

## **Radiotherapy of locally advanced laryngeal cancer: the Gliwice Center of Oncology experience, 1990-1996**

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*Introduction.* The aim of the study was to assess the efficacy of radiotherapy alone in patients with locally advanced laryngeal cancer T3-T4, and to establish the prognostic value of the size and the location of the extralaryngeal infiltrations and of emergency tracheostomy.

*Material and methods.* 296 patients with advanced squamous cell cancer of the larynx were radically treated with radiotherapy alone in Center of Oncology in Gliwice between the years 1990 and 1996. There were 221 cases of supraglottic cancer (75%) and 75 of glottic cancer (25%). The stages were as follows: supraglottic cancer: T3 – 113 (51%), T4 – 108 (49%), glottic cancer: T3 – 69 (92%), T4 – 6 (8%). Positive neck nodes were found in 100 patients with supraglottic cancer (45%), and only in 11 patients with glottic cancer (15%). In cases of extralaryngeal invasion (T4) the pyriform recess was involved in 33%, the base of tongue and valleculae glosso-epiglotticae in 30%, the hypopharyngeal wall in 9% of cases, while a massive involvement of the larynx, the pyriform recess and the base of the tongue was found in 6% of patients. Cartilage involvement was suspected in 22% of patients. Thirty six patients (12%) underwent emergency tracheostomy.

*Results.* Generally, the 3-year local control rate (LC) and disease free survival rate (DSF) were 46% and 41%, respectively. The probability of LC was similar in both supraglottic and glottic cancer: 44% and 47.5% respectively. The presence of involved neck nodes significantly decreased LC and DFS rates in both groups (about 20%). For stage T4 laryngeal cancer the LC rate was correlated with the location of the extralaryngeal infiltrations. Best prognosis was connected with the suspicion of cartilage infiltration – 56% of 3-year LC rate. The worst results were noted in cases of massive infiltrations spreading from larynx through the hypopharynx – 13.5% of 3-year LC rate. Emergency tracheostomy before radiotherapy was very significantly linked to poorer treatment results. The 3-year LC rate in tracheostomy patients was 6%, as compared to 51% in other patients. Multivariate analysis using Cox regression model showed that the worst prognosis was significantly and independently connected with the necessity of emergency tracheostomy before treatment, and neck lymph node involvement.

*Conclusions.* Conventional radiotherapy of advanced laryngeal cancer has limited efficacy as a method of radical treatment. Emergency tracheostomy and the involvement of neck lymph nodes are poor prognostic factors in the case of patients with advanced laryngeal cancer treated with radiotherapy alone. The efficacy of radiotherapy in stage T4 laryngeal cancer is directly connected with the localisation and the extent of extralaryngeal infiltrations.

### **Radioterapia chorych na miejscowo zaawansowanego raka krtani w materiale klinicznym Centrum Onkologii w Gliwicach w latach 1990-96**

*Wstęp.* Celem pracy jest ocena skuteczności samodzielnego, radykalnego, leczenia promieniami chorych na miejscowo zaawansowanego raka krtani (T3-T4), w latach 1990-96 w Centrum Onkologii w Gliwicach oraz ustalenie rokowniczego znaczenia wielkości i umiejscowienia nowotworowych nacieków pozakrtaniowych oraz tracheostomii, wykonanej przed leczeniem.

*Materiał i metody.* Materiał kliniczny stanowi 296 przypadków zaawansowanego płaskonabłonkowego raka krtani, leczonych radykalnie samodzielnym napromienianiem. Przedmiotem analizy jest grupa 221 przypadków raka nadgłośni (75%) i 75 przypadków raka głośni (25%). W grupie chorych na raka nadgłośni zanotowano następujące stopnie zaawansowania guza pierwotnego: T3 – 113 przypadków (51%) i T4 – 108 (49%), a w grupie chorych na raka głośni: T3 – 69 (92%)

i T4 – 6 (8%). U 100 chorych (45%) na raka nadgłośni stwierdzono obecność przerzutów do regionalnych węzłów chłonnych szyi, natomiast przerzutowo zajęte węzły chłonne w przypadku raka głośni zanotowano u 11 chorych (15%). W przypadkach naciekania raka poza krtani (T4) najczęściej był zajęty zachyłek gruszkowaty – 37 chorych (33%), prawie równie często dółek językowo-nagłośniowy i nasada języka – 34 chorych (30%); nacieki ścian gardła dolnego zanotowano u 10 chorych (9%), rozległe nacieki, szerzące się od zachyłka gruszkowatego do nasady języka, zanotowano u 7 chorych (6%). U 26 chorych (22%) podejrzewano naciekanie zrębu chrzęstnego krtani. W 36 przypadkach (12%) z powodu duszności wykonano tracheostomię przed rozpoczęciem leczenia.

*Wyniki.* Ogółem w 3-letnim okresie obserwacji wyleczenie miejscowe zanotowano w 46% przypadków, a przeżycie bezobjawowe w 41%. Odsetek miejscowego wyleczenia raka krtani dla obydwu lokalizacji był podobny i wynosił: 44% dla piętra górnego i 47,5% dla piętra środkowego krtani. Przerzutowo zajęte węzły chłonne szyi w sposób statystycznie znamienne obniżają odsetek wyleczeń miejscowych i przeżyć bezobjawowych w obydwóch stopniach zaawansowania o około 20%. W przypadku raka krtani o zaawansowaniu T4 wyleczenie miejscowe zależało od lokalizacji i wielkości nacieku pozakrtaniowego. Najlepsze rokowanie było związane z podejrzeniem naciekania zrębu chrzęstnego krtani i wynosiło 56% 3-letnich wyleczeń miejscowych, najgorsze wyniki leczenia zanotowano w przypadku rozległych nacieków, szerzących się z krtani poprzez gardło dolne do gardła środkowego, 13,5% 3-letnich wyleczeń miejscowych. Konieczność wykonania tracheostomii przed radioterapią była znamienne związane z najgorszymi wynikami leczenia, 3-letnie wyleczenie miejscowe u chorych z tracheostomią wynosiło 6% w porównaniu do 51% u chorych bez tracheostomii. Analiza wieloczynnikowa wykazała, że na złe rokowanie w wysoce znamienne i niezależny sposób wpływa tracheostomia wykonana przed leczeniem oraz obecność przerzutów w regionalnych węzłach chłonnych.

*Wnioski.* Konwencjonalna radioterapia chorych na zaawansowanego raka krtani jest metodą leczenia o ograniczonej skuteczności. Na wyniki leczenia w sposób statystycznie znamienne wpływa obecność przerzutów w regionalnych węzłach chłonnych oraz tracheostomia wykonana przed leczeniem. Skuteczność leczenia raka krtani o zaawansowaniu T4 jest ściśle związana z lokalizacją i wielkością nacieków pozakrtaniowych.

**Key words:** advanced laryngeal cancer, radiotherapy

**Słowa kluczowe:** zaawansowany rak krtani, radioterapia

## Introduction

Laryngeal cancer is the most common cancer of the head and neck region, accounting for approximately 6% of all malignancies. The methods of treatment are either surgery or radiotherapy alone or surgery followed by postoperative radiotherapy. Radiotherapy alone is a recognized method of treatment for stage I and II laryngeal cancer, allowing to achieve results comparable to surgery and, at the same time, ensure voice preservation [1, 2]. In such patients surgery is used only as a „salvage” procedure for the recurrences after radiotherapy. Surgery is recommended for stages III and IV laryngeal cancer. In cases with significant risk of recurrence surgery is combined with radiotherapy [3-6]. In these patients radiotherapy alone is applied only when the patient does not consent or is unsuitable for surgery. Patients not suitable for surgery due to the advanced stage of the disease are irradiated palliatively. In some of these cases attempts of radical radiotherapy are also made.

Results of treatment with radiotherapy alone in advanced laryngeal cancer are generally worse than the results achieved with surgery followed by radiotherapy. However, as a group these patients are clinically heterogeneous in term of radiocurability – a review of literature shows a wide range of cures, ranging from 10% to even 80% [2, 3, 7]. Such results suggest the possibility of the influence of many prognostic factors. Apart from those well known, such as clinical stage and type of infiltration (egzophytic, endophytic), a very important prognostic

factor is also the primary location of the cancer within the larynx. Supraglottic carcinomas usually do not keratinize or are poorly differentiated (G2 – 3), and generally grow more aggressively than glottic carcinomas [8, 9].

Glottic carcinomas usually keratinize, are well differentiated (G1), and grow less aggressively [10, 11]. The purpose of this study is to assess the efficacy of radiotherapy alone in patients with locally advanced laryngeal cancer T3 – T4 treated between the years 1990 and 1996 at the Centre of Oncology in Gliwice, and to establish the prognostic value of the size and location of extralaryngeal infiltrations and of emergency tracheostomy.

## Material and methods

Two hundred ninety six patients with advanced squamous cell cancer of the larynx were radically treated with radiotherapy alone at the Centre of Oncology in Gliwice between the years 1990 and 1996 (31% of all laryngeal cancers irradiated in this period of time); the characteristics of patients is presented in Table I. Two groups: 221 patients with supraglottic cancer (75%) and 75 patients with glottic cancer (25%) were analysed. No cases of infraglottic cancer were observed during this time.

In 36/296 cases (12%) emergency tracheostomy was performed before the onset of treatment because of dyspnea of these, 27 cases were supraglottic and 9 glottic.

In a majority of cases (70%), the performance status at the onset of treatment was assessed as very good (ZUBROD 0). The performance status of the remaining patients was pronounced as good (ZUBROD 1 – 28%) or medium (ZUBROD 2).

Clinical staging was established according to TNM UICC from 1984. Tables II and III show the size of primary tumor (T)

**Tab. I. The characteristics of patients**

	Category	Number of patients (%)	
		Supraglottis	Glottis
Sex	M	197 (89%)	73 (97%)
	F	24 (11%)	2 (3%)
Age	median	57 years	59 years
	minimum	33	35
	maximum	86	80
Extent of primary tumor	T3	113 (51%)	69 (92%)
	T4	108 (49%)	6 (8%)
Neck lymph nodes	N0	121 (54%)	64 (85.5%)
	N1	44 (21%)	7 (9%)
	N2	48 (22%)	3 (4%)
	N3	8 (3%)	1 (1.5%)
	N+	100 (46%)	11 (14.5%)
Tracheostomy	yes	27 (12%)	9 (12%)
	no	194 (88%)	66 (88%)
Performance status (ZUBROD)	0	153 (69%)	54 (72%)
	1	63 (29%)	20 (27%)
	2	5 (2%)	1 (1%)

and neck node involvement (N) in patients with supraglottic and glottic cancer, respectively. There were 160 (54%) stage III and 136 (46%) stage IV cases.

The size of the primary tumor was as follows: supraglottic cancer T3 – 113 (51%), T4 – 108 (49%), glottic cancer T3 – 69 (92%), T4 – 6 (8%). Positive neck nodes were found in 100 patients with supraglottic cancer (45%), and only in 11 patients with glottic cancer (15%). In a majority of cases they were staged as N1 and N2 (21% and 22% for supraglottic cancer and 9% and 4% for glottic cancer respectively) (Table II and III).

In cases of extralaryngeal infiltration (T4) the piriform recess was involved – in 37 cases (33%), the base of tongue and valleculae glosso-epiglotticae in 34 cases (30%), and the hypopharyngeal wall in 10 (9%). Massive involvement of the piriform recess, the valleculae glosso-epiglotticae and the base of the tongue was found in 7 cases (6%). Cartilage involvement was suspected on clinical examination in 26 cases (22%).

All patients were irradiated using a Cobalt 60 unit with two contralateral fields including the primary tumor and

the involved neck nodes. The total dose depended on the size of the primary tumor ranging from 60 Gy to 78 Gy (mean 66.8 Gy) and was conventionally fractionated. Metastatic neck nodes situated inside the fields including the primary tumor were irradiated with a fraction dose, which on the level of the node, was comparable to the fraction dose in the region of the primary tumor (the difference not exceeding 5%). The remaining neck nodes (outside the fields including primary tumor) were irradiated with an additional field matched individually. In cases of persistent, enlarged neck nodes (N2-3) a boost dose of about 10 Gy was given using the shrunk field technique. Clinically uninvolved neck nodes were electively irradiated to a total dose of 50 Gy given at a depth of 2.5 cm. The total treatment time ranged widely from 39 to 103 days (mean: 49 days).

Three criteria evaluating the efficacy of treatment were: 3-year local control (LC), disease free survival (DFS) and overall survival (OS). All these parameters were estimated with the Kaplan-Meier method. The differences in survival dependant

**Tab. II. The extent of primary supraglottic tumor (T) and neck lymph nodes involvement (N)**

Extent of primary tumor	Neck nodes involvement (number of patients)				
	N0	N1	N2	N3	TOTAL
T3	70 (31.0%)	23 (11.0%)	17 (8.0%)	3 (1.0%)	113 (51.0%)
T4	51 (23.0%)	21 (10.0%)	31 (14.0%)	5 (2.0%)	108 (49.0%)
TOTAL	121 (54.0%)	44 (21.0%)	48 (22.0%)	8 (3.0%)	221 (100%)

**Tab. III. The extent of primary glottic tumor (T) and neck lymph nodes involvement (N)**

Extent of primary tumor	Neck nodes involvement (number of patients)				
	N0	N1	N2	N3	TOTAL
T3	60 (80.0%)	7 (9.0%)	1 (1.5%)	1 (1.5%)	69 (92.0%)
T4	4 (5.5%)	-	2 (2.5%)	-	6 (8.0%)
TOTAL	64 (85.5%)	7 (9.0%)	3 (4.0%)	1 (1.5%)	75 (100%)

**Tab. IV. The relationship between selected clinical factors and 3-year DFS (disease free survival) and LC (local control) rates in patients with supraglottic and glottic cancer**

Clinical factor	Category	Supraglottic cancer (p)*		Glottic cancer (p)	
		3-year DFS	3-year LC	3-year DFS	3-year LC
Sex	M	40.0 NS	43.0 NS	43.0	46.0
	F	44.0	47.0	-	-
Extent of primary tumor	T3	45.0 NS	47.0 NS	44.0 NS	47.0 NS
	T4	35.0	40.5	50.0	50.0
	T3-T4	40.0	44.0	45.0	47.5
Extent of neck nodes involvement	N0	50.0 p=0.001	53.0 p=0.001	50.0 p=0.060	53.0 p=0.060
	N1	38.0	41.0	13.0	14.0
	N2	23.0	31.0	33.0	33.0
	N3	-	-	-	-
	N+	28.0	33.0	17.0	18.0
Tracheostomy	Yes	4.0 p=0.000	3.0 p=0.000	11.0 p=0.020	11.0 p=0.005
	No	47.0	51.0	49.0	53.0

\*(p) – probability of difference

on the selected clinical and therapeutic factors were compared with the log-rank test; p value below 0.05 was taken to be statistically significant. Multivariate analysis of the prognostic factors using Cox regression model was also performed.

## Results

The 3-year local control (LC) was noted in 46% of cases (Fig.1), disease free survival (DFS) in 41% (Fig.1) and overall survival (OS) in 48%. In the group of patients with supraglottic cancer the 3-year DFS was 40% and LC was 44%, as compared to patients with glottic cancer: 44% and 47.5%, respectively. The 3-year DFS was similar in male and female patients with supraglottic cancer – 40% and 44%, respectively. Due to a limited number of women with glottic cancer reliable analysis was impossible in this group (Tab. IV).

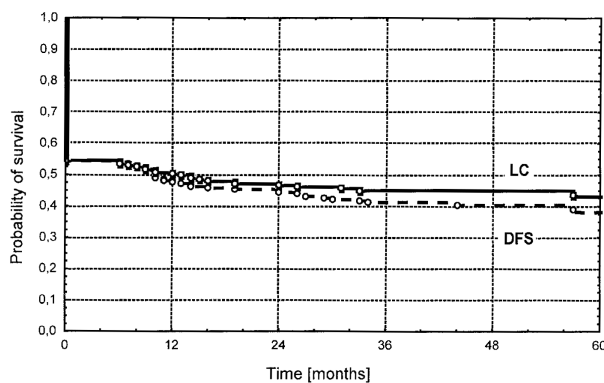


Fig. 1. Local control and disease free survival curves for patients with T3 – T4 laryngeal cancer.

The LC rates in patients with stage T3 were similar in both supraglottic and glottic cancer groups and equalled 47%. The group of patients with T4 glottic cancer was too small to perform a similar analysis (6 patients). The presence of involved neck nodes significantly worsened the LC and DFS rates. The 3-year LC rate in stage

T3 without neck node involvement (N0) was 54%, as compared to 30% in the N+ group (p=0.008) (Fig.2). In the group of patients with stage T4 similar results were observed – 50% and 33% respectively (p=0.060) (Fig. 3).

For stage T4 laryngeal cancer the LC rate was correlated with the location of the extralaryngeal infiltration. Best prognosis was connected with the suspicion of carti-

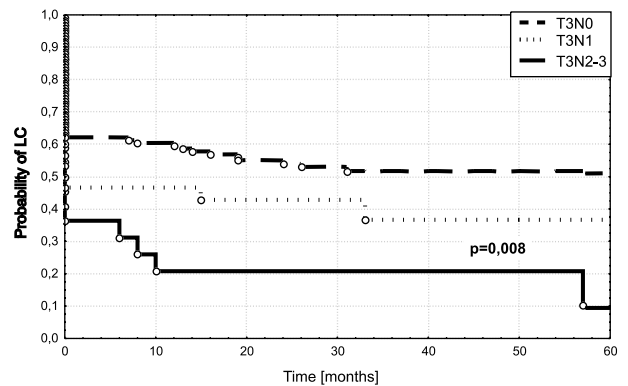


Fig. 2. Local control curves for patients with T3 laryngeal cancer according to the extent of neck nodes involvement

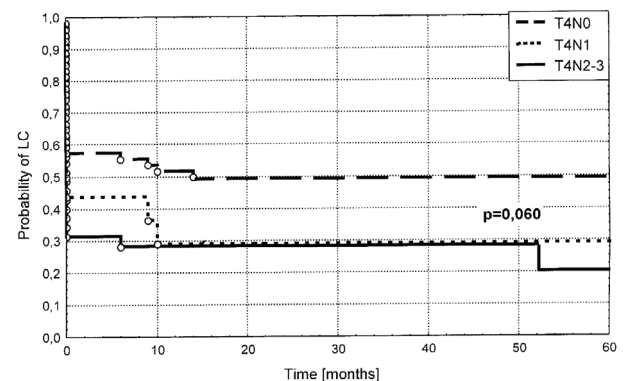


Fig. 3. Local control curves for patients with T4 laryngeal cancer according to the extent of neck nodes involvement

lage infiltration – 56% of 3-year LC rate (Fig. 4). The worst results were noted in cases of massive infiltrations spreading from larynx through the hypopharynx – 13.5% of 3-year LC rate ( $p=0.034$ ).

Emergency tracheostomy before radiotherapy was very significantly ( $p=0.000$ ) connected with worse treatment results. The 3-year LC rate in tracheostomy patients was 6%, as compared to 51% in non-tracheostomy patients (Fig. 5).

Multivariate analysis using the Cox regression model allowed to separate independent prognostic factors influencing the efficacy of radiotherapy of the advanced

laryngeal cancer (Tab. V). The DFS of patients with advanced laryngeal cancer was very significantly and independently influenced by the necessity of emergency tracheostomy before treatment and the presence of neck node involvement.

Distant metastases were observed in 16 cases (5%) (13 cases of supraglottic cancer and 3 cases of glottic cancer). In a majority of cases they were located in the lungs (13 cases). There were also a few cases of metastases to the bones, the brain and the mediastinal nodes.

Salvage treatment was performed only in 17 patients (12%) in whom treatment failure after radiotherapy was recognized.

## Discussion

Our study of a group of 296 patients shows, that conventional radiotherapy is of limited effectiveness in the treatment of advanced supraglottic and glottic cancer (T3-4 N0-3). The basic cause of failure is the lack of cure of either the primary tumor and/or large neck nodes metastases. Some authors suggest that higher total doses of radiation may lead not only to increased tumor cure but also to an increased risk of radiation-induced complications [8, 12, 13]. Our results resemble those found in literature and suggest that patients with advanced laryngeal cancer should be primarily treated surgically with possible adjuvant radiotherapy [3, 14, 15]. In our group, radiotherapy alone allows to achieve a 3-year LC rate of 40-47%, depending to the location of the primary tumor. Our results are consistent with the observations of Skofylszewski et al. [3].

Mendenhall et al., in a comparable clinical material, have achieved better treatment results. In case of irradiation with two daily fractions (hyperfractionation) 5-year LC after radiotherapy alone was approximately 65%, and after „salvage” surgery it reached even 90%. With conventional radiotherapy these results were 53% and 71%, respectively [7]. Similar results were reported by Wang. The 5-year LC equalled 67% after hyperfractionated radiotherapy, as compared to 42% after conventional treatment [16].

Our study shows that the extent of neck node involvement (N+) significantly worsens the prognosis for both

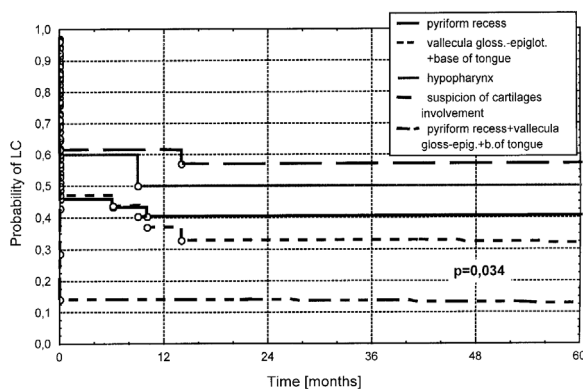


Fig. 4. Local control curves for patients with T4 laryngeal cancer according to the directions of extralaryngeal tumor infiltration

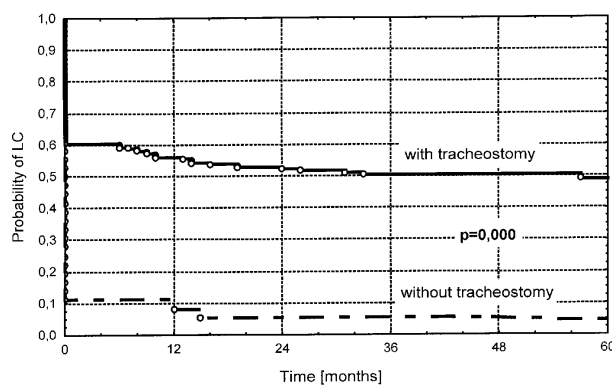


Fig. 5. Local control curves for patients with T3-T4 laryngeal cancer with or without emergency tracheostomy

Tab. V. The relationship between selected prognostic factors and DFS in patients with T3-4 laryngeal cancer after radiotherapy (final model:  $\chi^2=26,52$ ;  $df=3$ ,  $p=0.000$ )

Factor	Category	$\beta$	Standard error $\beta$	Relative risk (RR)	95% CI of RR	$p$
Tracheostomy	No	-		1.00	-	0.000
	Yes	0.742	0.197	2.10	1.43-3.09	
Enlarged neck nodes	N0	-		1.00	-	0.000
	N1	0.286	0.083	1.33	1.13-1.57	
	N2	0.572	0.083	1.77	1.50-2.08	
	N3	0.858	0.083	2.36	2.00-2.78	
Age	continuous from 33 to 86	0.013	0.008	1% for one year	1.00-1.03	0.115

locations of laryngeal cancer. The risk of neck node metastases is raised in supraglottic cancer, while the results are comparable with data from literature [17-20]. Skolyszewski et al. stressed the necessity of larger field irradiation, including the larynx and upper neck nodes in all patients with supraglottic cancer [3].

An assessment of five directions of extralaryngeal infiltration (T4) has shown, that the least unfavorable prognostic factor was the suspicion of cartilage infiltration (56% of 3-year LC rate). The significantly lowest 3-year LC rate (13.5%) was noted in cases of massive infiltration including anatomical structures of the hypopharynx (pyriform recess) and the oropharynx (base of tongue). It seems that the unexpectedly good results achieved in the group of patients in whom cartilage infiltration was suspected may be connected with a possible misdiagnosis of this symptom (at that time it was not possible to perform a precise CT examinations in all patients). A low LC rate in cases of pyriform recess and base of tongue infiltration is probably connected with the range and the depth of these infiltrations (large tumour mass and frequent ulcers suggest tumor radioresistance). Harwood et al. have also reported a higher LC rate in the case of carotid cartilage destruction, as compared to pyriform recess infiltration [21]. This part of our results suggests the necessity of performing routine accessory investigations (CT, USG) in order to define the exact extent of laryngeal cancer. The assessment of the extent of the advanced primary tumor should not be based only on clinical examination and laryngoscopy (direct or indirect), as such an attitude may sometimes lead to incorrect staging (usually downstaging) of the primary tumor. Helical computed tomography and nuclear magnetic resonance may be most useful in such cases [10]. Pre-treatment examination with CT scan and MRI may allow for the selection of patients with „favorable” tumors (egzophytic and superficial infiltrations of larynx), who stand a fair chance of cure and voice preservation after radiotherapy alone [7, 10].

The results of the performed analysis suggest that the necessity to perform an emergency tracheostomy before radiotherapy is significantly and independently connected with worse prognosis in patients with advanced laryngeal cancer. Emergency tracheostomy may favour local recurrence in this region, because of neoplastic cell inoculation during this procedure [22-24]. Kowalski and Terhaard report a higher risk of recurrence in the tracheostomy region and an increased risk of death [25, 26]. Some authors recommend primary surgery followed by radiotherapy in such patients [27]. It seems obvious that an emergency tracheostomy may be connected with a number of other factors, such as poor performance status, large mass of primary tumor, deep infiltration and destruction of adjacent structures i.e. a probability of higher radioresistance of the tumour.

Our material and literature data [7] draw attention to the small number of patients with stage T4 glottic cancer. A probable reason for this is the fact that the glottic

space is relatively small and that low staged, early symptomatic (voice hoarseness) cancers are diagnosed most often in this location. Extensive destructive cartilage infiltrations which spread outside the larynx are often diagnosed as supraglottic cancer (because of gross tumor volume) or as so-called „transglottic cancer”. Therefore it is difficult to establish either the glottic or supraglottic origin of advanced primary tumours.

Our material also draws attention to the very small number of patients who underwent „salvage surgery” after radiotherapy alone. This problem was already reported by Skolyszewski et al. [3], who had suggested that it may be caused by delayed diagnosis of recurrence brought on by irregular follow-up. In such cases radical surgery is impossible because of a large size of the tumour; such patient are usually treated palliatively. This problem extends beyond the subject of our report and we have performed no such analysis. However there is no doubt that this is a serious clinical problem, which calls for more frequent follow-up, especially during first 12 months after treatment and for establishing more effective methods of early detection of failures after radiotherapy. In the material analysed by Mendenhall et al. „salvage surgery” was performed in a majority of patients with uncured primary tumor or with locoregional recurrence [7]. It influenced significant improvement of treatment results in patients with advanced laryngeal cancer.

Treatment of advanced laryngeal cancer still remains the subject of many clinical trials while two main directions of investigations remain an integral element of radiotherapy research:

- (a) investigations on unconventional methods of fractionation (accelerated and hyperfractionated radiotherapy) [28-33].
- (b) investigations on chemo-radiotherapy [34].

The main purpose of many of these trials is voice preservation – total laryngectomy or lymphangectomy is reserved for the treatment of failures (salvage surgery). Results of the few completed randomised trials have not revealed any therapeutic benefit after conservative treatment (chemo-radiotherapy vs surgery+radiotherapy) assessed according to local control, regional control and overall survival, although 1/2 – 2/3 of patients survive 3 to 5 years with voice preservation after such treatment [34].

## Conclusions

1. Conventional radiotherapy of advanced laryngeal cancer has limited effectiveness (about 45% of 3-year DFS) as a method of radical treatment.
2. Poor prognostic factors in patients with advanced laryngeal cancer (T3-4) undergoing radiotherapy alone are: emergency tracheostomy and the presence of enlarged neck nodes.
3. The location and extent of extralaryngeal infiltrations influences the efficacy of radiotherapy in stage T4 laryngeal cancer.

4. A low percentage of patients, who underwent salvage surgery after radiotherapy failures, indicates the necessity of developing more effective methods of early detection and treatment of failures.

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