NOWOTWORY Journal of Oncology • 2003 • volume 53
Number 4• 414–421

Radiotherapy for squamous cell carcinoma of the oropharynx: long term results and multivariate analysis of prognostic factors

Zbigniew Szutkowski, Andrzej Kawecki, Andrzej Hliniak, Elżbieta Kraszewska

Introduction. The aim of the study was to analyse the results of treatment and prognostic factors related to clinical and therapeutic characteristics in patients with oropharyngeal cancer.
Methods. 241 patients with proven oropharyngeal cancer were irradiated with radical intent at the Maria Sklodowska-Curie Memorial Cancer Centre and Institute of Oncology in Warsaw between 1984 and 1995. The total dose ranged between 66 and 72Gy delivered in 2Gy fractions 5-times weekly. The majority of patients presented as advanced cases T3, T4 – 152 patients (63%) and N2, N3 – 89 patients (37%).
Curves of overall survival and local, regional control were estimated using the Kaplan-Meier method. Analysis of the prognostic factors was performed using Cox's multivariate proportional risk model.
Results. 5-year overall survival probability was 25%. 5-year local regional control probability in patients with complete regression after radiotherapy was 55%. WHO-2 performance status had a significantly negative influence on overall survival, as compared to WHO-0 (p=0.02). T4 stage reduced overall survival probability, as compared with others stages (p=0.04). The analysis has also shown unfavourable influence of the clinical stage N2c on overall survival. Patients with stage N2c had a three-fold higher risk of death, as compared to others (p=0.002). Hemoglobin level higher than 13g/dL reduced the risk of death, as compared to patients with hemoglobin level equal or lower than 13g/dL (0.0002). Patients with breaks during irradiation (prolonged overall treatment time) had worse prognosis, as compared to patients without breaks. This relationship was marginally significant (p=0.06). Loco-regional control analysis showed that only the hemoglobin level was significant. In patients with hemoglobin level over 13g/dL the risk of recurrence was lower than in patients with hemoglobin equal or lower than 13g/dL (p=0.013).
Conclusion. Performance status, advanced T and N stage, hemoglobin concentration and breaks during the treatment influence the overall survival of patients with oropharyngeal cancer undergoing radical radiotherapy. The level of hemoglobin was found to be the only factor influencing loco-regional control.

Radioterapia raka płaskonabłonkowego ustnej części gardła – wyniki odległe i analiza czynników prognostycznych

Cel. Celem pracy jest ocena wpływu wybranych czynników klinicznych na wyniki radioterapii stosowanej jako wyłączne leczenie chorych na raka ustnej części gardła.
Materiał i metoda. Analizie poddano 241 chorych na raka ustnej części gardła, leczonych napromienianiem z założeniem radykalnym w Centrum Onkologii w Warszawie w latach 1984-1995. U 152 chorych (63%) stwierdzono zaawansowanie miejscowe T3-4, a u 89 chorych (37%) przerzuty do węzłów chłonnych szyi o zaawansowaniu N2-3. U wszystkich chorych przeprowadzono radioterapię z założeniem radykalnym (frakcjonowanie konwencjonalne, założona dawka całkowita 66--72 Gy). Krzywe przeżycia całkowitego i przeżycia bez nawrotu miejscowego i regionalnego estymowano przy użyciu metody Kaplana-Meiera. Wpływ czynników klinicznych na czas przeżycia i czas bez nawrotu miejscowego i regionalnego oceniono za pomocą wielowariantowego modelu proporcjonalnego ryzyka Coxa.
Wyniki. 5-letnie przeżycie całkowite wyniosło 25%. 5-letnie przeżycie bez nawrotu loko regionalnego u chorych, u których uzyskano całkowitą regresję nowotworu, wyniosło 55%. Analiza statystyczna dotycząca czasu przeżycia całkowitego wykazała, że chorzy ze stopniem sprawności WHO-2 mieli znamiennie gorsze rokowanie w porównaniu z chorymi ze stopniem WHO-0 (p=0,02). Zaawansowanie miejscowe raka T4 wiązało się ze skróceniem czasu przeżycia całkowitego chorych w porównaniu do pozostałych, o mniejszym zaawansowaniu (p=0,04). Stwierdzono wyjątkowo niekorzystny wpływ na przeżycie całkowite obustronnego lub przeciwległego do guza pierwotnego zajęcia węzłów chłonnych, wykazując 3-krotnie więk-

Department of Head and Neck Cancer
The Maria Sklodowska-Curie Memorial Cancer Center
and Institute of Oncology, Warsaw, Poland

sze ryzyko zgonu u chorych z cechą N2c (p=0.002). Istotnym czynnikiem wpływającym niekorzystnie na czas przeżycia całkowitego, okazał się niski poziom hemoglobiny (p=0,0002). Również chorzy, u których stosowano przerwy w napromienianiu, mieli gorsze rokowanie w porównaniu do pozostałych (p=0,06). Jedynym istotnym statystycznie czynnikiem, wpływającym na czas przeżycia bez progresji miejscowej lub regionalnej, w oparciu o wyniki analizy wielowariantowej, okazało się stężenie hemoglobiny (p=0,013).

W n i o s k i. Czynnikami wpływającymi na czas przeżycia chorych na raka ustnej części gardła, poddanych radykalnej radioterapii, są stopień sprawności, zaawansowanie loko regionalne raka, stężenie hemoglobiny oraz przerwy w napromienianiu. Jedynym czynnikiem wpływającym na ryzyko nawrotu loko regionalnego okazało się stężenie hemoglobiny.

Key words: oropharyngeal cancer, radiotherapy, prognostic factors
Słowa kluczowe: rak ustnej części gardła, radioterapia, czynniki prognostyczne

Introduction

Oropharyngeal cancer is a relatively frequent malignancy of the head and neck. In 1999 more than 700 new cases of the oropharyngeal cancer were diagnosed in Poland [1]. The most frequent pathological type of oropharyngeal cancer is squamous cell carcinoma. Other pathological types are very rare in this localization.

Squamous cell carcinoma of the oropharynx may, potentially, be treated with irradiation, as it has a relatively low rate of distant metastases – less than 20%. Conventionally fractionated radiotherapy alone seems to be an effective treatment for early stages of the disease (T1-2; N0-1). In more advanced stages of oroharyngeal cancer (T3-4 and / or N2-3) the results of radical radiotherapy are poor. It is expected that about 60% of patients with locally advanced disease are not cured after radiotherapy, or have local recurrence. Alternative treatment is surgery, followed by adjuvant radiation. Combined modality treatment with surgery is the method of choice in the United States and in some centers in Western Europe. However, the rate of loco-regional failure after surgery and radiotherapy is also high. Surgical procedures are also problematic because the cosmetic and functional effects of wide resection and reconstruction are often unsatisfactory. Currently the majority of patients with locally advanced oropharyngeal cancer are referred for modern treatment, such as concomitant radiochemotherapy, or unconventionally fractionated radiotherapy.

Results of radiotherapy for oropharyngeal cancer depend on both tumor and patient characteristics, as well as on several factors connected with the treatment. The influence of factors which characterize the patient and the tumor is rather well known, while the predictive and prognostic value of the othert factors remains unclear, and even controversial. The importance of the total dose, dose per fraction, overall treatment time, and the presence, reasons for and duration of breaks in radiotherapy have been discussed for a long time.

The aim of this study is to summarize the long-term results and to estimate the influence of the clinical and treatment-related factors on radiotherapy outcome in patients with oropharyngeal cancer.

Material and methods

Between February 1984 and December 1995, 432 patients with microscopically proven squamous cell carcinoma of the oropharynx have been registered in the Department of Radiotherapy of the Maria Sklodowska-Curie Memorial Cancer Center and Institute of Oncology in Warsaw. 241 patients were referred for radical radiotherapy. Another 7 patients were qualified for surgery followed by radiation. 133 patients were referred for palliative irradiation. 30 patients were suitable for symptomatic care only due to a poor performance status. The remaining 21 patients decided to be treated in other centers.

All 241 patients referred for radical radiotherapy were analysed. The clinical stages of the disease were established based on the TNM UICC classification from 1987[2].

The analysis was performed basing on the data from individual registered case reports. Patients who had received below 50 Gy were excluded from the local control analysis – i.e. a few patients who discontinued therapy due to medical reasons or refusal. All patients were included into overall survival analysis. Between 1984 and 1995 the same medical staff was engaged in the radiation treatment according to a uniform therapeutic protocol. Cobalt-60 therapy was applied in 234 (97%) patients. Seven patients were treated with photon beams of energy range between 4 and 15 MeV.

Immobilization of the head and neck region with orfit or celon shells and simulator for treatment planning were applied in all cases. The medical physics team performed the calculations of dose homogeneity in the irradiated volume. Initially we used manually prepared outlines. Mevaplan system basing on CT imaging has been used for treatment planning since 1987. The primary site and the upper neck lymph nodes were irradiated with the parallel opposite fields technique. The one-field technique was used for lower neck, supraclavicular and superior mediastinal lymph nodes if irradiation of this region was necessary.

Conventional dose fractionation (1.8-2.0 Gy per fraction once daily for 5 days a week) was usually used (98% of patients). The planned total dose was 66-70 Gy. Deviations from protocol were made in patients who showed a lack of complete regression after the prescribed dose. In these cases the total dose was increased. During irradiation of the primary site and of upper neck nodes, after delivering a dose of 44 Gy the spinal cord was protected. The dose to the posterior necks lymph nodes was increased to 50-60 Gy with 9-10 MeV electron. In case of lack of complete regression of the metastatic lymph nodes after the prescribed dose the total dose was increased with electrons. The usual elective dose for lower neck, supraclavicular and upper mediastinal lymph nodes was 50 Gy.

Patient and tumour characteristics are presented in Table I. Factors connected with the applied therapy are presented in Table II. The retrospective character of the analysis limits the possibilities to investigate the influence of the total doses and doses per fraction, because the method of dose fractionation and the total dose do not exceed routinely used radical doses.

Table I. Clinical material

	N=241
Sex	
Female	27 (11%)
Male	214 (89%)
Age	
(min, max)	(35, 86)
median (std. dev.)	58 (10.5)
WHO	
0	88 (37%)
1	130 (54%)
2	22 (9%)
Incomplete data	1
Localisation	
Tonsil	96 (40%)
Soft palate	17 (7%)
Base of the tongue	34 (14%)
Retromolar trigone	10 (4%)
Lateral/posterior wall	10 (4%)
2, 3 subsite	74 (31%)
Histopathology	
Well differentiated	39 (16%)
Moderate differentiated	79 (33%)
Poor differentiated	54 (22%)
Not defined	69 (29%)
T	
T1	17 (7%)
T2	72 (30%)
T3	109 (45%)
T4	43 (18%)
N	
N0	81 (34%)
N1	60 (25%)
N2 ab	51 (21%)
N2 c	14 (6%)
N3	34 (14%)

Table II. Treatment characteristics

	N=241
Beam	
4 MeV	1 (0.4%)
9 MeV	4 (2%)
10 MeV	1 (0.4%)
15 MeV	1 (0.4%)
Co60	234 (97%)
Dose per fractions	
150	1 (0.4%)
160	1 (0.4%)
180	55 (23%)
200	180 (75%)
220	1 (0.4%)
225	1 (0.4%)
300	2 (1%)
Total dose	
(min, max)	(700, 7600)
medium (25%, 75%)	6600 (6600, 7000)
Treatment interruptions	138 (57%)
< 5 days	24 (17%)
6 - 10 days	51 (37%)
> 10 days	63 (46%)
Complete remission (CR) at the end of treatment	153 (63%)
CR 4 weeks after end of treatment	175 (73%)

The influence of the overall treatment time on survival and local control was estimated indirectly by analyzing the length of the breaks divided in 3 categories: up to 5 days, between 6-10 days and above 10 days. The reasons for breaks were also analyzed. The influence of complete regression (with reference to survival and local control) was estimated up to 4 weeks from the end of treatment.

Statistical methods

Parameters characterizing patients were analyzed using standard statistic tools: mean and standard deviation, median and quartile and the frequency tables. Curves of overall survival and local control were estimated using the Kaplan-Meier method. Analysis of the prognostic factors was performed using Cox's multivariate proportional risk model. With the use of backward selection the statistically significant variables were set at $p=0.05$.

The following factors were included into analysis: WHO performance status, primary tumor site, pathology, clinical T N stage, blood count (RBC, Hb, HCT), presence and length of the breaks during treatment.

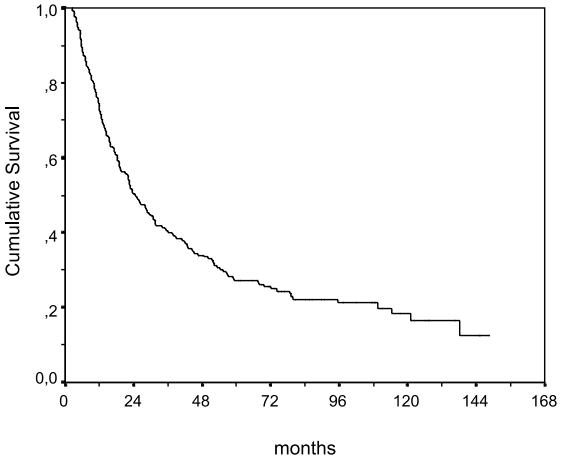
The correlation between the WHO performance status and hemoglobin concentration was investigated using the $\chi 2$ test.

Results of the treatment

Overall survival analysis

Five year overall survival for all 241 analyzed patients was 25%. The overall survival curve is presented in Figure 1. Median survival time was 24 months, 95% C.I. = (19.7, 29.1). Five year overall survival was 39% (6 patients) for clinical stage T1, 36% (21 patients) for T2, 25% (23 patients) for T3 and 13% (5 patients) for T4. Statistical analysis showed that in the case of clinical stage T4 the risk of death was 2 times higher, as compared to patients with clinical stage T1 ($p=0.04$). This correlation is presented in Table III.

233 patients (8 patients were excluded from this analysis due to incomplete data) were included in the multivariate analysis aimed at estimating the influence of the analyzed factors on the overall survival. Results of



241	118	75	41	21	nb. events	mediana
100%	50%	34%	25%	21%	184	24.4 [19.7, 29.1]

Figure 1. Overall survival

Table III. Overall survival analysis

N=233	RR	95% C.I. dla RR	p
WHO			
2 vs 0	1.9	[1.1, 3.3]	0.02
1 vs 0			0.44
N			
N2c vs N0	2.6	[1.4, 5.0]	0.002
N3 vs N0			0.15
N2 ab vs N0			0.97
N1 vs N0			0.74
T			
T4 vs T1	2.2	[1.0, 4.7]	0.04
T3 vs T1			0.33
T2 vs T1			0.97
HB			
> 13 vs ≤ 13	0.54	[0.40, 0.75]	0.0002
Interruption during the treatment yes vs no breaks	1.3	[1.0, 1.8]	0.06

this analysis stress the significant influence of the following factors on survival: WHO performance status, clinical stage T and N, hemoglobin concentration and the presence and length of the breaks during treatment. The results of this analysis are presented in Table III. We have proven the influence of the WHO performance status on survival. Patients with WHO performance status 2 had significantly worse prognosis, than patients with ratio WHO performance status 0 (p=0.02). The influence of clinical stage T on survival was statistically significant in patients with stage T4, as compared to those with stage T1 (p=0.04). For clinical stages T2 and T3 no statistical significance was noticed. Influence of the presence or lack of metastases to lymph nodes of the neck (N0 versus N+) was not proven. However, the analysis has shown the unfavorable influence of clinical stage N2c for survival. Patients with clinical stage N2c had three-fold higher risk of death, as compared to all others (p=0.002). Hemoglobin (Hb) concentration was also found to be a factor with significant influence on survival. Hb level above 13g/dL reduced the risk of death by half, as compared to the patients with Hb level equal or lower than 13g/dL (p=0.0002). We have also found a correlation between Hb level lower than 13g/dL and poor performance status (WHO 2) (p=0.034). This correlation is presented in Table IV.

Patients with breaks during radiation resulting in prolonged overall treatment time had worse prognosis, as compared to patients without treatment breaks. This relationship was marginally significant (p=0.06). Statistically significant influence on survival was observed in patients with treatment breaks lasting up to 5 days (p=0.01). No significant influence on survival was observed in patients with longer breaks in the treatment. Other analyzed factors, such as tumor localization within the oropharyngeal region, cancer differentiation and blood count parameters other than Hb had no significant influence on survival.

Overall survival curves, including significant factors such as the WHO performance status, clinical stages T and N, breaks in treatment and hemoglobin level are presented on Figure 2.

Table IV. WHO performance status and hemoglobin concentration influences

WHO	≤ 13	> 13	p
0	24 (31%)	63 (40%)	0.034
1	41 (53%)	86 (54%)	
2	12 (16%)	9 (6%)	
Total	77 (100%)	158 (100%)	

Local control analysis

Survival period without recurrences in the primary site and necks lymph nodes was defined for patients who had complete regression (CR) up to 4 weeks after the end of the irradiation. This is a period between the end of treatment and the diagnosis of loco-regional recurrence or the latest follow up visit without symptoms of recurrence. Patients, who had died within 2 months after the last follow up visit, when no recurrence was observed have been assessed according to the date this visit.

The survival curve without loco-regional recurrence for 175 patients who had CR after the treatment is presented in Figure 3. The probability of 5-year survival without loco-regional recurrence was 55%. The probability of 5-year survival without loco-regional recurrence was 65% for patients with stage T1 (5 patients), 68% (16 patients) for stage T2, 51% (17 patients) for stage T3 and 39% (5 patients) for stage T4. 166 patients entered the multivariate analysis. Five patients were withdrawn due to incomplete data and four due to control time equal to 0. Multivariate analysis showed that only Hb level had a significant influence on survival without loco-regional recurrence. In the group of patients with Hb level above 13g/dL the risk of recurrence was lower by 40%, as compared to patients with Hb level equal or lower than 13g/dL (p=0.013). These results are presented in Table V. Other analyzed factors had no significant influence on survival without loco-regional recurrence.

Table V. Loco - regional control analysis

N=166	RR	95% C.I. dla RR	p
HB			
> 13 vs ≤ 13	0.62	[0.43, 0.9]	0.013

Curves illustrating the influence of the Hb level on survival without loco-regional recurrence are presented in Figure 4.

Figure 2. Survival curves for different prognostic factors

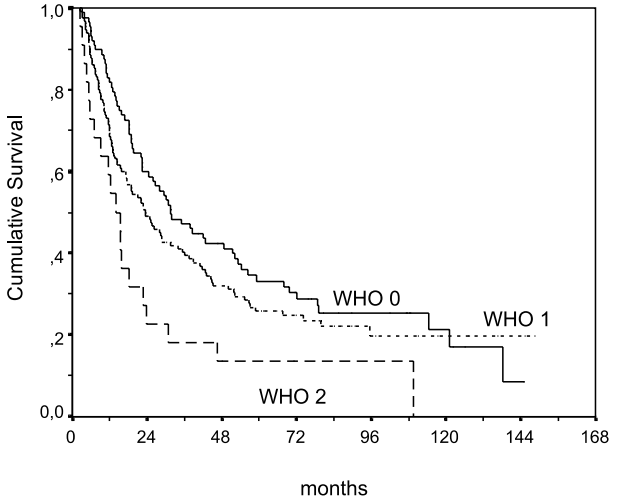


Figure 2 (1)

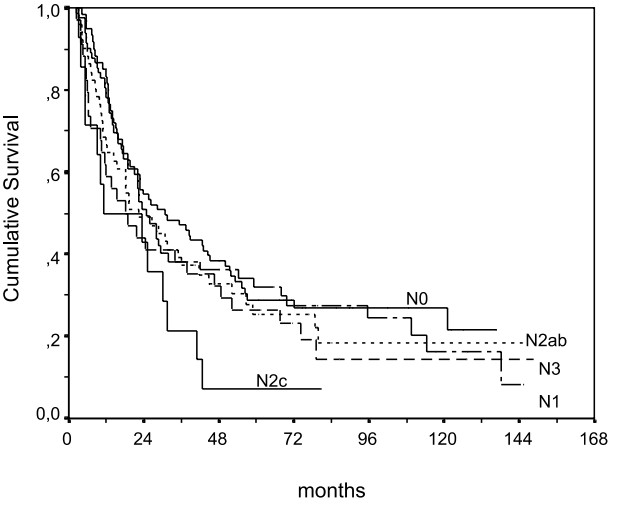


Figure 2 (2)

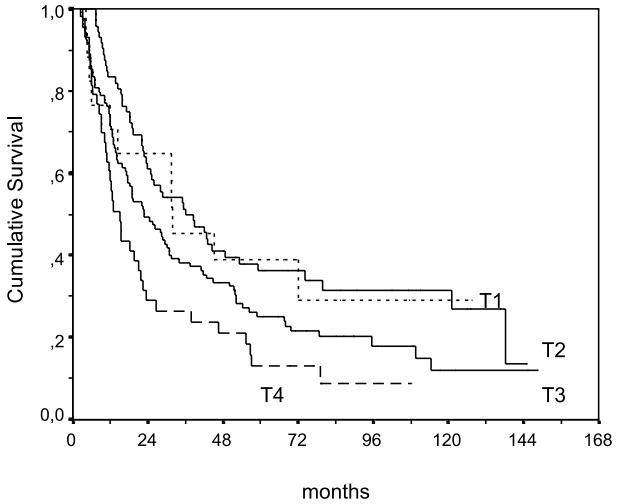


Figure 2 (3)

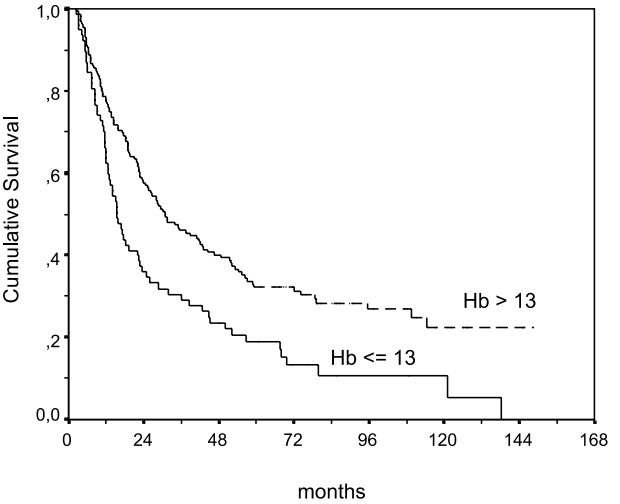


Figure 2 (4)

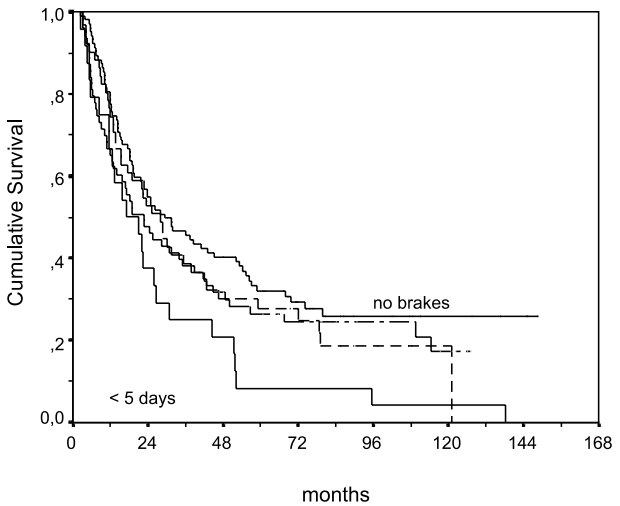


Figure 2 (5)

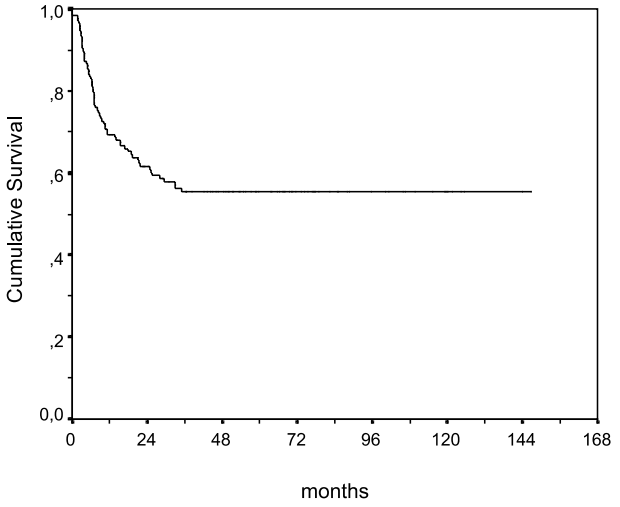
Pattern of failure

Failures connected with cancer were observed in 57% (138 patients). 76% (184 patients) died.

Failures in the primary site (no complete regression after radiotherapy or recurrences) were observed in 47% (112 patients). Neck lymph node recurrences were frequently accompanied by progression in the primary site and amounted to 23% (56 patients). Distant metastases occurred in only 6% (14 patients). Second primary malignancies occurred in 4% (10 patients). These results are presented in Table VI.

Table VI. Treatment failures

Failures	138 (57%)
Local recurrences	112 (47%)
Lymph node metastases	56 (23%)
Distant metastases	14 (6%)
Second malignancy	4 (10%)
Death	184 (76%)



175	81	59	30	16	nb. events	mediana
100%	62%	55%	55%	55%	68	-

Figure 3. Loco - regional control

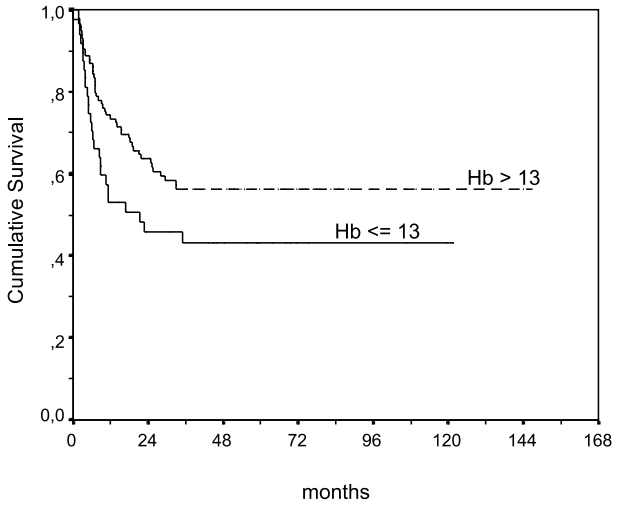


Figure 4. Loco - regional control curves depending on haemoglobin concentration

Treatment tolerance

Early toxicity was estimated according to modified Dische scale. Acute radiation reactions in patients treated before 1990 were re-classified basing on the case record entries. Numerical and percentage comparison of early reactions is presented in Table VII. The use of the feeding tube, justified by heavy dysphagia, was necessary in 21% of patients. Dry desquamation of epidermis occurred in 81% patients while the moist reaction in 30%. Despite of the confluent mucositis in 62% of patients and intensive pain on swallowing in 29% cases, opioids were used only in 2% of patients.

Late toxicity was estimated during follow up visits after the termination of treatment and after disappearance of early reaction. Intensive xerostomia was observed in 6% of patients of the 51% with this symptom. Laryngeal oedema was observed in 3% cases. Cartilage necrosis was not observed. Post-radiation bone necrosis is one of the most serious side effects after radiotherapy. Bone necrosis had occurred in 4 cases, which amounts to 2% of all analyzed patients. Late reactions are presented in Table VIII.

Table VII. Early toxicity

	N=241
Pain at swallowing	
No	8 (3%)
Moderate	163 (68%)
Severe	69 (29%)
Missing	1
Dysphagia	
No	27 (11%)
Moderate	163 (68%)
Severe	49 (21%)
Missing	2
Need for analgesia	
General analgesia	222 (98%)
Narcotics	5 (2%)
Missing	14
Erythrema	
No	4 (2%)
Moderate	126 (52%)
Severe	111 (46%)
Dry desquamation	
Yes	195 (81%)
No	45 (18%)
Missing	1
Moist desquamation	
Yes	72 (30%)
No	167 (70%)
Missing	2
Mucositis	
No	21 (9%)
Patchy	69 (29%)
Confluent	151 (62%)

Table VIII. Late toxicity

	N=241
Xerostomia	
No	93 (42%)
Moderate	114 (51%)
Severe	14 (6%)
Missing	20
Larynx oedema	
Yes	225 (97%)
No	6 (3%)
Others	1 (0.4%)
Missing	9
Osteonecrosis	
No	227 (98%)
Yes	4 (2%)
Missing	10

Discussion

Retrospective analysis refers to patients with squamous cell carcinoma of the oropharynx qualified and treated with radical radiotherapy at the Department of Radio-

therapy of the Maria Sklodowska-Curie Memorial Cancer Center and Institute of Oncology in Warsaw over a period of 11 years. The object of this work was not only to present our results, but also to estimate the prognostic role and impact of the clinical factors as well as the factors connected with treatment on the overall survival and loco-regional control.

Five-year overall survival amounts to 25% and is similar to results presented by other authors basing on clinical material with similar loco-regional stages of the disease [3, 4]. In the presented material 152 patients (63%) had T3 or T4 stage tumours, and 89 patients (37%) had N2 or N3 metastatic lesions in the neck lymph nodes. T stage is a well known clinical factor influencing the radiotherapy outcome. Some published data has proven that, when combined with its localization, the primary site advancement could be the only statistically significant prognostic factor in patients with oropharyngeal cancer treated with radiotherapy [3-6]. Five-year survival presented by different authors ranged from 70 to 90% in T1 patients, 50 to 60% in T2 patients, 30 to 50% in T3 patients and from 10 to 25% in T4 patients [5]. In the presented analysis we observed a significant influence of the T stage on overall survival. These results agree with data of other authors.

Looking at the survival curves (Figure 2) one can notice that curves for T1 and T2 almost overlap. The course of the T3 curve correlates with a lower survival ratio, but statistical significance was not proven for this stage. Friesland [4] presents similar statistical insignificance between survival in patients with T2 and T3. He explains it with the high percentage of metastases in cervical lymph nodes in T2 with N3 supremacy. It seems that the presence of N2abc and N3 in 37% cases in our material explains the obtained results.

The presence and magnitude of metastases in the neck lymph nodes is an important factor with influence on the overall survival in patients with oropharyngeal cancer [6, 7].

Although the percentage of 5-year overall survivals shows the influence on the presence of metastases in lymph nodes (N0 versus N+), no statistical significance was found in these groups. In the analysis of separate categories (N0, N1, N2abc, N2c and N3) statistically significant difference was observed for group N2c. It correlated with a three-fold risk of death while other categories were not statistically significant.

Lack of the significant influence of stage N+ on survival was also observed in other published data, while the unclear selective significance of worse prognosis of N2c patients is not more surprising than worse results in N0 versus N1 patients obtained by other authors [4].

According to the present opinion overall treatment time with the constant total dose has influence on local and regional recovery, thus resulting in survival. Prolongation of the treatment time is connected with worse prognosis [8-12]. Only Bataini's study [6] presents different results. It was also confirmed by own earlier experiences [13]. In the presented analysis we observed the influence of the prolongation of overall treatment time on survival by analyzing the influence treatment breaks in 3 categories: up to 5 days, 6-10 days and over 10 days. The highest ratio of 5-year survival was observed in patients without treatment breaks. The increase of the risk of death was found in patients with breaks, as compared to patients without breaks. The influence of breaks above 5 days was not statistically significant while breaks up to 5 days influenced worse prognosis.

Radio-resistance arising from hypoxia, is still a controversial issue to be discussed. The influence of Hb concentration – the factor responsible for oxygenation of tissues – on local recovery was proven by other authors [14]. In the presented analysis Hb over 13 g/dL had significant influence on treatment results (overall survival) and, as the only statistically significant factor, on loco-regional control.

Performance status is a patient-dependant prognostic factor. Many papers show that poor performance status is connected with worse response to treatment [13, 15]. Analysis of our data has proven the influence of worse performance status on survival. WHO-2 was connected with 2 times higher risk of death, as compared with WHO 0-1. We have also shown a correlation between worse performance status and lower Hb level. The connection between Hb concentration and the performance status has been suggested by other authors [13, 15].

Other clinical factors and factors connected with the treatment did not influence overall survival and local control.

Oropharyngeal cancer belongs to a group of malignancies in which patient and tumor characteristics may dominate over treatment-related factors [16]. According to some authors the T and N stages are the only significant prognostic factors which influence survival [3-6]. Improvement in radiotherapy outcomes may result from the administration of significantly higher doses while minimizing the risk of late reactions – after the application of a few fractions per day [17-19], using accelerated fractionation schedules as well as new possibilities of scheduled therapy. 3D planning allows for a precise definition of the irradiated volume and for the maximum protection of critical organs.

Summary

Oropharyngeal cancer in the initial T stage is hardly recognizable. We have proved that at the moment of classification we usually deal with locally advanced tumor T3, T4, N2abc, N3, which influences treatment results. Moreover, 1/5 of patients with stage T2 had metastases in lymph nodes (N2abc, N3). It explains the lack of differences in the survival curve for T2 and T3.

In the analysis of overall survival a constant decrease of the survival ratio is observed. When comparing survival without loco-regional recurrence with overall survival we can state that local and regional recurrence occurs up to 2 years after treatment, while later the risk of occurrence is close to nill.

The decrease of the survival ratio 3 years after treatment termination should be explained in detail, since the death of patients is connected with generalization of the disease – distant metastases were observed in 6% of patients and second primary carcinoma was observed in 4% of patients. These patients have died for other reasons, which should be identified and the role and significance of which should be estimated.

Hemoglobin level turned out to be an important factor, which influences the possibility of local and regional recovery as well as overall survival and survival without symptoms. Clinical observations and the results of the analysis have proved the correlation between Hb level and patients' WHO performance status. Both factors influence treatment results, while a lower Hb level accompanied by worse performance status defines the group of patients with worse prognosis.

Zbigniew Szutkowski MD, PhD
Department of Head and Neck Cancer
The Maria Sklodowska-Curie Memorial Cancer Center
and Institute of Oncology
Roentgena 5 str. 02-781 Warsaw, Poland

References

1. Didkowska J, Wojciechowska U, Tarkowski W et al. *Nowotwory złośliwe w Polsce w 1999 roku*. Warszawa: Centrum Onkologii – Instytut w Warszawie, 2002.
2. TNM classification of malignant tumours, 4th edn, UICC, Geneve, Switzerland, Springer-Verlag, Heidelberg, 1987.
3. Perez CA, Mihir MP, Patel BA et al. Carcinoma of the tonsillar fossa: prognostic factors and long-term therapy outcome. *Int J Radiation Oncol Biol Phys* 1998; 42: 1077-84.
4. Friesland S, Fernberg JO, Lundell G et al. Prognostic impact of complete remission after preoperative irradiation of tonsillar carcinoma: a retrospective analysis of the Radiumhemmet data, 1980-1995. *Int J Radiation Oncol Biol Phys* 1999; 45: 1259-66.
5. Million RR, Cassisi JN, Mancuso AA. *Management of head and neck cancer: a multidisciplinary approach*. 2nd ed. Philadelphia: J.B. Lippincott; 1994.
6. Bataini JP, Asselain B, Jaulerry CH et al. A multivariate primary tumour control analysis in 465 patients treated by radical radiotherapy for cancer of the tonsillar region: clinical and treatment parameters as prognostic factors. *Radiother Oncol* 1989; 14: 265-77.
7. Lindelow B., Hansen H.S. The impact of lymph nodes metastases on the results of treatment by primary radiotherapy and secondary surgery in oropharyngeal cancer. *Acta Oncol* 1995; 34: 965-8.
8. Withers HR, Taylor JMG, Maciejewski B. The hazard of accelerated tumor clonogen repopulation during radiotherapy. *Acta Oncol* 1988; 27: 131-46.
9. Fowler JF, Tanner MA, Bataini JP et al. Further analysis of the time factor in squamous cell carcinoma of the tonsillar region. *Radiother Oncol* 1990; 19.
10. Taylor JMG, Withers HR, Mendenhall WM. Dose – time considerations of head and neck squamous cell carcinomas treated with irradiation. *Radioth Oncol* 1990; 17: 95-102.
11. Zajonc-Słowakiewicz A, Maciejewski B, Mistur A. Radioterapia raka migdałka. I. Ocena wyników leczenia i powikłań popromiennych. *Nowotwory* 1989; 39: 44-52.
12. Maciejewski B, Withers HR, Taylor JMG et al. II. Radioterapia raka migdałka. II. Repopulacja guza i tolerancja zdrowych tkanek. *Nowotwory* 1989: 39: 99-110.
13. Szutkowski Z, Wasilewski M, Burzykowski T. Czynniki prognostyczne w radioterapii raka ustnej części gardła. *Nowotwory* 1990; 43: 143-9.
14. Overgaard J. Sensitization of hypoxic tumor cells – clinical experience. *Int J Radiation Oncol Biol Phys* 1989; 56: 801-11.
15. Fazekas JT, Scott C, Marcial V et al. The role of hemoglobin concentration in the outcome of misonidasole-sensitized radiotherapy of head and neck cancers. *Int J Radiaton Oncol Biol Phys* 1989; 17: 1177-81.
16. Bentzen SM, Johanson LV, Overgaard J et al. Clinical radiobiology of squamous cell carcinoma of the oropharynx. *Int J Radiation Oncol Biol Phys* 1991; 1197-206.
17. Horiot JC, Bontemps P, van den Bogaert W et al. Hyperfractionation vs conventional fractionation in oropharyngeal carcinoma: Final analysis of randomised trial of the EORTC. *Radiother Oncol* 1992; 25: 231-41.
18. Mendenhall WM, Parsons JT, Cassisi NJ et al. Squamous cell carcinoma of the tonsillar region treated with radical irradiation. *Radiother Oncol* 1987; 10: 23-30.
19. Wang CC. Improved local control for advanced oropharyngeal carcinoma following twice daily radiation therapy. *Am J Clin Oncol* 1985; 8: 512-6.

Paper received: 5 March 2002
Accepted: 2 April 2003