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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