

Original contributions

The results of postoperative irradiation for locally advanced carcinoma of the larynx

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Introduction. The aim of the study was to conduct a retrospective analysis of advanced laryngeal cancer patients treated with postoperative radiotherapy in order to assess the clinical outcome and identify prognostic factors which may alter their prognosis.

Material and methods. We retrospectively reviewed the medical records of 165 patients with advanced laryngeal carcinoma treated with postoperative radiotherapy between 1984 and 1996. Initially all patients underwent total laryngectomy combined, in 91 cases, with unilateral or bilateral neck dissection. Postoperative irradiation was initiated within 15 to 162 days after surgery (mean – 53 days). The total dose varied between 50-70 Gy with the fraction size of 2.0 Gy. The analysis of overall survival and local control was performed using the actuarial method according to Kaplan and Meier. Sex, age, performance status, T, N stages, primary tumor site, hemoglobin level, histological grade, involvement of lymph nodes, extracapsular lymph node extension, surgical margin status, presence of extension of the primary beyond larynx and/or thyroid cartilage invasion and/or subglottic extension and time from operation to start of radiotherapy were studied in multivariate analysis for the prognostic significance for both overall survival and local control.

Results. The actuarial survival for the entire group of postoperatively irradiated patients was 0.70, 0.56 and 0.43 at two, five and ten years respectively. The actuarial local control for the entire group of patients was 0.86, 0.78 and 0.75 at one, two and three years respectively and remained stable thereafter. For the overall survival – sex, positive lymph nodes and time interval between surgery and radiotherapy were found to be the significant prognostic factors. For the local control the extracapsular lymph node extension was found to be the only significant prognostic factor.

Conclusions. Combined surgery and postoperative radiotherapy is an effective treatment modality in the management of locally advanced laryngeal cancer. In multivariate analysis pathologically positive lymph nodes and the time interval between surgery and radiation were found to be the significant prognostic factors influencing the overall survival. The extra-capsular lymph node extension was found to be the only significant prognostic factor affecting local control.

In order to decrease the local recurrence rate we postulate the use of the boost dose up to 70 Gy to the small volume in the cases where capsular rupture was noticed. We recommend to start postoperative radiotherapy as soon as healing is adequate. Shortening the interval between surgery and radiation is not associated with a significant increase in treatment toxicity.

Ocena wyników pooperacyjnego napromieniania chorych na miejscowo zaawansowanego raka krtani

Wstęp. Celem pracy była retrospektywna analiza wyników pooperacyjnej radioterapii u chorych na zaawansowanego raka krtani oraz ocena wpływu czynników prognostycznych klinicznych i terapeutycznych na rokowanie.

Materiał. Materiał kliniczny stanowiła grupa 165 chorych na miejscowo zaawansowanego raka krtani, leczonych w latach 1985-1996, u których przeprowadzono uzupełniające pooperacyjne napromienianie. Wszyscy chorzy mieli wcześniej wykonany zabieg operacyjny, polegający na całkowitym usunięciu krtani, połączonym w 91 przypadkach z jednostronną lub obustronną operacją węzłów chłonnych szyi. Czas od operacji do rozpoczęcia napromieniania po operacji wyniósł od 15 do 162 dni (średnia 53). Dawka całkowita wahała się od 50 Gy do 70 Gy przy dawce frakcyjnej 2 Gy. Analizie poddano czas przeżycia oraz czas do miejscowego nawrotu. Prawdopodobieństwo przeżycia obliczano metodą Kaplana-Meiera. Zbadano wpływ: płci, wieku, stopnia sprawności, stopni zaawansowania T i N, lokalizacji nowotworu, poziomu hemoglobiny, stopnia zróżnicowania

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histologicznego, zajęcia usuniętych węzłów chłonnych, przejścia nacieku poza torebkę węzła, stopnia doszczętności zabiegu operacyjnego, obecności niekorzystnych cech rokowniczych, związanych z rozrostem guza pierwotnego (zejście pod głośnię, przejście nacieku poza granice anatomiczne krtani, naciekanie chrząstek lub kombinacja powyższych cech) oraz czasu od operacji do rozpoczęcia radioterapii na czas przeżycia oraz czas do wystąpienia miejscowego nawrotu, posługując się modelem proporcjonalnego ryzyka D.R. Cox'a.

Wyniki. Prawdopodobieństwo przeżycia 2, 5 i 10 lat wyniosło odpowiednio: 0,70, 0,56, 0,43. Prawdopodobieństwo 1,2 i 3-letniego czasu przeżycia bez miejscowej wznowy wyniosło odpowiednio: 0,86, 0,78 i 0,75 i po trzech latach pozostało na niezmiennym poziomie. Stwierdzono statystycznie istotny wpływ na przeżycie trzech czynników: płci, zajęcia węzłów chłonnych oraz czasu od operacji do rozpoczęcia radioterapii oraz jednego czynnika: obecności przejścia nacieku poza torebkę węzła chłonnego, potwierdzonego w badaniu histopatologicznym na miejscową wyleczalność.

Wnioski. Uzyskane wyniki wskazują, że pooperacyjna radioterapia jest skuteczną metodą leczenia chorych na zaawansowanego raka krtani. W analizie wielowymiarowej zmiennymi statystycznie czynnikami rokowniczymi w odniesieniu do przeżyć ogólnych są: potwierdzone w badaniu histopatologicznym zajęcie węzłów chłonnych przez przerzuty raka i długość czasu między zabiegiem operacyjnym i radioterapią oraz w odniesieniu do wyleczalności miejscowej przejście nacieku poza torebkę węzła chłonnego. W celu poprawienia miejscowej wyleczalności proponujemy podwyższenie dawki na małą objętość do 70 Gy u chorych z obecnością przejścia nacieku poza torebkę węzła. Uzupełniająca radioterapia powinna być rozpoczęta możliwie szybko po wygojeniu się rany pooperacyjnej. Skrócenie czasu pomiędzy zabiegiem operacyjnym i radioterapią nie wpływa w znaczący sposób na nasilenie odczynów popromiennych.

Key words: cancer larynx, postoperative radiotherapy, retrospective analysis

Słowa kluczowe: rak krtani, pooperacyjna radioterapia, analiza retrospektywna

Introduction

Advanced laryngeal squamous cell carcinoma (Stage III and IV) is commonly managed by radical surgery and postoperative radiotherapy. The use of adjuvant irradiation was developed empirically as elective treatment of subclinical disease present at tumour bed and regional lymphatic areas after primary operation [1]. The concept of combining both treatment modalities has been widely applied since the early sixties [2-4]. The problem of the efficacy of such a treatment policy compared to surgery alone has never been evaluated in prospective randomised clinical trials. It was only assessed in retrospective analyses [3-5]. The rationale for postoperative irradiation has been to decrease the risk of tumour recurrence at the primary site and in cervical and supraclavicular nodal regions and therefore to improve the treatment outcome. An advantage attributed to postoperative irradiation over preoperative one is better outcome and ability to identify the patients at risk for tumour recurrence following the detailed study of surgical specimens [5].

Although postoperative radiotherapy is the mainstay of treatment of advanced laryngeal cancer, yet many clinical problems connected with this sequential therapeutic option remain unanswered. The purpose of our study was to conduct a retrospective analysis of advanced laryngeal cancer patients treated with postoperative radiotherapy in order to assess their clinical outcome and identify prognostic factors which may alter the prognosis.

Material and methods

We retrospectively reviewed the medical records of 165 patients with advanced laryngeal carcinoma treated with postoperative radiotherapy between 1984 and 1996 at The IInd Department of Radiotherapy of The Maria Skłodowska-Curie Memorial Cancer Center in Warsaw. The patient population consisted of 150 men

and 15 women. Mean age was 55.6 years (range 29-80 SD \pm 9.8). The staging was performed according to the TNM UICC-classification of 1987 [6] and was based on preoperative clinical examination. There were 5 (3%) stage T2 patients, 67 (42%) T3 and 88 (55%) T4 cases. In 5 patients the T stage was not assessed. The clinical nodal stage was described as N0 in 90 (56%) patients, N1 in 33 (21%), N2 in 31 (19%) and N3 in 7 (4%) cases. In 4 patients the N stage was not assessed. In 90 cases the tumour was located in supraglottic larynx, in 46 cases it was described as transglottic, in 28 cases glottic carcinoma was discerned, in the remaining 1 patient the tumour was described as subglottic carcinoma. Initially all patients underwent total laryngectomy combined, in 91 cases, with unilateral or bilateral neck dissection. The surgical procedures were performed at the laryngology departments of the Mazovian region, mainly (147 patients) in Warsaw laryngology departments. The unilateral neck dissection was carried out in 73 patients (radical 54, modified 28 and adenectomy in 9 cases) and bilateral in 18 patients (radical-1, modified-5, radical and modified or adenectomy-12 cases).

In all cases but one (low differentiated solid carcinoma) pathology reports revealed squamous cell carcinoma G1 in 15 (9%) patients, G2 in 69 (42%) and G3 in 17 (10%) cases. In 63 (38%) patients the histologic grade was not assessed.

Surgical margins were free of the tumor in 131 patients. Residual mass was found in 2 patients. Nineteen patients had microscopic involvement and 12 had close surgical margins. Pathologically positive lymph nodes were found in 61 patients; in 31 cases accompanied by extracapsular extension. Extension of the the primary beyond larynx, thyroid cartilage invasion, subglottic extension or their combination were found in 134 patients. All patients with poor prognostic features present in pathological findings were referred to the IInd Department of Radiotherapy of our institution. The indications for postoperative radiotherapy were: close or positive margins, extension of the primary beyond larynx, thyroid cartilage invasion, subglottic extension, tumor grade G3, positive nodes with or without extracapsular extension.

The haemoglobin level assessed before radiotherapy varied between 9.5 g/dl and 15.4 g/dl (mean: 13.1 g/dl SD \pm 1.5).

Postoperative irradiation was initiated within 15 to 162 days after surgery (mean: 53 \pm 27). The patients were treated with 60-Co unit using the shrinking field technique. The daily dose was 2.0 Gy in all cases. The wedged parallel opposed lateral head and neck fields were used with doses prescribed to the

midplane in 160 patients. At 44-46 Gy the field size was reduced to eliminate the spinal cord from the treatment volume. The total dose of 60 Gy was given to 118 patients. The doses of 64 to 70 Gy were given to 27 patients with positive or close surgical margins after another field reduction at 60.0 Gy. The total dose below 60 Gy was given to 15 patients (range from 50-58). In 120 patients, the posterior neck was supplemented with the electrons uni or bilateral to doses ranged from 50 to 60 Gy. The stoma was boosted additionally with electrons in 8 patients with subglottic extension up to 10-16 Gy. The lower neck was irradiated through an anterior supraclavicular portal with the dose prescription to the maximum in 145 cases. The average total dose was 50 Gy in 20 fractions (132 patients). Only in 13 patients the dose of 45 Gy in 18 fractions was given. In the early eighties (5 patients) an old technique with the one anterior field with doses 50-56 Gy in 25-28 fractions had been used. The total treatment time varied between 30 and 107 days (mean: 50 SD \pm 11). Acute and late radiation morbidity were scored according to the EORTC/RTOG scale [7].

The follow-up ranged from 5 to 163 months. In 50% of living patients the observation period was longer than 60 months and in 75% – longer than 39 months. Only two patients were lost from the follow-up after a time shorter than two years (5 and 21 months). The follow-up studies included clinical evaluations, chest x-rays and other diagnostic procedures wherever appropriate. The overall survival and local control was calculated using the actuarial method according to Kaplan and Meier. The prognostic factor analysis was performed by means of the Cox's proportional hazards model using a backward selection method.

Results

The actuarial survival with standard deviation for the entire group of postoperatively irradiated patients was 0.70 ± 0.04 , 0.56 ± 0.04 and 0.43 ± 0.05 at two, five and ten years respectively (Figure 1). Local recurrence was defined as any recurrence above the clavicles, and 41 such events were observed. In 15 cases distant metastases oc-

curred. Both types of relapses were lethal in all cases. The total number of deaths in the observed group was 78. Apart from the treatment failure listed above, other causes of death were: a second malignancy (mainly lung cancer) in 15 cases, cardiac disease in 5 cases. Death from unknown causes occurred in 2 patients.

The actuarial local control with standard deviation for the entire group of the patients was 0.86 ± 0.03 , 0.78 ± 0.04 and 0.75 ± 0.03 at one, two and three years respectively and remained stable thereafter (figure2).

Sex, age, performance status, T, N stages, primary tumor site, hemoglobin level, histological grade, involvement of lymph nodes, extracapsular lymph node extension, surgical margin status, presence of extension of the primary beyond larynx and/or thyroid cartilage invasion and/or subglottic extension and the time from operation to start of the radiotherapy were studied in the multifactors analysis for prognostic significance for both overall survival and local control.

For overall survival – sex, positive lymph nodes and the time interval between surgery and radiotherapy were found to be the significant prognostic factors. The relative risk of death for men was 4 fold higher than the appropriate risk for women ($p=0.05$). The relative risk of death in patients with positive lymph nodes was almost 3.5 fold higher than in those with the negative lymph nodes ($p=0.006$). According to the length of time from operation to radiotherapy patients were divided uniformly into 5 groups: <32, [32, 44), [44, 52), [52, 73) and ≥ 73 days. Longer periods between operation and radiation were associated with poorer prognosis. The relative risk of death for patients waiting about two months to start postoperative radiotherapy was 3 fold bigger than those waiting less than one month ($p=0.007$).

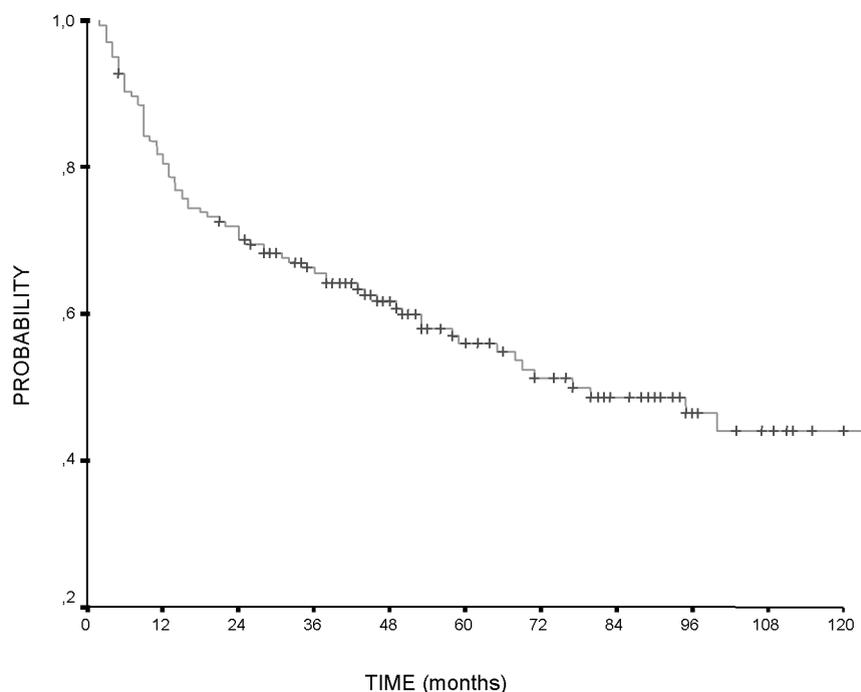


Figure 1. Overall survival probability

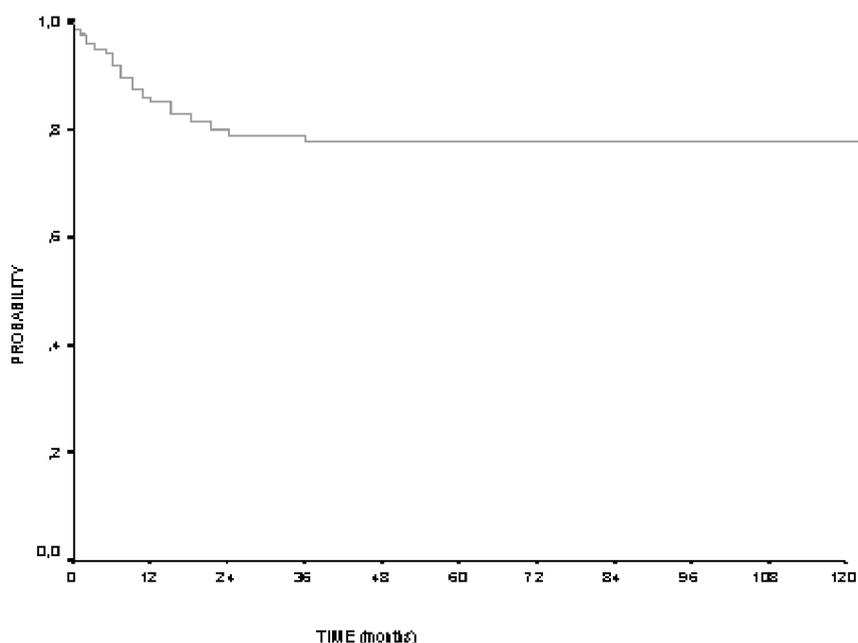


Figure 2. Local control probability

For patients waiting longer than 73 days a decrease in the relative risk of death to 1.29 was observed. The results of the regression analysis for death risk function were presented in Table I. The survival probability for signifi-

cant prognostic factors is presented in Table II and Figures 3 and 4.

Extracapsular lymph node extension was found to be the only significant prognostic factor for local control.

Table I. Multivariate analysis of factors influencing overall survival

Variable (reference level)	B - coefficient	Standard deviation	Critical level of test (p)	Relative risk (RR)
Sex (male)	-1.42	0.73	0.050	0.24
Nodal Status (without lymphadenectomy)			0.002	
pN-	-0.56	0.44	0.208	0.57
pN+	0.67	0.24	0.006	1.95
Time from operation to radiotherapy (days)				
(>32)			0.043	
[32, 44)	0.56	0.41	0.175	1.74
[44, 52)	0.83	0.40	0.035	2.30
[52, 73)	1.04	0.38	0.007	2.83
≥ 73	0.26	0.44	0.556	1.29

Table II. Survival probability for statistically significant variables

Survival	2 - years	5 - years	10 - years
Sex			
males	0.70 \pm 0.04	0.53 \pm 0.04	0.43 \pm 0.05
females	0.93 \pm 0.07	0.93 \pm 0.07	0.47 \pm 0.33
pN			
pN-	0.86 \pm 0.08	0.75 \pm 0.10	0.66 \pm 0.11
pN+	0.62 \pm 0.07	0.35 \pm 0.07	0.26 \pm 0.07
Time from operation to radiotherapy (days)			
<32	0.74 \pm 0.08	0.63 \pm 0.09	0.63 \pm 0.09
[32, 44)	0.69 \pm 0.08	0.61 \pm 0.09	0.46 \pm 0.12
[44, 52)	0.65 \pm 0.08	0.44 \pm 0.09	0.39 \pm 0.10
[52, 73)	0.61 \pm 0.08	0.43 \pm 0.09	0.23 \pm 0.10
≥ 73	0.83 \pm 0.07	0.70 \pm 0.09	0.50 \pm 0.14

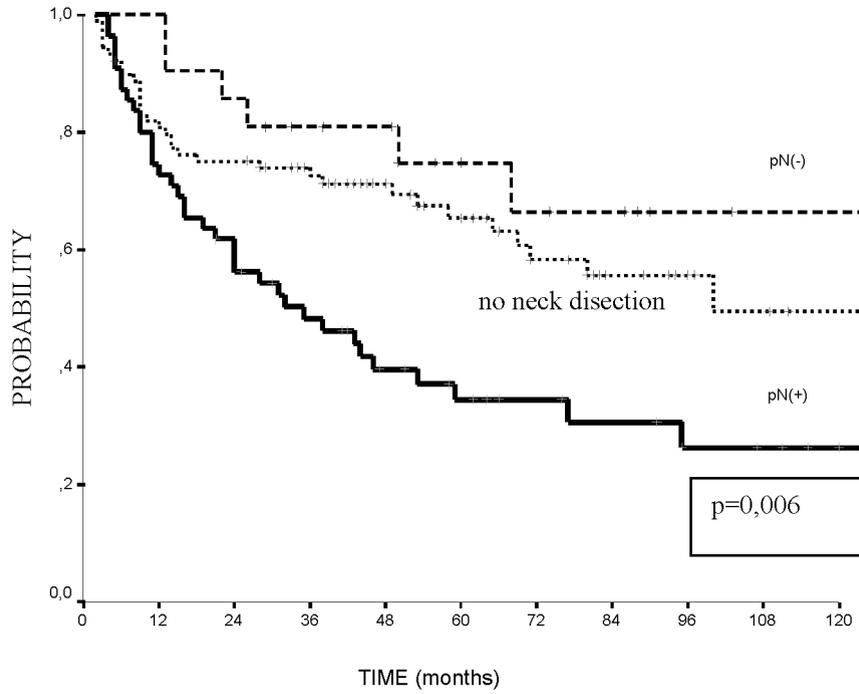


Figure 3. Overall survival probability according to pathologic nodal status

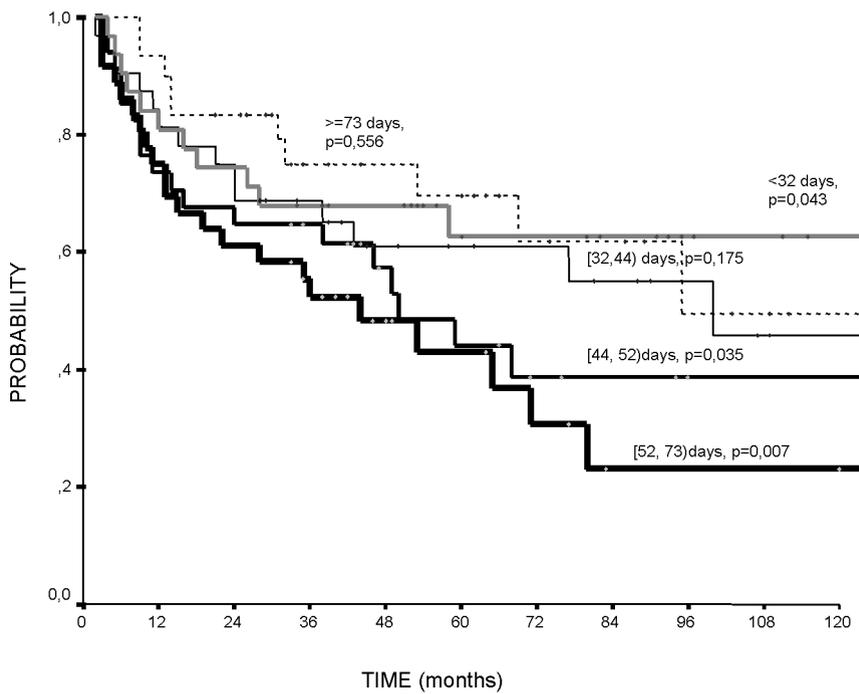


Figure 4. Overall survival probability according to interval between radiotherapy and surgery

The patients with the presence of this pathologic feature had a 3.5 fold higher relative risk of failure above the clavicles than the group in which the extracapsular lymph

node extension was not observed (p=0.007). The results of regression analysis for risk of local failure function are presented in Table III. The probability of freedom from

Table III. Multivariate analysis of factors influencing local control

Variable (reference level)	B - coefficient	Standard deviation	Critical level of test (p)	Relative risk (RR)
Extracapsular lymph node extension	1.30	0.49	0.007	3.68

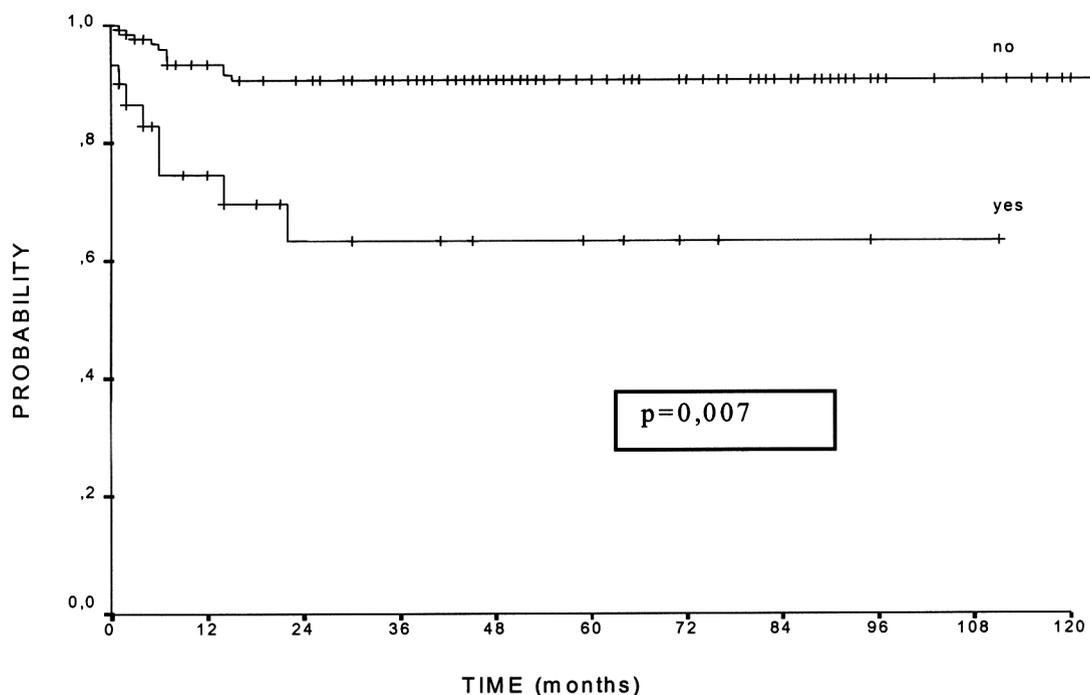


Figure 5. Local control probability according to extracapsular lymph node extension

locoregional recurrence according to the extracapsular lymph node extension is shown in Figure 5.

In most cases acute and late toxicity was low or moderate (G0, G1, G2). Severe acute side effects were observed in a minority of the patients and were manageable. The most affected organ was the skin, with 65 (40%) cases of G3 and 5 (3%) with G4 grade toxicity. Severe acute morbidity from the mucous membrane and the pharynx and oesophagus was less frequent. There were 19 (12%) cases of G3, 2 (1%) cases of G4 and 15 (9%) cases of G3 toxicity respectively. Severe late skin radiation morbidity (G3 and G4) was observed in 11 (7%) patients. All these patients were managed with conservative treatment. One patient needed surgical intervention because of oesophageal stricture and it was the only case of severe late toxicity observed in other than cutaneous tissues. In order to assess the intensification of both acute and late toxicity we compared in an additionally performed statistical analysis of the group of patients who started radiotherapy before 32 days from the operation to the rest of our patients. We did not observe any statistically significant differences between the studied groups. We only observed increased early skin toxicity in the patients who started radiotherapy earlier than 32 days from the surgery but this reached only borderline statistical significance ($p=0.051$).

Discussion

The locally advanced laryngeal carcinoma remains a serious clinical problem, however combined surgery and postoperative radiotherapy allow to achieve high rates of local control and improved survival. In our study overall survival was 56% and 43%, respectively, at 5 and 10 years. It should be emphasized that patient population with the ad-

vanced laryngeal carcinoma includes a large proportion of heavy smokers who are at higher risk of having heart and lung diseases and a propensity for developing second malignancies, mainly in the aerodigestive tracts. In our study 28% causes of death were related to this phenomenon. Second malignancies and cardiovascular diseases constituted all causes of death in the patients with longer than five year periods of observation causing over-mortality in the studied population. Treatment failure (local and/or distant) remains the main cause of death during first five years of observation in the study group – 72% of all deceases. Local recurrence was the leading reason of mortality (53% causes of death) and dominated during the first two years of the observation. The three-year local control in our group of patients was 75% and remained stable thereafter.

The clinical results of the combined treatment in our institution were similar to those achieved in other institutions worldwide [8-11]. The distant metastases occurred in 15 patients and constituted 9% of the entire studied group and 19% of all causes of death. In the published studies the percentage of the occurrence of distant failure varied from 4.4% to 25% [8, 9, 12-16].

The extracapsular lymph node extension was found to be the only significant prognostic factor affecting the local control in the multivariate analysis performed on our group of patient. The literature concerning prognostic factors reported that the involvement of lymph nodes accompanied by the extracapsular extension [3, 9-13, 17-20] and the positive surgical margin status [4, 8, 14, 20-26] are the strongest pathologic features affecting negatively disease control above the clavicles.

The finding of pathologically positive nodes without capsular rupture is also recognized as a prognostically si-

gnificant factor for local control in the patients treated with postoperative irradiation [8, 9, 11, 12, 15, 21, 26]. Only few reports found that low histological grade [14, 26, 27], presence of the extension of the primary beyond the larynx [21], the thyroid cartilage invasion [21] and the subglottic extension [28, 29] could be assumed as having influence on locoregional recurrence.

In our treatment policy we did not use the boost doses over 60 Gy for the nodal areas affected by the extracapsular extension. We now recognize the extracapsular extension as the similar clinical situation to the non-radical surgical excision and therefore based on our present experience we are going to introduce the use of the boost dose up to 70 Gy to small volume where the capsular rupture was noticed. Such a treatment policy requires careful description in the pathological report affected groups of the cervical lymph nodes according to the Robbins Classification and the very precise 3-D treatment planning [30].

In our study pathologically positive nodes were found to be a statistically significant factor in the multivariate analysis having negative influence on the overall survival. In a series published elsewhere this factor [8, 9, 11, 12, 15, 21, 26] along with positive surgical margin status [4, 8, 14, 20-25] and high histological grade [11, 16, 26] were claimed as increasing risk of death in the head and neck cancer patients managed with postoperative radiotherapy.

Analyses of the dose-response relationship for radiation therapy of subclinical disease have suggested, that the interval between operation and radiotherapy could influence the clinical outcome of the treatment [31, 32]. It is commonly accepted that a delay in the initiation of the postoperative irradiation beyond 6 weeks after surgery worsens prognosis. Although such a belief is very strong among clinicians there were, however, few available data to support it [33-35].

In our study the interval between surgery and radiation was a statistically significant factor influencing overall survival. We did not observe this feature to be a variable predicting the local control and we cannot find any reason to explain this fact.

We did not notice increased radiation morbidity in the patients who started treatment earlier than 32 days from the operation compare to those starting later.

In the recently published retrospective analysis of postoperatively irradiated patients with head and neck cancer [36] and randomised trial addressing time factors of surgery plus radiotherapy in advanced head and neck cancer [37] a prolonged interval between operation and radiotherapy was found to be associated with a significantly lower local control [36, 37] and survival [37]. The cumulative duration of combined therapy was also found in both papers to significantly impact on the local control [36, 37] and survival [37] rates. Based on our experience, despite the interval between surgery and radiation in our study proved to be affecting only overall survival, and on cited above results of the recently published papers, we recommend to start postoperative radiotherapy as soon

as healing is adequate. The shortening of the interval between surgery and radiation is not associated with the significant raise in the treatment toxicity.

The reasons for the radiotherapy delay in our study were not assessed because of the insufficient data in the analysed clinical material. In a recently published series [36, 37] the reasons of delay of radiotherapy were specified, but they were not considered as variables for the statistical analyses. We think that performing such an analysis would be valuable and may elucidate the ways of influencing clinical outcome by prolonging total treatment time.

Radical surgery and postoperative radiotherapy should be considered as one treatment that needs to be delivered in a timely and coordinated fashion.

There is still room for improving the outcome of this treatment by exploring the role of accelerated radiotherapy [37] and combining chemotherapy with irradiation [38].

Conclusions

Combined surgery and postoperative radiotherapy is an effective treatment modality in the management of locally advanced laryngeal cancer. In multivariate analysis pathologically positive lymph nodes and time interval between surgery and radiation were found to be the significant prognostic factors influencing the overall survival. The extra-capsular lymph node extension was found to be the only significant prognostic factor affecting local control.

In order to decrease the local recurrence rate we postulate the use of the boost dose up to 70 Gy to the small volume in the cases where capsular rupture was noticed.

We recommend to start postoperative radiotherapy as soon as healing is adequate. The shortening of interval between surgery and radiation is not associated with the significant raise in treatment toxicity.

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