# Postoperative Irradiation of Laryngeal Carcinoma

## *The Prognostic Value of Tumour-Free Surgical Margins*

Jonathan Naudé and Werner Dobrowsky

Department of Radiotherapy and Radiobiology, University of Vienna, Vienna General Hospital, Vienna, Austria

Correspondence to: Dr Jonathon Naudé, Department of Radiotherapy and Radiobiology, University of Vienna, Vienna General Hospital, Währinger Gürtel 18-20, A-1090 Vienna, Austria

Acta Oncologica Vol 36, No. 3, pp. 273–277, 1997

Between 1972 and 1987, two hundred and five carcinoma patients were treated with surgery and postoperative radiotherapy. The histological confirmation of tumour-free margins was only predictive of significant differences in locoregional control in locally advanced disease. In addition, macroscopically assessed margins in advanced cases were predictive of survival probability. We suggest that the adjuvant radiotherapy was able to reduce the incidence of locoregional recurrence in the early stage microscopic positive group, hence the lack of a significant difference in the control rates. The effect on survival is therefore indirect. The advanced cases showed significantly reduced locoregional control rates and disease-specific survival times after macroscopic assessment of positive margins, possibly a sign of tumour extension beyond the margins of the radiation field. We compare our results with published reports of cases not receiving adjuvant therapy.

*Received 24 June 1996*
*Accepted 2 February 1997*

The importance of tumour-free resection margins has been debated for many years despite underestimation of tumour extension becoming less of a problem since the advent of intraoperative frozen sections. Problems still remain in frozen section analysis of surgical margins (1), and in function-preserving operations of the larynx, such as stripping of the vocal cords and in laser surgery (2).

In 1989, Fini-Storchi et al. (3) came to a somewhat provocative conclusion: In conservative surgery of the larynx, cases with positive resection margins not receiving any further treatment do not necessarily lead to recurrence. Their study of 56 patients was interesting as it gave us an insight into the fate of cases with laryngeal carcinoma receiving no further treatment after surgery. A recurrence in 3–7 years developed in 36% of the cases, 23% in the negative- and 57% in the positive margin group respectively. For purposes of comparison we grouped those cases in Fini-Storchi's study initially having in-situ cancer and precancerous lesions in their margins in the positive margin group. Bauer et al. (4) found an 18% recurrence rate in their positive margins group and in 6% of the negative margins in T3 glottic tumours after hemilaryngetomy in 5–12 years. Lam et al. (5) found 48% and 11% recurrence rates in positive and negative margins after laryngectomy. Loree & Strong (6) on the other hand found tumour-free surgical margins to be a highly significant factor in locoregional control and to give a small but significant 5-year survival benefit in oral cavity tumours. Yet they found adjuvant radiotherapy to be relatively ineffective in improving the rate of locoregional control in cases with positive margins. Amdur et al. (7) found surgical margins to be an important prognostic factor of locoregional control and survival in head and neck cancer. The consensus in other papers was that, provided the prescribed radiation dose was at least 60 Gy (8) or the operation-radiation interval was less than 6 weeks (9), positive surgical margins could be managed effectively to excellently with radiotherapy.

It would seem reasonable to assume that correctly prescribed radiotherapy does kill any microscopic tumour cell deposits remaining after the operation. As some authors found a correlation between surgical margin status and locoregional control and/or survival probability (7, 10) while others found no significant improvement after radiotherapy (6,11), we focused our analysis on these questions.

 ISSN 0284-186X

**Table 1**

*Patient characteristics*

| Macroscopic | Positive | St. Dev. | Negative | St. Dev. | t-test |
|---|---|---|---|---|---|
| No. of patients | 21 | | 184 | | |
| Median age | 60.7 years | 13.2 | 58.6 years | 10.3 | NS |
| Median RT-time | 50.5 days | 11.2 | 49.3 days | 12.3 | NS |
| Median total dose | 63.38 Gy | 3.86 | 61.91 Gy | 5.33 | NS |
| Percentage stage III/IV | 48 | | 43 | | |
| Microscopic | | | | | |
| No. of patients | 82 | | 100 | | |
| Median age | 60.1 years | 11.9 | 58.4 years | 9.2 | NS |
| Median RT-time | 51.4 days | 13.5 | 47.7 days | 9.8 | $p < 0.05$ |
| Median total dose | 63.827 Gy | 472.8 | 60.863 Gy | 531.4 | $p < 0.001$ |
| Percentage stage III/IV | 38 | | 49 | | |

NS = not significant.

## MATERIAL AND METHODS

Between January 1972 and December 1987, two-hundred and five cases of laryngeal carcinoma were treated in our department with postoperative irradiation. Fifty-seven other patients were excluded from this study for the following reasons: Non-megavolt treatment, a total dose of less than 40 Gy, distant metastases and non-squamous cell histology.

Ninety-five per cent of the patients were male, the median age was 59 years, and 73 (36%) had received a total laryngectomy. There were fifty stage T1 patients, seventy-three T2, twenty-eight T3 and fifty-four T4 cases. Seventy-seven per cent of the patients were treated using a Co 60 source, and with the exception of 8 cases who received electron treatment only, the rest were treated with 6 MeV photons. Most of the cases were treated with bilateral opposing cervical fields with sparing of the spinal cord above 40 Gy. The total dose ranged from 40 to 70 Gy. The histology report in 23 of these 205 cases did not assess the tumour margins in adequate detail, the 'microscopic group' thus has 182 cases. Table 1 shows the characteristics of the 'positive' and 'negative' subgroups to be quite similar, despite a typically retrospective bias to higher total doses (statistically significant) and longer treatment periods (marginally significant) in the cases with positive margins. The follow-up for this study was 3 to 18 years. Our study also showed a 5-year intercurrent mortality rate of 27% for the whole group with a variation of 15–28% amongst the subgroups. This high rate is not unusual amongst head and neck tumour patients, and so for the actuarial analyses pertaining to survival we utilised the concept of disease specific survival.

### *Statistical analysis*

The probabilities of locoregional control and survival were calculated by the Kaplan-Meier product limit method using the SPSS for Macintosh™ 6.1.1 software package. Univariate comparison of the survival data was done using the log-rank test. Comparison of non-survival data was done by the t-test method.

## RESULTS

One hundred and eighty-four patients had macroscopically negative resection margins; 21 cases showed gross tumour in the margin. The histology showed 100 cases to be tumour-free, 82 were positive and in the remaining 23 cases no adequate histological assessment of the surgical margins was found. In 99 of the 182 comparable cases the margins were both macroscopically and microscopically tumour-free. In 62 cases the macroscopic assessment underestimated, in one case overestimated, the size of the tumour. Thus, just over one-third of the comparable cases showed a discrepancy between histology and gross (intraoperative) pathology. In 20 of the 21 cases with macroscopic positive margins the microscopic assessment concurred.

We summarized the results of 20 actuarial analyses in Table 2. With one exception, all 20 analyses showed a better prognosis for patients with tumour-free margins (albeit that few were significantly so), and this despite the above-mentioned bias often seen in retrospective studies with higher radiation doses being given to cases with positive margins.

Analysis of the Kaplan-Meier curves for macroscopic margin assessment showed all cases with negative margins to have better 5-year survival- and locoregional control rates than those with tumour positive margins, but these were not statistically significant when all stages were tested for as a single group.

To check whether these results remained constant in early and advanced tumour stages we tested for locoregional control and survival in T1–2 and T3–4 tumours. Amongst the T3–4 patients macroscopic tumour-free margins showed a significant survival benefit ($p = 0.009$) and also locoregional control was significantly better ($p = 0.012$).

**Table 2**

*Actuarial survival analysis of laryngeal carcinoma according to surgical margin status and stage*

| | Macroscopic | | | | | Microscopic | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Cases | 5a DSS | Log rank | 5a LRC | Log rank | Cases | 5a DSS | Log rank | 5a LRC | Log rank |
| All stages | 205 | 73% − | p = NS | 71% − | p = NS | 182 | 70% − | p = NS | 68% − | p = NS |
| | | 60% + | | 54% + | | | 70% + | | 62% + | |
| T1–2 | 123 | 81% − | p = NS | 82% − | p = NS | 110 | 85% + | p = NS | 81% − | p = NS |
| | | 75% + | | 81% + | | | 81% − | | 79% + | |
| T3–4 | 82 | 53% − | p = 0.009 | 48% − | p = 0.012 | 72 | 58% − | p = NS | 58% − | p = 0.02 |
| | | 14% + | | 14% + | | | 39% + | | 34% + | |
| Node neg. | 139 | 82% − | p = NS | 79% − | p = NS | 122 | 85% − | p = NS | 84% − | p = NS |
| | | 69% + | | 61% + | | | 79% + | | 73% + | |
| Node pos. | 66 | 44% − | p = NS | 56% − | p = NS | 60 | 47% − | p = NS | 48% − | p = NS |
| | | †16% + | | 33% + | | | 41% + | | 36% + | |

Cases = number of cases. 5a DSS = 5 year disease specific survival rate. 5a LRC = 5 year locoregional control. + = positive margins. − = negative margins. † = only 3 year rate available. NS = not significant ($p > 0.05$).

In the early tumour stages T1–2 and the grouping according to lymph node status this factor conveyed no significant benefit. The lymph node positive group showed a small but significant improvement in locoregional control ($p = 0.03$), again the improvement was not translated into longer disease-free survival. The comparison of the microscopical tumour positive and negative margins as one group also showed no significant differences in locoregional control (Fig. 1) and disease-specific survival. Likewise, the analysis of the early tumour stages showed no benefit in disease-specific survival and locoregional tumour control (Fig. 2). The patients with tumour-free margins (Fig. 3) showed a significant improvement in locoregional tumour control ($p = 0.02$), but no significant improvement in disease specific survival time. Here again, the histological margin assessment had no predictive value when the group was divided according to lymph node status.

Keeping in mind the limitations of retrospective analysis, we then compared the rates of tumour recurrence in patients with microscopic margin analysis in our study with those patients in the literature who did not receive adjuvant radiotherapy. In the Fini-Storchi study (3) with a 3–5-year locoregional failure of 57%, our patients had 33%. Fini-Storchi's recurrence rates in both groups are somewhat higher, but a comparison is difficult due to the different subgroups of patients studied. The Bauer study (4) with stage $T_3$ $N_0$ tumours showed 18% developing a biopsy-proven local recurrence, 6% with uninvolved margins over 5–12 years. Our figures for 5 years were 34 and 22%. The figures by Lam et al. (5) of 48% vs 11% in 5 years after total laryngectomy were worse than ours for positive margins and better for negative margins.

## DISCUSSION

The log-rank tests show a significant benefit in locoregional tumour control for advanced cases with histologically tumour-free margins. The reason for this is unclear, these cases possibly have a large numbers of individual tumour cells already migrating a good distance away from the tumour mass and are thus less amenable to adjuvant

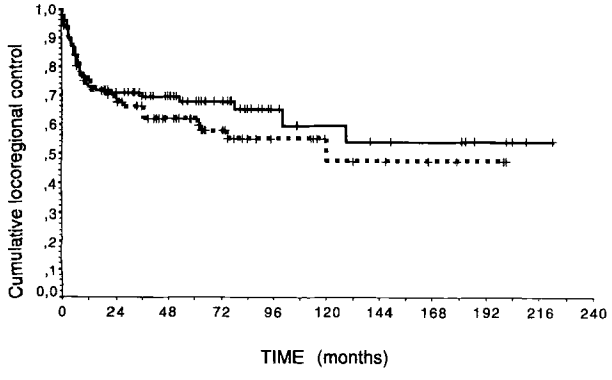


*Fig. 1.* Kaplan-Meier analysis of locoregional control in all 182 cases with microscopically assessed surgical margins; 68% and 62% probability of survival at 5 years for negative and positive margins respectively. Result not statistically significant. Log rank: $p = 0.37$ . . . − margins, $n = 100$ __ + margins, $n = 82$.

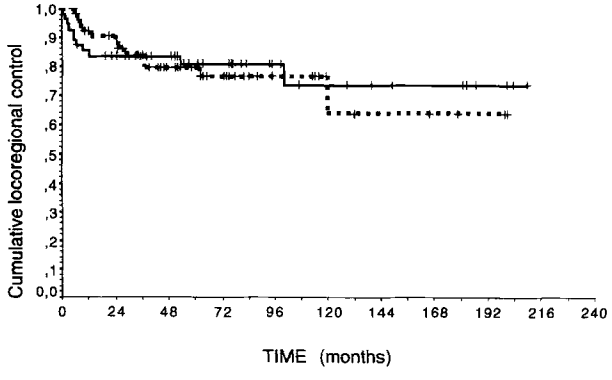


*Fig. 2.* Kaplan-Meier analysis of locoregional control in T1–2 cases; 81% and 79% probability of survival after five years for microscop. neg. and pos. margins respectively. No benefit. Log rank: $p = 0.83$ . . . + margins, $n = 54$ __ − margins, $n = 56$.

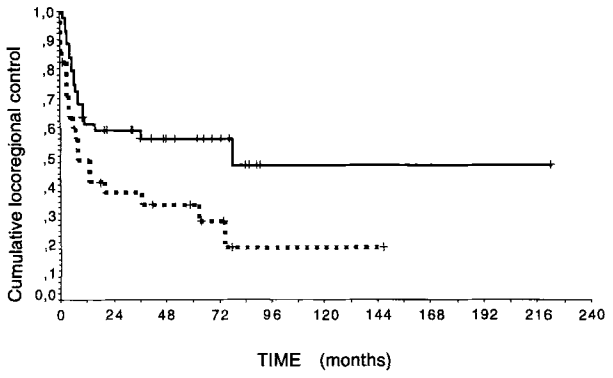


*Fig. 3.* Kaplan-Meier analysis of locoregional control in T3–4 cases. 58% and 34% probability of survival after five years for microscop. neg. and pos. margins respectively. Significant benefit. Log rank: p = 0.02 ... −margins, n = 44 __+margins, n = 28.

radiotherapy. Conversely there are fewer free tumour cells which have also not migrated as far from the tumour mass in the early stages, increasing the impact of local radiation treatment. This in turn leaves fewer tumour cells (reduced tumour load) for the patient's immune system to deal with. The end result is that the adjuvant treatment 'levels the playing field' and enables those cases with microscopic positive margins to achieve equally good locoregional tumour control as the cases with 'tumour-free' margins, where the tumour load is already reduced. The rate of locoregional control correlated in most cases strongly with disease specific survival, which explains the indirect effect of the status of the surgical margins on this parameter. In those cases with histologically negative margins the fine balance between tumour cell kill and immune response may be shifted towards lowering the immune response without a corresponding cell kill rate. This could explain the observed worsening of prognosis between our adjuvantly irradiated patients with negative margins and those with histologically negative margins in the literature without adjuvant treatment after surgery (see below).

When we compare our results with studies of patients receiving no adjuvant therapy (3–5) we do see an overall benefit for the patients with positive surgical margins receiving irradiation. As Fini-Storchi claimed, not all the cases with positive margins developed recurrent tumours. If a correlation with Karnofsky performance index or age can be ruled out (with the patient dying before his recurrent tumour is detected) and provided the follow-up is of sufficient duration, immune mechanisms could be found to play a role (12). Whether they also play a part in the relatively worse prognosis for patients with histologically negative surgical margins after adjuvant radiotherapy is a question worthy of further investigation.

In the macroscopic group comparison, the results show a significant actuarial survival benefit for the patients with negative margins in the advanced stages. (Fig. 4) This benefit remains constant for local recurrence when the resection margins are negative.

A possible explanation is that the macroscopically positive margins were an indication of underlying gross disease outside the treatment fields. The combination of advanced tumour stage and significant tumour bulk left after the operation was not manageable by the bimodal approach using conventional radiotherapy as the sole adjuvant after laryngeal surgery. In such a constellation, additional chemotherapy or the prescription of large volume hyperfractionated radiotherapy (13) may improve survival and locoregional control rates.

In summary we find that the macroscopic aspect of the surgical margins does show prognostic value in determining the probability of survival of locally advanced cases of laryngeal cancer after adjuvant radiotherapy. If satisfactory gross resection margins cannot be achieved, the patient is going to need multimodal adjuvant treatment or at least high-volume hyperfractionated radiotherapy. This applies particularly if the tumour is in an advanced stage, which it usually is. In these cases the presence of visible tumour in the margin is also prognostic for local recurrence if conventional radiotherapy is the only adjuvant treatment.

The microscopic status of the resection margins is a prognostic factor of locoregional control in all advanced cases of laryngeal carcinoma receiving postoperative radiotherapy. In our patient cohort radiotherapy appears to be of no benefit to locoregional control in cases with histologically verified tumour-free surgical margins. Animal studies are needed to test the radiobiological theories described earlier in the discussion. Our results need confirmation through prospective studies before they can affect therapy concepts.

Considering the discrepancy of 35% between the clinical assessment and the final histology report the importance of microscopic assessment of surgical margins is emphasized, particularly in advanced cases when adjuvant radiation is planned.

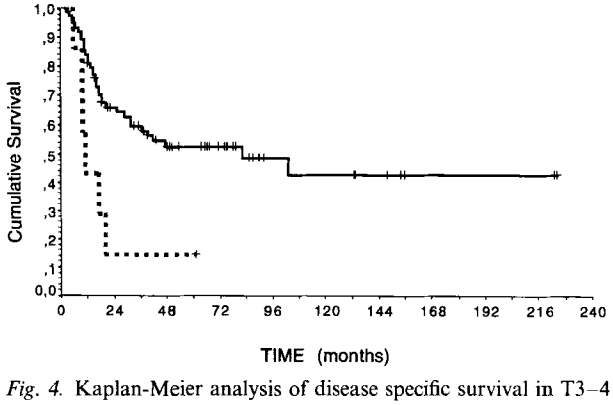


*Fig. 4.* Kaplan-Meier analysis of disease specific survival in T3–4 cases. 53% and 14% probability of survival after five years for macroscop. neg. and pos. margins respectively. Statistically significant benefit. Log rank: p = 0.009 ... −margins, n = 74 __+ margins, n = 8.

## ACKNOWLEDGEMENTS

We thank Dr. Susanna Naudé for expert advice in the assessment of the histology reports.

## REFERENCES

1. Davidson TM, Haghighi P, Astarita R, Baird S, Seagren S. Microscopically oriented histologic surgery for head and neck mucosal cancer. Cancer 1987; 60: 1856–61.
2. Ambrosch P, Brinck U, Fischer G, Steiner W. Spezielle Aspekte der histopathologischen Diagnostik bei der Lasermikrochirurgie von Karzinomen des oberen Aerodigestivtraktes. (Special aspects of histopathologic diagnosis in laser microsurgery of cancers of the upper aerodigestive tract). Laryngorhinootologie 1994; 73: 78–83.
3. Fini-Storchi O, Agostini V, Mani R. Significato e prognosi dei margini di sezione positivi nella chirurgia del cancro laringeo. (Significance and prognosis of positive surgical section margins in surgery of laryngeal cancer). Acta Otorhinolaryngol (Ital) 1989; 9: 587–98.
4. Bauer WC, Lesinski SG, Ogura JH. The significance of positive margins in hemilaryngectomy specimens. Laryngoscope 1975; 85: 1–13.
5. Lam KH, Lau WF, Wei WI. Tumour clearance at resection margins in total laryngectomy. A clinicopathologic study. Cancer 1988; 61: 2260–72.
6. Loree TR, Strong EW. Significance of positive margins in oral cavity squamous carcinoma. Am J Surg 1990; 160: 410 147.
7. Amdur RJ, Parsons JT, Mendenhall WM, Million RR, Stringer SP, Cassisi NJ. Postoperative irradiation for squamous cell carcinoma of the head and neck: an analysis of treatment results and complications. Int J Radiat Oncol Biol Phys 1989; 16: 25–36.
8. Zelefsky MJ, Harrison LB, Fass DE, Armstrong JG, Shah JP, Strong EW. Postoperative radiation therapy for squamous cell carcinomas of the oral cavity and oropharynx: impact of therapy on patients with positive surgical margins. Int J Radiat Oncol Biol Phys 1993; 25: 17–21.
9. Mantravadi RV, Haas RE, Liebner EJ, Skolnik EM, Applebaum EL. Postoperative radiotherapy for persistent tumour at the surgical margin in head and neck cancers. Laryngoscope 1983; 93: 1337–40.
10. Manni JJ, Terhaard CH, de Boer MF, et al. Prognostic factors for survival in patients with T3 laryngeal carcinoma. Am J Surg. 1992; 164: 682–7.
11. Devineni VR, Simpson JR, Sessions D, et al. Supraglottic carcinoma: impact of radiation therapy on outcome of patients with positive margins and extracapsular nodal disease. Laryngoscope 1991; 101: 767–70.
12. Dobrowsky W, Naudé J, Millesi W, et al. Atypische Fraktionierung bei fortgeschrittenen Plattenepithel- Karzinomen der Kopf-Hals Region. (Atypical fractionation in advanced squamous cell carcinomas of the head and neck region). Strahlenther Onkol 1992; 12: 686–91.
13. Maier H, Daniel V, Heimlich F, Frank C, Opelz G. Zellulärer Immundefekt durch postoperative Nachbestrahlung bei Patienten mit Platttenepithelkarzinomen des oberen Aerodigestivtraktes. (Cellular immune defects caused by postoperative irradiation in patients with squamous epithelial carcinomas of the upper aerodigestive tract). HNO 1995; 43: 364–70.