primary tumour, stage of disease, size of involved nodes, location of the nodes, and response to neoadjuvant chemotherapy.

In single-variable analysis, significantly poorer results were obtained in patients with primary tumour stage T4, nodal involvement N3, and in patients with progression or stabilisation of disease after chemotherapy (P, NC, MR). Detailed results are listed in table 2. The most important factor negatively influencing the prognosis of outcome in multivariable analysis was lack of regression of the disease after neoadjuvant chemotherapy.

Population and clinical features or treatment	Number of patients	Probability of overall 5-year survival	Statistical significance
Total:	82	52.0	
Sex:			
Female	28	58.0	
Male	54	46.0	p = 0.29
Age:			
≤39 years	17	61.0	
>39 years	65	49.0	p = 0.66
Karnofsky's performance status:			
<80%	23	31.0	
≥80%	59	61.0	p = 0.08
Site:			
nasopharynx	57	49.0	
oropharynx	25	58.0	p = 0.9
Primary tumour*:			
T 1 - 3	64	65.0	
T4	18	21.0	p = 0.008
Nodes*:			
N 1 - 2	32	83.0	
N 3	50	39.0	p = 0.005
Node site:			
Upper	62	54.0	
Lower	20	44.0	p = 0.08
Size of bulky nodes:			
1 - 8 cm.	69	56.0	
> 8 cm.	13	33.0	p = 0.25
Number of chemotherapy cycles:			
1	8	45.0	
2 - 3	74	51.0	p = 0.61
Response after chemotherapy:			
MR, NC, P	14	29.0	
CR, PR	68	60.0	p = 0.007

*assessed according to UICC (Beretta).

Table 2. 5-year overall survival versus clinical characteristics and response to chemotherapy.

DISCUSSION

The group studied consisted of 82 patients with PDCNO with cervical node involvement (N1 – 3), with median 5.5 cm of diameter. In this group, 52% of the overall 5-year actuarial survival rate and 47% of disease-free survival rate were achieved using combined neoadjuvant chemo- and radiotherapy. In comparison with a historical group of patients with disease at a similar stage, treated in the years 1970 - 1985 with radiotherapy alone or radiotherapy combined with adjuvant monochemotherapy using methotrexate, 3-year disease-free survival was obtained in 22% of the patients. The observed improvement of the results of treatment appears to be of clinical importance. This improvement was related to the reduced risk of distant metastases. However, it should be emphasised that our investigations are still at an experimental stage. PDCNO is a relatively rare neoplasm, therefore we have to base our comparison on a historical group, which is of limited value.

It is difficult to compare our results with those of other authors, due to the immense diversity of the groups studied (Lee et al., 1992; Garden et al., 1996; Geara et al., 1997). Nevertheless, we note that neoadjuvant chemotherapy is becoming increasingly applied in the case of advanced carcinoma of the head and neck, and it is especially recommended for poorly differentiated nasopharyngeal - type carcinoma (Chan et al.1998; Munro, 1995). Attempts to use a new system of dose fractionation in PDCNO have not improved the results, since over 80% of patients die mainly due to metastatic spread (Lee et al., 1992; Chan et al.1998). The role of neoadjuvant chemotherapy in nasopharygeal carcinoma has been examined in three randomized trials. In each trial a different approach was used with respect to drug combinations, time sequence of chemotherapy and radiotherapy administration, and radiotherapy technique and dose. In the chemotherapy arm a tendency to reduce the incidence of recurrences and improvement of disease-free survival were seen in the subgroup of patients with bulky neck lymph nodes greater than 6 cm (Chua et al., 1998; Chan et al., 1995; International Nasopharynx Cancer Study Group). The only trial to date that has shown any improvement in overall survival with the addition of chemotherapy is the recently completed Head and Neck Intergroup trial (Al.-Sarraf et al.,1995; Fu KK, 1998). One hundred and forty-seven patients with stage III and IV nasopharynx carcinoma were randomized to receive radiotherapy plus concurrent as well as adjuvant chemotherapy or radiotherapy alone. 3-year progression-free survival rates were significantly higher in the combined therapy group (69% versus 24%), P<.001), as well as the overall survival rates (78% versus 47%, P =.002).

Several authors concur with our observation that the level of regression of disease following neoadjuvant chemotherapy is the main prognostic factor (Garden et al., 1996; Geara et al., 1997). Our studies suggest that the possibility of achieving CR or PR is directly related to the number of given chemotherapy cycles.

In the group studied, we used neoadjuvantly cisplatin combined with 5-fluorouracil. Other authors used combinations of various therapeutic agents including doxorubicin, bleomycin, methotrexate, 5-fluorouracil, cisplatin, vinblastin, and epirubicin (Chua et al., 1998; Chan et al., 1998). Further investigations should follow, to develop the optimum time combinations of chemo- and radiotherapy, the most effective chemotherapy regimen, and the most appropriate target group.

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