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Radiochemotherapy versus surgery plus radio(chemo)therapy for stage T3/T4 larynx and hypopharynx cancer – Results of a matched-pair analysis

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ABSTRACT

The standard treatment for non-metastatic T3/T4 larynx and hypopharynx cancer varies. This study compared definitive radiochemotherapy to surgery followed by radio(chemo)therapy. Forty-four patients treated with radiochemotherapy were matched to 88 patients receiving surgery plus radio(chemo)therapy. Groups were matched 1:2 for eight factors including age, gender, performance status, tumour site, histologic grade, T-/N-category and AJCC stage. Groups were compared for loco-regional control, metastases-free survival, overall survival and toxicity. Two-year loco-regional control rates were 75% after surgery plus radio(chemo-therapy) and 66% after radiochemotherapy ($p = 0.39$). Metastases-free survival rates were 76% and 77%, respectively ($p = 0.76$). Overall survival rates were 67% and 63%, respectively ($p = 0.95$). During follow up, 60% and 9% of the patients, respectively, received a total laryngectomy ($p = 0.004$). Grade $\geqslant 3$ oral mucositis and haematologic toxicity rates were higher with radiochemotherapy. Other toxicities were similar. Outcomes of radiochemotherapy appeared similar to those of surgery plus radio(chemo)therapy. The larynx preservation rate was higher after radiochemotherapy.

1. Introduction

The best treatment regimen for locally advanced larynx and hypopharynx cancer is controversial. According to randomised trials that compared induction chemotherapy followed by radiotherapy to total laryngectomy plus postoperative radiotherapy, the larynx preserving regimen did not result in significantly worse disease control or overall survival.[1–3] Another phase III trial demonstrated that concurrent radiochemotherapy was more effective than the sequential approach of induction chemotherapy followed by radiotherapy.[4] A randomised trial of 119 patients compared surgery followed by radiotherapy to definitive concurrent radiochemotherapy in stage III/IV non-metastatic squamous cell carcinoma of the head and neck at different sites.[5] In that trial, both treatment regimens were not significantly different with respect to disease-free survival. In the subgroup of patients with larynx/hypopharynx cancer, the organ preservation rate was higher than in patients with other tumour sites. The authors suggested that organ preservation should be attempted in partic-

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ular for patients with larynx/hypopharynx cancer. A randomised trial focusing on these patients would be desirable. However, such a randomised trial is difficult to perform, because patients are unlikely to agree to have a 50/50 chance of larynx preservation if a non-surgical option appears a possible and reasonable choice. In the present study, the matched-pair (1:2) design was chosen. It compared surgery followed by radiotherapy or radiochemotherapy to definitive concurrent radiochemotherapy with respect to loco-regional control, metastases-free survival, overall survival and toxicity.

2. Patients and methods

2.1. Study design

A total of 132 patients treated with definitive or postoperative irradiation for non-metastatic stage III/IV hypopharynx or larynx cancer at the University of Lubeck (N = 73) or at the University of Hamburg (N = 59) between 2000 and 2009 were included in the analysis. The data of these patients were obtained from a database including 596 head-and-neck cancer patients. The treatment concepts have not changed considerably during this period (Table 1) and depended mostly on the patient's as well as on the treating physicians' preference. The data were obtained from the patients, their general practitioners, treating oncologists and patient charts (manual review). Tumour staging was based on computed tomography and endoscopy. Treatment was based on interdisciplinary protocols favoured at the treating institutions at certain periods of time. Data from 44 patients treated with definitive radiochemotherapy were matched (1:2) to 88 patients treated with surgery plus radio(chemo)therapy for nine potential prognostic factors: age (<55 versus 55–59 versus >59 years), gender, Karnofsky performance score (KPS 70 versus >70), tumour site (hypopharynx versus larynx), histologic grade (G1–2 versus G3), T-category (T3 versus T4), N-category (N0–2a versus N2b–3) and American Joint Committee of Cancer (AJCC) stage (III versus IV according to AJCC classification, 6th edition[6]). All of these factors were matched (Table 1).

Table 1 – Patient characteristics of both treatment groups.

	Surgery plus radio(chemo)therapy (n = 88) N (%)	Radio-chemotherapy alone (n = 44) N (%)	p
Age			
<55 years	30 (34)	15 (34)	
55–59 years	26 (30)	13 (30)	
>59 years	32 (36)	16 (36)	1.00
Gender			
Female	14 (16)	7 (16)	
Male	74 (84)	37 (84)	1.00
Karnofsky-PS			
70	30 (34)	15 (34)	
>70	58 (66)	29 (66)	1.00
Tumour site			
Hypopharynx	36 (41)	18 (41)	
Larynx	52 (59)	26 (59)	1.00
Histologic grade			
G 1–2	50 (57)	25 (57)	
G 3	38 /43)	19 (43)	1.00
T-category			
3	44 (50)	22 (50)	
4	44 (50)	22 (50)	1.00
[4a]	[44]	[12]	
[4b]	[0]	[10]	
N-category			
0–2a	40 (45)	20 (45)	
2b–3	48 (55)	24 (55)	1.00
AJCC-stage			
III	18 (20)	9 (20)	
IV	70 (80)	35 (80)	1.00
Treatment period			
2000–2004	49 (56)	25 (57)	
2005–2009	39 (44)	19 (43)	0.97

2.2. Treatment

2.2.1. Surgery plus radio(chemo)therapy

Surgery was performed as resection of the primary tumour plus bilateral modified radical neck dissection. Fifty-two patients (59%) received a total laryngectomy, 28 patients (32%) a partial laryngectomy and 8 patients (9%) a tumour resection with preservation of the entire larynx. A microscopically complete resection (R0-resection) was achieved in 65 of the 88 patients (74%), a microscopically residual tumour (R1-resection) was found in 23 patients (26%). Conventionally fractionated radiotherapy (five fractions per week) with doses per fraction of 2.0 Gy, was delivered 3–6 weeks following surgery. Radiotherapy was performed with a linear accelerator and 4–6 MV photons. The total dose delivered to the primary tumour and involved lymph nodes depended on the extent of resection. Patients received 60 Gy after R0-resection and 66 Gy after R1-resection. The total dose administered to the clinically uninvolved cervical and supraclavicular lymph nodes was 50–60 Gy.

The surgery group included 41 patients (51%) with high risk factors such as positive surgical margins, extracapsular spread of lymph node metastasis and lympho-vascular or perineural invasion. These patients received concurrent chemotherapy in addition to radiotherapy. Concurrent chemotherapy consisted of 100 mg/m^2 of cisplatin on radiotherapy days 1, 22 and 43 (10 patients), of 20 mg/m^2 of cisplatin on radiotherapy days 1–5 and 29–33 (4 patients), or 20 mg/m^2 of cisplatin plus 600 or 1000 mg/m^2 of 5-fluorouracil on radiotherapy days 1–5 and 29–33 (27 patients). All chemotherapy patients received prophylactic hydration and antiemetic agents.

2.2.2. Definitive radiochemotherapy

Forty-four patients received conventionally fractionated radiotherapy (five fractions per week) with doses per fraction of 2.0 Gy. Radiotherapy was performed with a linear accelerator and 4–6 MV photons. The total dose delivered to the primary tumour and the involved lymph nodes was 70 Gy. The total dose administered to the clinically uninvolved cervical

and supraclavicular lymph nodes was 50–60 Gy. Concurrent chemotherapy consisted of 100 mg/m^2 of cisplatin on radiotherapy days 1, 22 and 43 (13 patients), of 20 mg/m^2 of cisplatin on radiotherapy days 1–5 and 29–33 (9 patients), or of 20 mg/m^2 of cisplatin plus 600 or 1000 mg/m^2 of 5-fluorouracil on radiotherapy days 1–5 and 29–33 (22 patients). Chemotherapy patients received prophylactic hydration and antiemetic agents.

2.2.3. *Study end-points and statistical considerations*

Both treatment groups were compared for loco-regional control (LC), metastases-free survival (MFS) and overall survival (OS), referenced from the last day of radiotherapy. The patients were followed until death or from 13 to 56 months (median: 26 months) in those alive at last evaluation. Furthermore, acute and late radiotherapy and radiochemotherapy related toxicity were compared. Acute toxicity was evaluated according to Common Toxicity Criteria (CTC 2.0), late toxicity according to RTOG/EORTC criteria.[7,8] Late toxicity was defined as toxicity occurring later than 90 d after radiotherapy commenced.

LC, MFS and OS rates were calculated with the Kaplan–Meier-method.[9] The differences between the Kaplan–Meier curves were calculated with the Wilcoxon test. The prognostic factors found to be significant ($p < 0.05$) in the univariate analysis were included in a multivariate analysis, performed with the Cox proportional hazards model. The primary goal of this study was to compare the results of definitive radiochemotherapy to surgery followed by radio(chemo)therapy. For statistical calculations, the loco-regional rate at 2 years was defined as the primary end-point. A total of 132 patients included in this study allowed to detect a loss of clinical efficacy in the radiochemotherapy alone-group of 20% with a statistical power of 80% (level of significance = 5%).

3. Results

On univariate analysis, tumour site ($p = 0.027$), histologic grade ($p = 0.031$) and T-category ($p = 0.030$) were associated with LC. The treatment regimen had no significant impact on LC ($p = 0.39$, Fig. 1). The results of the univariate analysis of LC are summarised in Table 2. On multivariate analysis of LC, tumour site (risk ratio [RR] 2.05; 95%-confidence interval [CI] 1.06–4.05; $p = 0.034$), maintained significance. Histologic grade (RR 1.92; 95%-CI 1.00–3.77; $p = 0.052$) and T-category (RR 1.91; 95%-CI 0.99–3.81; $p = 0.053$) were almost significant.

At the time of recurrence, 4 of 44 patients (9%) in the radiochemotherapy group received a salvage laryngectomy. Of the 36 patients in the surgery plus radio(chemo)therapy group, who initially had no complete laryngectomy, one patient (3%) received a total laryngectomy at the time of recurrence. Thus, during the period of follow up, 9% in the radiochemotherapy group and 60% in the surgery plus radio(chemo)therapy group received a total laryngectomy ($p = 0.004$). The median follow up time was 21.5 months in the entire radiochemotherapy group and 20.5 months in the entire surgery plus radio(chemo)therapy group. In the patients who were alive at the last follow up visit, the median follow up times were 25 months and 25.5 months, respectively.

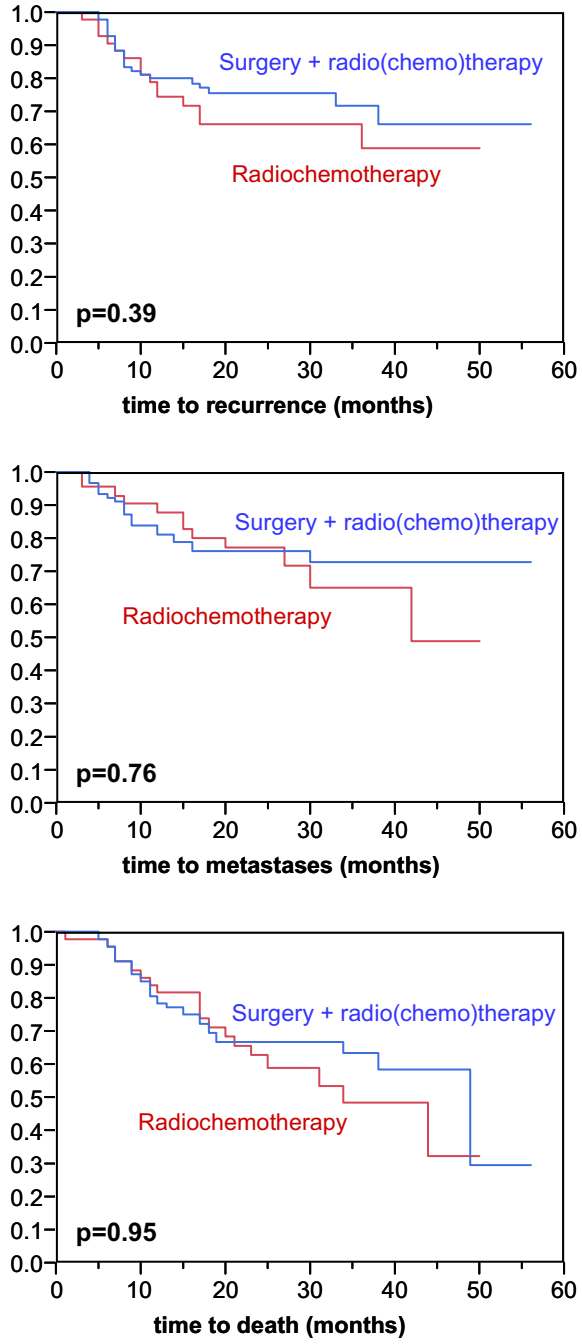

Fig. 1 – Comparison of both treatment groups surgery plus radio(chemo)therapy and radiochemotherapy with respect to loco-regional control (top), metastases-free-survival (middle) and overall survival (bottom).

On univariate analysis, gender ($p = 0.035$), tumour site ($p = 0.003$), histologic grade ($p < 0.001$) and N-category ($p = 0.021$) were associated with MFS. The treatment regimen was not significantly associated with MFS ($p = 0.76$, Fig. 1). The results of the univariate analysis of MFS are summarised in Table 3. On multivariate analysis of MFS, tumour site (RR 2.33; 95%-CI 1.12–5.08; $p = 0.024$) and histologic grade (RR 2.65; 95%-CI 1.30–5.74; $p = 0.007$) maintained significance.

Table 2 – Univariate analysis of loco-regional control.

	At 1 year (%)	At 2 years (%)	p
Treatment			
Surgery plus radio (chemo)therapy	80	75	
Radiochemotherapy	74	66	0.39
Age			
<55 years	81	78	
55-59 years	71	67	
>59 years	81	71	0.61
Gender			
Female	91	85	
Male	75	70	0.14
Karnofsky-PS			
70	79	76	
>70	78	71	0.72
Tumour site			
Hypopharynx	68	62	
Larynx	85	79	0.027
Histologic grade			
G 1–2	84	79	
G 3	69	62	0.031
T-category			
3	86	80	
4	70	64	0.03
N-category			
0–2a	85	76	
2b–3	73	69	0.15
AJCC-stage			
III	89	79	
IV	75	71	0.16
Entire cohort	78	72	

Table 3 – Univariate analysis of metastases-free survival.

	At 1 year (%)	At 2 years (%)	p
Treatment			
Surgery plus radio(chemo)therapy	81	76	
Radiochemotherapy	88	77	0.76
Age			
<55 years	93	85	
55–59 years	76	74	
>59 years	81	71	0.21
Gender			
Female	95	95	
Male	81	72	0.035
Karnofsky-PS			
70	75	66	
>70	88	81	0.06
Tumour site			
Hypopharynx	75	61	
Larynx	89	86	0.003
Histologic grade			
G 1–2	93	87	
G 3	70	61	<0.001
T-category			
3	85	81	
4	82	71	0.37
N-category			
0–2a	90	88	
2b–3	78	66	0.021
AJCC-stage			
III	89	85	
IV	82	74	0.39
Entire cohort	84	76	

Gender (RR 4.22; 95%-CI 0.81–77.52; $p = 0.10$) and N-category (RR 1.44; 95%-CI 0.70–3.12; $p = 0.33$) were not significant.

On univariate analysis, gender ($p = 0.045$), tumour site ($p = 0.001$), histologic grade ($p < 0.001$) and N-category ($p = 0.013$) were associated with OS. The T-category was almost significantly associated with OS ($p = 0.055$). The treatment regimen had no significant impact ($p = 0.95$, Fig. 1). The results of the univariate analysis of OS are summarised in Table 4. On multivariate analysis, tumour site (RR 2.00; 95%-CI 1.11–3.75; $p = 0.023$) and histologic grade (RR 1.97; 95%-CI 1.12–3.52; $p = 0.019$) maintained significance. Gender (RR 1.99; 95%-CI 0.71–7.12; $p = 0.20$) and N-category (RR 1.36; 95%-CI 0.76–2.50; $p = 0.31$) were not significant.

The rates of acute grade $\geqslant 3$ oral mucositis leading to dysphagia were 18% (16 patients) in the surgery plus radio(chemo)therapy group and 43% (19 patients) in the radiochemotherapy group ($p = 0.015$). Grade $\geqslant 3$ acute skin toxicity occurred in 19% (17 patients) and in 18% (8 patients) of patients, respectively ($p = 0.97$). Grade $\geqslant 3$ haematologic toxicity was higher in the radiochemotherapy group (23% versus 7%, $p = 0.026$). Grade $\geqslant 3$ nausea/emesis rates were similar in both groups (9% versus 7%, $p = 0.92$). Grade 3 ototoxicity was not observed; grade 2 ototoxicity occurred in one patient of each treatment group (2% versus 1%, $p = 0.97$). A treatment related death occurred in one patient (2%) of the radiochemotherapy group and in no patient (0%) of the surgery plus radio(chemo)therapy group, respectively ($p = 0.93$). Grade $\geqslant 3$ late toxicity such as xerostomia, neck fibrosis, skin toxicity and lymph oedema were observed in 6% (5 patients) of the surgery plus radio(chemo)therapy group and 11% (5 patients) of the radiochemotherapy group ($p = 0.65$).

4. Discussion

The most appropriate treatment for non-metastatic T3/T4 larynx and hypopharynx cancer is controversial. Many centres worldwide favour surgery followed by radiotherapy or, if specific risk factors are present, followed by radiochemotherapy. However, this regimen entails certain surgery and anaesthesia related risks. Therefore, definitive radiochemotherapy would be a good alternative option if it provided similar treatment results as surgery plus radio(chemo)therapy. Furthermore, larynx preservation by avoiding surgery is an important issue. In the present study, concurrent radiochemotherapy did not result in significantly worse outcomes in terms of loco-regional control, metastases-free survival and overall survival but in a significantly higher rate of larynx preservation when compared to surgery followed by

Table 4 – Univariate analysis of overall survival.

	At 1 year	At 2 years	p
Treatment			
Surgery plus radio(chemo)therapy	78	67	
Radiochemotherapy	82	63	0.95
Age			
<55 years	80	69	
55–59 years	79	62	
>59 years	79	64	0.81
Gender			
Female	91	83	
Male	77	62	0.045
Karnofsky-PS			
70	76	63	
>70	82	67	0.34
Tumour site			
Hypopharynx	71	47	
Larynx	86	77	0.001
Histologic grade			
G 1–2	89	74	
G 3	66	53	<0.001
T-category			
3	85	73	
4	74	57	0.06
N-category			
0–2a	88	76	
2b–3	72	56	0.013
AJCC-stage			
III	93	79	
IV	76	61	0.08
Entire cohort	80	65	

radio(chemo)therapy. A randomised trial comparing these two treatment regimens particularly in patients with larynx/hypopharynx cancer has not yet been published.

However, several randomised trials have compared induction chemotherapy followed by radiotherapy to surgery followed by radiotherapy.[1–3] The Veterans Affairs Laryngeal Cancer Study Group presented a randomised trial of 332 patients with stage III/IV larynx cancer.[1] The patients received either three courses of cisplatin/5-fluorouracil followed by definitive radiotherapy (66–76 Gy) or surgery and radiotherapy. After two courses of chemotherapy, tumour response was assessed. In case of no response or progressive disease, the patients received a salvage laryngectomy. A response was observed in 85% of patients. The 2-year overall survival rates were 68% for both groups ($p = 0.98$). Patients of the chemotherapy group had more local recurrences ($p < 0.001$) and fewer distant metastases ($p = 0.016$) than patients of the surgery group. A phase III trial of the EORTC Head and Neck Group including 194 eligible patients with pyriform sinus cancer compared surgery plus 50–70 Gy of postoperative radiotherapy to patients who responded to induction chemotherapy with cisplatin/5-fluorouracil and received 70 Gy of radiotherapy following three courses of chemotherapy.[2] Median survival times were 25 months in the surgery plus radiotherapy group and 44 months in the chemotherapy plus radiotherapy group ($p = 0.006$). Loco-regional control rates were similar in both groups, whereas distant failure was more common in the surgery plus radiotherapy group (36% versus 25%, $p = 0.041$). In contrast to these two studies that favoured the larynx preserving approach, a third randomised study of 68 patients with T3 larynx cancer demonstrated overall survival to be worse in patients receiving induction chemotherapy plus radiotherapy than in patients receiving total laryngectomy followed by radiotherapy.[3] However, no randomised study so far has compared surgery followed by radiotherapy to concurrent (instead of sequential) radiochemotherapy.

Because of investigator biases in terms of therapy, such a randomised trial may be difficult to perform. Physicians often favour one combination of therapy, convinced that their regimen is best, and may not offer qualified patients participation in a trial. Furthermore patients who wish to keep their larynx are not likely to participate in a randomised trial offering them only a 50% chance of larynx preservation. Instead of a randomised trial, we performed a matched pair analysis on our retrospective data. Eight potential prognostic factors were considered for matching the patients and all of these factors had to be conformal. Lacking a phase III trial, this approach provides the highest quality data possible. Despite the fact that the eight potential prognostic factors and the treatment period were very well balanced between both treatment groups (Table 1), hidden selection biases cannot be excluded from the present study because of its retrospective nature. This fact should be considered when interpreting our results. Taken into account the retrospective nature of this study and relatively small number of patients, our findings must be considered exploratory and not conclusive.

The present study revealed that the treatment regimens did not significantly differ with respect to loco-regional control, metastases-free survival and overall survival. It is further possible that the results of definitive radiochemotherapy may be further improved by using hyperfractionated radiation therapy instead of conventional fractionation.[10–12] Another option to improve the results of radiochemotherapy would be the use of more effective chemotherapy regimens such as docetaxel/ciosplatin/5-fluorouracil. In the subgroup analysis of patients with locally advanced larynx or hypopharynx cancer included the TAX 324 study, the patients who received induction chemotherapy with three courses of either PF (100 mg/m^2 of cisplatin on day 1 plus 1000 mg/m^2 of 5-fluorouracil on days 1–5) or TPF (75 mg/m^2 of docetaxel on day 1 plus 100 mg/m^2 of cisplatin on day 1 plus 1000 mg/m^2 of 5-fluorouracil on days 1–5).[13] Responders in both groups received additional radiochemotherapy with weekly carboplatin (area under the curve 1.5). The 3-year laryngectomy-free survival rates were 52% with TPF and 32% with PF, respectively ($p = 0.030$).

The present study revealed that the treatment outcomes were significantly associated with tumour site and histologic grade, and were almost significantly associated with T-category. These findings were consistent with the available data from the literature. Tumour site and histological grade have been previously described as independent prognostic factors for loco-regional control and for overall survival in patients with locally advanced head and neck cancer.[10,14] The impact

of T-category on treatment outcome has also been described before.[10,15–17]

In summary, the results of definitive radiochemotherapy did not appear inferior to those of surgery plus radio (chemo)therapy for patients with T3/T4 larynx and hypopharynx cancer with respect to loco-regional control, metastases-free survival, overall survival. In addition, the larynx preservation rate was significantly higher after definitive radiochemotherapy. However, the findings of this study can only be considered exploratory rather than conclusive and should be confirmed in a larger series of patients.

Conflict of interest statement

None declared.

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