Original paper

Histopathological factors influencing results of combined treatment in patients with laryngeal cancer

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The aim of the study was to assess the prognostic value of postoperative histopathological factors as well as the clinical usefulness of the modified risk score for recurrence. In a group of 197 patients with laryngeal cancer who underwent surgery followed by radiation therapy, partial resection was performed in 21.5% of patients and total resection in 78.5%. The majority of patients had T3 or T4 (74%) and N0 (63%) cancer. Macroscopically positive margins were reported in 10% of patients after partial resection and in 7% of patients after total resection, whereas microscopically positive margins were observed in 31% and 20% of cases, respectively. Extracapsular extension was observed in 22% of patients. In order to estimate local and nodal recurrence risk rates, criteria developed by Peters were used. Five-year local control (LC) was achieved in 88% of patients, disease-free survival (DFS) in 68% of patients and overall survival (OS) in 73% of patients. In the case of macroscopically positive margins, the 5-year DFS was 33% lower compared to radical surgery and 25% lower in the case of microscopically positive margins. The 5-year DFS was reduced by 29% due to extracapsular extension. Cox model analysis indicated that the degree of recurrence risk was the most potent independent prognostic factor for postoperative radiation therapy in laryngeal cancer.
Negative histopathological factors influencing results of combined treatment of laryngeal cancer include macro- and microscopically positive margins, neck lymph node involvement and extracapsular extension.

Key words: histological factors, laryngeal cancer, radiotherapy, combined treatment.

Introduction

Surgery and radiotherapy, which may be used independently or in combination, are the basic treatment methods for laryngeal cancer. The choice of treatment strategy for laryngeal cancer varies in different oncology centres and depends mainly on the acquired clinical experience as well as on the adopted guidelines regarding therapeutic management in a given centre [1, 2, 3, 4, 5, 6, 7, 8, 9, 10]. The majority of indications for adjuvant radiotherapy are based on the data obtained from microscopic analysis of the surgical specimen [11]. The decision regarding potential adjuvant therapy is also influenced, to some extent, by the type of surgical procedure (partial, total) [12]. Correlations between various clinical and pathological parameters and the risk of recurrence have been described in numerous reports [9, 13, 14, 15, 16].

In 1993, Peters *et al*. [17] analysed a number of prognostic factors in patients with head and neck cancers who underwent surgery. Based on the assessment of surgical margins, tumour grade and number of involved lymph nodes, Peters proposed a point scale of local and nodal recurrence risk, which may be useful in selection of optimal adjuvant radiotherapy strategy. This fact became a basis for the present authors to develop a similar index including emergency tracheostomy.

The aim of this study was to evaluate the efficacy of combined treatment of patients with laryngeal cancer and to assess the clinical usefulness of a modified scale of the recurrence risk of laryngeal cancer based on the criteria proposed by Peters.

Material and methods

A group of 197 patients with squamous cell laryngeal carcinoma, who had undergone surgery followed by radical irradiation between 1994 and 1996 in the Cancer Centre and Institute of Oncology in Gliwice, were included in a retrospective analysis. The studied group included 172 men (87%) and 25 (13%) women; the mean age was 56 years (range: from 34 to 73 years). The majority of patients (122 cases, 62%) had a good (ZUBROD 1) or a very good performance status (75 patients, 38%) (ZUBROD 0) prior to radiotherapy. The original location of cancer infiltration in the larynx as well as the clinical stage of cancer were established during patient recruitment for adjuvant radiation therapy, based on the description of laryngological examination prior to surgical treatment as well as on the CT scan description.

The neoplasm was most frequently located in the supraglottis (115 patients, 58%), and in the glottis (82 patients, 42%). According to T stages, there were 52 (26%) T2, 88 (45%) T3, and 57 (29%) T4 tumours. According to N stages, there were 124 (63%) N0, 39 (20%) N1, 30 (15%) N2, and 4 (2%) N3 cases.

All patients received combined treatment: surgery with adjuvant radiotherapy. Partial resection was performed in 42 patients (21.5%), while total laryngeal resection was performed in 155 patients (78.5%). In some cases partial pharyngectomy was also performed. Lymph nodes were dissected in 103 patients (52%). A total of 29 patients (15%) had undergone an emergency tracheotomy prior to surgery due to dyspnoea.

Patient distribution in terms of macroscopically and microscopically positive margins is shown in Table I. In 16 patients (22%) out of 73, who showed lymph node involvement in histopathological examination, extracapsular extension (ECE) of nodal metastases was found.

In order to estimate local and nodal recurrence risk rates, criteria developed by Peters were used. These criteria were subject to the author's modification consisting in the inclusion of preoperative tracheostomy in the assessment of local recurrence risk. Three local recurrence risk groups were identified; group I: 0-1 point – low risk; group II: 2-4 points – medium risk; group III: ≥ 5 points – high risk. Three groups of nodal recurrence risk were also established; group I: 0-1 point – low risk; group II: 2-4 points – medium risk; group III: ≥ 5 points – high risk (Table II). Postoperative risk of local recurrence was assessed in the overall group of patients, while the risk of nodal recurrence was assessed in 103 patients (52%) who had undergone lymph node dissection (Table III).

The average period between surgery and radiotherapy was 63 days (range: 12-131 days). Patients received irradiation with gamma rays from cobalt-60 (Co60) in a conventional manner. Two opposing lateral fields including the postoperative tumour bed and neck nodes and the anterior field including supraclavicular nodes and tracheostomy were used. The uninvolved lymph nodes were treated electively up to a total dose of 50 Gy measured at a depth of 2.5 cm. The average total dose was 63 Gy (median: 66 Gy, range: 50-72 Gy). The spinal cord was shielded after a total dose of 40 to 44 Gy. Posterior neck nodes were additionally irradiated with 9 MeV electrons. Radiation therapy intervals lasting 3 days were reported in 124 patients (63%). In most cases (115, 93%) these were incidental intervals due to holidays, machine breakdown or absence of patients. In 5 cases (4%) intervals were caused by acute reaction, and in 4 cases (3%) by concurrent diseases.

The efficacy of combined treatment was assessed using the Kaplan-Meier method for local control, disease-free survival and overall survival. A univariate analysis was performed using a multiple-sample test,

Table I. Data concerning type of surgery and surgical margins

Type of surgery	Macroscopic margins			Microscopic margins		
	negative	positive	no data	negative	positive	no data
Partial resection	35 (83%)	4 (10%)	3 (7%)	21 (50%)	13 (31%)	8 (19%)
Total resection	128 (83%)	11 (7%)	16 (10%)	88 (57%)	31 (20%)	36 (23%)
Total	163 (83%)	15 (7%)	19 (10%)	109 (56%)	44 (22%)	44 (22%)

Table II. Criteria of local and nodal recurrence risk assessment according to modified Peters' scale

Risk factor		Number of points
Surgical margin	negative	0
	positive	5
	no data	2
Microscopic margin	negative	0
	1 positive	2
	≥ 1 positive	3
	no data	1
Histological grade	1-2	0
	3	2
	no data	1
Emergency tracheostomy	no	0
	yes	2
Total		0-12
Number of involved lymph nodes	1 (when Crile dissection was performed and ≥ 10 lymph nodes were removed)	1
	1 (when Crile dissection was done and < 10 lymph nodes were removed)	2
	1 (when the number of removed lymph nodes is unknown)	2
	1 (when selective lymphadenectomy was performed)	2
	≥ 2	3
Extracapsular extension	absent	0
	present	3
	no data	1
Histological grade	1-2	0
	3	3
	no data	1
Total		0-9

which is an extension of the log-rank test. Multivariate analysis was performed based on Cox proportional risk model analysis.

Results

In the analysed group of 197 patients, the 5-year actuarial LC, DFS and OS rates were 88%, 68% and 73%, respectively. Table IV shows the results of univariate analysis for the correlation between the selected prognostic factors and the 5-year LC, DFS and OS.

In the univariate analysis, performance status, nodal involvement, ECE, macro- or microscopically positive margins and emergency tracheostomy had a statistically significant effect on the treatment outcomes. There was a statistically significant correlation between the risk of tumour recurrence and treatment outcomes. The probability of 5-year LC decreased by 30% in the group of patients with high risk of recurrence compared to the group with low recurrence risk, while the 5-year DFS and 5-year OS decreased by 34% (Table IV).

When analysing treatment outcomes in the individual groups of local recurrence risk, depending on the type of performed surgery, it was found that a significant relation between the degree of risk and treatment outcomes occurred only in patients who had undergone total resection (Table IV).

It was also found that the risk of distant metastases increased from 4% in the group with low recurrence risk (I) to 15% in the high risk group (III). Similarly, there was a highly statistically significant correlation between the degree of risk of nodal recurrence and the rate of DFS and OS (Table IV). The rate of 5-year DFS decreased from 78% in the low recurrence risk group to 11% in the high risk group. Similarly, the rate of 5-year OS decreased from 85% to 11%. A correlation between the risk of nodal recurrence and the risk of distant metastases was observed; it increased from 4% in the low recurrence risk group to 12% in the high risk group.

With regard to radiotherapy parameters, only radiation treatment prolonged over 46 days had a statistically significant effect on 17% decrease in DFS (Table IV).

Multivariate analysis was performed separately for two groups of patients: group I – no lymph node dissection; group II – apart from laryngeal surgery, lymph node dissection was also performed. The analysis performed in the first group showed that the degree of recurrence risk was the most potent independent prognostic factor for postoperative radiotherapy in laryngeal cancer. Other significant prognostic factors were macroscopically positive margins and lymph node involvement (Tables V-VII). Cox multivariate analysis performed in the second group showed that the following factors independently affected treatment outcomes: performance status, the degree of nodal recurrence risk and local recurrence risk as well as emergency tracheostomy (Tables VIII-X).

Table III. Local and nodal recurrence risk, assessed on the basis of modified Peters' scale, according to type of surgery

Local recurrence risk	Partial resection	Total resection	Total
low	26 (62%)	92 (59%)	118 (60%)
medium	12 (28%)	47 (30%)	59 (30%)
high	4 (10%)	16 (11%)	20 (10%)
Nodal recurrence risk			
low	4 (80%)	49 (50%)	53 (51%)
medium	1 (20%)	32 (33%)	33 (32%)
high	0-	17 (17%)	17 (17%)

Discussion

Our results of combined treatment in patients with laryngeal cancer do not differ from the outcomes that have been obtained over a period of 30 years in different cancer centres [6, 7, 11, 14, 15, 18, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31].

Strong *et al*. [15] confirmed the efficacy of combined treatment in patients with head and neck cancers not only in relation to the primary lesion but also in relation to the regional lymphatic system; he achieved a reduction in the risk of nodal recurrence (in case of the involvement of one neck level) from 71% to 37% compared to radiotherapy alone. Lindberg and Jesse [25] also noted that in the case of multiple and/or bilateral nodal involvement, the results improve by 50% after postoperative radiotherapy. They also reported a decreased risk of contralateral cervical node metastases from 25% to 3% compared to surgery alone.

High rates of 5-year LC in patients with advanced laryngeal cancer after combined treatment were also achieved by Hinerman *et al*. [29], Smee *et al*. [30], and Akman *et al*. [31]. Thus, many years of clinical experience clearly demonstrate that postoperative radiotherapy in patients with advanced laryngeal cancer is an effective treatment. Numerous literature reports confirm that the main predictive factors are related to intraoperative and histopathological evaluation of the surgical specimen [13, 16, 17, 18, 19, 21, 29, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40].

The cervical node involvement confirmed in the histological examination (pN+) of the analysed material had a statistically significant effect on the decrease of 5-year DFS and OS rates. Literature reports highlight the effect of this factor on the prognosis in patients with head and neck cancers [16, 28, 32, 33, 34, 36]. Layland *et al*. [28] observed reduced survival in patients with N+ disease compared to N0. Wang *et al*. [38] found a significant decrease of long-lasting LC from 88% for N0 to 49% if the postoperative material contained more than 3 metastatic lymph nodes. However, Parsons *et al*. [37] and Peters *et al*. [17] did not demonstrate independent prognostic significance of the number of involved lymph nodes. Meredith *et al*. [22] reported a significant reduction of survival rates in patients with laryngeal cancer with clinically involved lymph nodes, depending on tumour location in the larynx. Furthermore, DFS and OS were negatively affected by ECE confirmed by histological examination. Similar observations have been reported by other authors [19, 32, 35, 40, 41, 42]. Peters *et al*. [17] support the significant effects of ECE on combined treatment outcomes. Snyderman *et al*. [40] noted increased rates of locoregional failures as well as distant metastases in relation to ECE. Our results also confirm the negative influence of ECE on DFS and OS.

Macroscopically positive margin is yet another unfavourable factor in the analysed material. The relatively high percentage of LC (65%) in the analysed group of patients who had undergone macroscopically non-radical surgery was related to appropriate choice of irradiation parameters (higher total dose). Similar results were also obtained by other authors [29, 32, 39, 43]. Jacobs *et al*. [36] observed a two-fold more frequent development of locoregional recurrence in patients with laryngeal cancer who had undergone macroscopically non-radical surgery. Most reports indicate that histologically negative margin is associated with a 30% decrease of the recurrence risk following combined treatment (surgery with subsequent radiotherapy) [13, 17, 18, 21, 29, 37, 38]. Hinerman *et al*. [29] noted that 5-year DFS decreased from 89% to 56% in the case of positive margins. Our results are consistent with these observations. Peters *et al*. [17], on the other hand, did not provide support for significant predictive value of postoperative margins in his studies. However, due to the lack of selection, randomisation and stratification, an inappropriate interpretation of the results is impossible in these studies. Patients with positive margins and unfavourable primary tumour localization received higher doses than patients with negative margins and different localization. In the analysed group of patients, emergency tracheostomy was an independent negative prognostic factor

Table IV. Results of univariate analysis of correlations between selected prognostic factors and 5-year LC, DFS and OS

Factor	Category	5-year LC	5-year DFS	5-year OS
Sex	M	87%	67%	73%
	F	95%	77%	84%
		ns	ns	ns
Age	≤ 56 years	86%	70%	76%
	>56 years	90%	66%	72%
		ns	ns	ns
Performance status before radiotherapy (ZUBROD)	0	92%	73%	77%
	1	82%	65%	73%
		p = 0.043	ns	ns
Histological grade	G1	87%	73%	76%
	G2	94%	88%	94%
	G3	93%	59%	72%
	no data	86%	63%	66%
		ns	ns	ns
Localization of primary tumor	supraglottis	89%	66%	73%
	glottis	86%	71%	75%
		ns	ns	ns
T stage	T2	94%	79%	83%
	T3	87%	64%	72%
	T4	78%	60%	62%
		ns	ns	ns
N stage	N0	89%	75%	81%
	N1	79%	50%	63%
	N2	70%	46%	47%
	N3	45%	40%	42%
		ns	p = 0.001	p = 0.001
ECE	no	85%	50%	67%
	yes	74%	21%	23%
		ns	p = 0.032	p = 0.035
Type of surgery	partial	83%	70%	76%
	total	90%	68%	73%
		ns	ns	ns
Macroscopically positive margins	no	91%	70%	77%
	yes	65%	37%	46%
	no data	83%	72%	72%
		p = 0.003	p = 0.003	p = 0.004
Microscopically positive margins	no	91%	75%	79%
	yes	76%	50%	61%
	no data	92%	71%	75%
		p = 0.013	p = 0.004	p = 0.032
Emergency tracheostomy	no	89%	71%	78%
	yes	77%	47%	46%
		ns	p = 0.004	p = 0.000

Table IV. Cont.

Factor	Category	5-year LC	5-year DFS	5-year OS
Local recurrence risk according to Peters' criteria	low	93%	76%	83%
	medium	86%	57%	64%
	high	63%	42%	49%
		p = 0.000	p = 0.000	p = 0.000
Local recurrence risk according to Peters' criteria for partial resections	low	88%	77%	80%
	medium	83%	60%	73%
	high	50%	60%	50%
		ns	ns	ns
Local recurrence risk according to Peters' criteria for total resections	low	94%	76%	84%
	medium	88%	56%	62%
	high	65%	40%	50%
		p = 0.005	p = 0.000	p = 0.000
Nodal recurrence risk according to Peters' criteria*	low	94%	78%	85%
	medium	88%	70%	81%
	high	79%	11%	11%
		ns	p = 0.000	p = 0.000
Time from surgery to radiotherapy	≤ 63 days	89	72	77
	> 63 days	88	64	71
		ns	ns	ns
Total dose	< 66 Gy	92	76	79
	≥ 66 Gy	84	61	69
Overall time of radiotherapy	≤ 46 days	90	73	76
	> 46 days	84	56	71
		ns	p = 0.02	ns
Gaps during radiotherapy	yes	90	66	73
	no	86	72	75
		ns	ns	ns

DFS – disease-free survival; ECE – extracapsular extension; LC – local control; OS – overall survival; ns – no significance.
** Nodal recurrence risk according to Peters' criteria assessed in the group of 103 patients who had undergone nodal resection*

and nearly quadrupled the risk of death. Maillard *et al*. [44] observed eight times higher risk of death in patients who underwent laryngectomy after emergency tracheostomy compared to those who had laryngectomy at the same time. Meredith *et al*. [22] and Pradier *et al*. [45] also found a statistically significant effect of this negative factor on treatment outcomes in patients with laryngeal cancer. Meredith *et al*. [22] suggest irradiation of the pre-existing tracheostomy region. In the literature reports, the recurrence rates in patients who have undergone emergency tracheostomy range between 27% and 71% [7, 43, 46, 47, 48]. Prognostic significance of this factor is controversial, as it is most frequently related to higher tumour stage as well as poorer overall performance status of patients and thus may not be an independent prognostic factor. It should be noted that the procedure alone may result in tumour cell implantation and, consequently, the development of recurrence [32, 46, 47, 49].

The performed analysis and the above-cited literature reports indicate that individual prognostic factors, when considered alone, may sometimes lack prognostic significance. In 1993, Peters *et al*. [17] confirmed in his studies that a combination of several nodal and/or local recurrence risk factors has an effect on combined treatment outcomes. A similar analysis was performed by Parsons *et al*. [37]. Peters and Parsons suggested establishing a hierarchy of some of the prognostic factors in a point scale to use it as a basis, in order to form risk groups for local and nodal recurrence. The studies by Peters *et al.* [17] were subsequently used in a randomised phase III trial conducted by Ang *et al*. [50] which

Table V. Results of multivariate analysis of correlations between selected prognostic factors and local control after combined treatment in patients without nodal dissection

Factor	Category	n	Recurrence risk (RR)	p
Local recurrence risk groups	I + II	84 (89%)	1.00	–
	III	10 (11%)	5.37	0.0032

Table VI. Results of multivariate analysis of correlations between selected prognostic factors and the risk of recurrence after combined treatment in patients without nodal dissection

Factor	Category	n	Recurrence risk (RR)	p
N stage	N0	75 (80%)	1.00	–
	N+	19 (20%)	17.30	0.0000
Local recurrence risk groups	I + II	84 (89%)	1.00	–
	III	10 (11%)	5.02	0.0109

Table VII. Results of multivariate analysis of correlations between selected prognostic factors and overall survival after combined treatment in patients without nodal dissection

Factor	Category	n	Recurrence risk (RR)	p
N stage	N0	75 (80%)	1.00	–
	N+	19 (20%)	6.05	0.0001
Macroscopic radicality of surgery	radical + unknown	85 (90%)	1.00	–
	non-radical	9 (10%)	3.67	0.0112

Table VIII. Results of multivariate analysis of correlations between selected prognostic factors and local control after combined treatment in patients who underwent nodal dissection

Factor	Category	n	Recurrence risk (RR)	p
Performance status before radiotherapy (ZUBROD)	0	32 (31%)	1.00	–
	1	71 (69%)	5.47	0.0182
Local recurrence risk groups	I + II	93 (90%)	1.00	–
	III	10 (10%)	5.79	0.0321

Table IX. Results of multivariate analysis of correlations between selected prognostic factors and the risk of recurrence after combined treatment in patients who underwent nodal dissection

Factor	Category	n	Recurrence risk (RR)	p
Nodal recurrence risk according to Peters' criteria	low + medium+ unknown	90 (87%)	1.00	–
	high	13 (13%)	5.80	0.0012
Local recurrence risk groups	I + II	93 (90%)	1.00	–
	III	10 (10%)	4.17	0.0124

Table X. Results of multivariate analysis of correlations between selected prognostic factors and overall survival after combined treatment in patients who underwent nodal dissection

Factor	Category	n	Recurrence risk (RR)	p
Nodal recurrence risk according to Peters' criteria	low + medium+ unknown	90 (87%)	1.00	–
	high	13 (13%)	5.91	0.0000
Emergency tracheostomy	no	88 (85%)	1.00	–
	yes	15 (15%)	3.73	0.0533

assessed, among other things, the usefulness of recurrence risk rate for the selection of an appropriate fractionation method and total dose in the adjuvant radiotherapy.

Literature reports [17, 37, 50] have become the basis for an attempt to develop a similar recurrence risk scale for patients with laryngeal cancer who have undergone surgery. Three local and nodal recurrence risk groups were identified among the analysed patients. Our own univariate and multivariate analyses support the significance of assigning patients to certain local and nodal recurrence risk groups, which shows a significant increase in the risk of recurrence for the coexistence of numerous factors with poor prognosis. Establishing recurrence risk groups in postoperative laryngeal cancer patients may prove essential for the improvement of treatment outcomes through a precise individual selection of radiotherapy parameters such as the total dose, irradiation method and the size of irradiated fields as well as treatment duration. The introduction of intensity-modulated radiation therapy (IMRT) into clinical practice enabled optimal dose distribution in target tissues with simultaneous protection of organs at risk. However, IMRT requires very high precision in determining the target volumes in order to avoid marginal misses. There are reports in the literature indicating an increased risk of recurrence in the margins of the irradiated field [51, 52, 53]. Chen *et al*. [54] reported the need for careful analysis of preoperative imaging studies, operative notes and histopathological reports to determine the appropriate target volumes and postoperative radiotherapy doses. Unfortunately, there are no convincing randomized trials showing superiority of IMRT to conventional radiotherapy in adjuvant treatment of head and neck cancers.

Conclusions

Postoperative radiotherapy in patients with laryngeal cancer ensures high local efficacy of treatment. The most important negative prognostic factors include macro- and microscopically positive margins, neck nodes involvement, extracapsular extension and emergency tracheostomy. The present results support the previous suggestions regarding the effects of several prognostic factors on combined treatment outcomes in patients with laryngeal cancer. A simultaneous evaluation of these factors, expressed by the estimation of postoperative cancer recurrence risk, may be used in an individual selection of physical and geometric parameters for adjuvant radiotherapy.

The authors declare no conflict of interest.

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