A Total Radiation Dose of 70 Gy Is Required After Macroscopically Incomplete Resection of Squamous Cell Carcinoma of the Head and Neck

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Abstract. *Aim: To contribute to the definition of the optimal total radiation dose and to determine the role of concurrent chemotherapy after macroscopically incomplete resection of squamous cell carcinoma of the head and neck (SCCHN). Patients and Methods: Twenty-six patients treated with postoperative radio(chemo)therapy following macroscopically incomplete resection were evaluated. Total radiation dose (70 Gy vs. 59.4-66 Gy), concurrent chemotherapy (yes vs. no) plus six factors were investigated for locoregional control (LRC) and overall survival (OS). Results: On analyses of LRC, 70 Gy was significantly superior to 59.4-66.0 Gy. Two-year LCR rates were 94% and 25%, respectively (p<0.001). Concurrent chemotherapy significantly improved 2-year LRC (90% vs. 0%, p<0.001). Both 70 Gy (92% vs. 11%, p<0.001) and concurrent chemotherapy (80% vs.0%, p<0.001) also resulted in better OS. Conclusion: A total radiation dose of 70 Gy was significantly superior to lower doses regarding both LCR and OS. Concurrent chemotherapy is also very important to achieve optimal outcomes.*

Many patients with locally advanced squamous cell carcinoma of the head-and-neck (SCCHN) are treated with surgical resection followed by radio(chemo)therapy (1-3). In most patients receiving surgery, the primary tumor and the involved lymph nodes can be resected completely. In some patients, histopathological examination reveals that the tumor was not entirely resected (microscopically incomplete resection, R1). In few patients, the resection is macroscopically incomplete (R2), mostly if the primary tumor or the lymph nodes are adjacent to or have even infiltrated large cervical blood vessels or nerves (1-3). In these situations, a second surgery to achieve a complete resection is often not reasonably possible. The vast majority of these patients are planned to receive postoperative radiochemotherapy. However, some patients refuse chemotherapy and are, therefore, treated with radiotherapy alone. Since macroscopically incomplete resection of a SCCHN is quite uncommon, there is a lack of data regarding the postoperative treatment of these patients. Particularly, the optimal total radiation dose is yet to be defined. In the present study, two total radiation dose levels, 70 Gy and 59.4-66.0 Gy, were compared for treatment outcomes in terms of locoregional control (LRC) and overall survival (OS). In addition, the value of concurrent cisplatin-based chemotherapy was investigated.

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Patients and Methods

Twenty-six patients treated with postoperative radio(chemo)therapy following macroscopically incomplete resection of locally advanced SCCHN were included in this retrospectively study. The primary goal was to compare a total radiation dose of 70 Gy given to the incompletely resected regions (fractionation: five times 2.0 Gy per week) to lower total doses (59.4-66.0 Gy with doses per fraction of 1.8 or 2.0 Gy) with respect to LRC and OS. Secondly, the impact of concurrent cisplatin-based chemotherapy on these two endpoints was evaluated. Cisplatin-based chemotherapy consisted of 30-40 mg/m^2 of cisplatin given once per week (n=2), 100 mg/m^2 of cisplatin on days 1, 22 and 43 (n=10), 20 mg/m^2 of cisplatin on days 1-5 + 29-33 (n=2) or the latter regimen plus 600 or 1,000 mg/m^2 5-fluorouracil (5-FU) also administered on days 1-5 and 29-33 (n=7).

In addition to the total radiation dose and concurrent chemotherapy, six other factors were investigated with respect to LRC and OS, including tumor stage (T1-2 *vs.* T3-4), lymph node

Table I. *Analysis of locoregional control (LRC).*

	At 1 year (%)	At 2 year (%)	*p*-Value
Total radiation dose			
70 Gy (n=17)	94	94	
59.4-66 Gy (n=9)	25	25	**<0.001**
Concurrent chemotherapy			
Yes (n=21)	90	90	
No (n=5)	0	0	**<0.001**
Tumor stage			
T1-2 (n=4)	50	n/a	
T3-4 (n=22)	76	76	0.85
Lymph node stage			
N0-2a (n=8)	75	75	
N2b-3 (n=18)	75	75	0.95
Karnofsky performance score			
KPS 80-100 (n=19)	83	83	
KPS ≤70 (n=7)	54	54	0.11
Gender			
Female (n=5)	80	80	
Male (n=21)	74	74	0.74
Age			
≤58 years (n=13)	84	84	
≥59 years (n=13)	66	66	0.25
Tumor site			
Oropharynx (n=13)	91	91	
Hypopharynx (n=3)	33	33	
Larynx (n=5)	50	50	
Oral cavity or floor of the mouth (n=5)	80	80	0.09

n/a, Not available; bold *p*-values are significant after Bonferroni correction.

Table II. *Analysis of overall survival (OS).*

	At 1 year (%)	At 2 year (%)	*p*-Value
Total radiation dose			
70 Gy (n=17)	100	92	
59.4-66 Gy (n=9)	22	11	**<0.001**
Concurrent chemotherapy			
Yes (n=21)	86	80	
No (n=5)	20	0	**<0.001**
Tumor stage			
T1-2 (n=4)	50	n/a	
T3-4 (n=22)	77	72	0.054
Lymph node stage			
N0-2a (n=8)	88	70	
N2b-3 (n=18)	67	60	0.72
Karnofsky performance score			
KPS 80-100 (n=19)	79	72	
KPS ≤70 (n=7)	57	38	0.032
Gender			
Female (n=5)	100	80	
Male (n=21)	67	60	0.34
Age			
≤58 years (n=13)	85	74	
≥59 years (n=13)	62	54	0.08
Tumor site			
Oropharynx (n=13)	85	74	
Hypopharynx (n=3)	67	33	
Larynx (n=5)	40	40	
Oral cavity or floor of the mouth (n=5)	80	80	0.07

n/a, not available; bold *p*-values are significant after Bonferroni correction.

stage (N0-2a *vs*. N2b-3), the Karnofsky performance score (KPS 80-100 *vs*. KPS ≤70), gender, age (≤58 *vs*. ≥59 years, median age=58.5) and site of the primary tumor (oropharynx *vs*. hypopharynx *vs*. larynx *vs*. oral cavity or floor of the mouth).

For the analyses of LRC and OS, the Kaplan-Meier method plus the log-rank test were applied (4). After Bonferroni correction for multiple tests (n=8), p-values <0.006 were considered significant, which represented an α-level of <0.05. Both LRC and OS rates were referenced from the last day of radiotherapy. Median follow-up times were 17 months (range=1-74) in the entire series and 22.5 months (range=12-74) in those patients who were alive at the time of the last follow up.

Results

The LRC rates of the entire cohort were 75% at 1 year and 75% at 2 years, respectively. A total radiation dose of 70 Gy was significantly superior to total doses of 59.4-66 Gy. The LRC rates after 70 Gy were 94% at 1 year and 94% at 2 years, respectively, compared to 25% and 25%, respectively, after 59.4-66.0 Gy ($p<0.001$). Furthermore, the addition of concurrent cisplatin-based chemotherapy led to better LRC rates at 1 year (90% *vs*. 0%) and 2 years (90% *vs*. 0%) ($p<0.001$). The results of the entire analyses of LRC are shown in Table I.

The 1- and 2-year OS rates for the entire cohort were 73% and 64%, respectively. A total radiation dose of 70 Gy resulted in significantly better OS rates than total doses of 59.4-66.0 Gy at both 1 year (100% *vs*. 22%) and 2 years (92% *vs*. 11%), respectively ($p<0.001$). The addition of concurrent chemotherapy resulted in improved OS both at 1 year (86% *vs*. 20%) and at 2 years (80% *vs*. 0%) ($p<0.001$). The results of the complete survival analyses are summarized in Table II.

Discussion

The outcomes after the treatment of advanced SCCHN have been improved for both metastatic disease and locally advanced tumors (5-11). A considerable number of patients with locally advanced tumors are treated with resection of

the primary tumor and bilateral neck dissection (1-3). In most cases, both the primary tumor and the involved lymph nodes are resected completely. However, in some patients, the tumor or the lymph nodes cannot be completely removed and the result of the surgical procedure is only a macroscopically incomplete resection. Often, a re-resection entails significant risks, including severe damage of blood vessels, nerves or soft tissues and, therefore, cannot be safely performed (1). Furthermore, a considerable number of patients refuse a second surgery, which may be debilitating. After a macroscopically incomplete resection of a SCCHN, the patients generally require concurrent radiochemotherapy (1, 3). However, patients may refuse the additional chemotherapy or may not be able to withstand combined treatment. These patients generally receive radiotherapy alone. Since a macroscopically incomplete resection of a SCCHN is very uncommon, comparably little data are available regarding the treatment of these patients. For example, uncertainty exists with respect to the (i) appropriate total radiation dose required for this situation and (ii) value of adding concurrent chemotherapy to radiation treatment.

This analysis addressed both issues. Based on these findings, a total radiation dose of 70 Gy resulted in significantly better LRC and OS when compared to total doses of 59.4-66 Gy. Therefore, 70 Gy are recommended to achieve optimal results after R2 resection. The retrospective nature of the data and the relatively small number of patients included in this study should be taken into account when considering this recommendation. However, since macroscopically incomplete resection of SCCHN is a rare situation, prospective trials will likely not address this issue in the near future.

Furthermore, the results of the present study suggested that, in addition to an appropriate total radiation dose, the concurrent administration of cisplatin-based chemotherapy is important to achieve the best possible LRC and OS rates. The finding that the addition of concurrent chemotherapy to irradiation improves the outcomes of patients with an incompletely resected SCCHN has previously been demonstrated after microscopically incomplete resection of SCCHN in a secondary analysis of two randomized trials (12). In addition, it has already been shown that patients with SCCHN receiving definitive treatment benefit from concurrent chemotherapy in terms of improved outcomes (13, 14). Therefore, it appeared quite reasonable that patients who had a macroscopically incomplete resection of a locally advanced SCCHN would benefit from the addition of chemotherapy to radiotherapy. This hypothesis was confirmed in the present study. Additional studies are required to identify the most appropriate chemotherapy regimen used for radiochemotherapy after macroscopically incomplete resection of a SCCHN.

In conclusion, based on the findings of this study, a total radiation dose of 70 Gy is the appropriate dose after macroscopically incomplete resection of a locally advanced SCCHN. In order to achieve optimal LRC and OS, radiotherapy must be supplemented with concurrent chemotherapy.

Conflicts of Interest

On behalf of the Authors, the corresponding Author states that there are no conflicts of interest related to this study.

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