The Journal of Laryngology and Otology
May 1993, Vol. **107**, pp. 437–440

Uni- and multivariate analysis of eight indications for post-operative radiotherapy and their significance for local-regional cure in advanced head and neck cancer

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Abstract

Eighty consecutive patients with advanced head and neck cancer were treated with combined therapy of radical surgery and post-operative radiotherapy. Indications for post-operative radiotherapy were pathological staging of the primary tumour (pT3 or pT4), poorly differentiated or undifferentiated carcinoma (G3, G4), tumour thickness, tumour invasion in the surrounding tissues with slender tumour strands and solitary tumour cells, perineural spread, lymphangio-invasive tumour growth, multiple positive neck nodes or extranodal spread, and microscopical irradicality of the surgical margins. The contribution for prognosis of these indications for post-operative radiotherapy were retrospectively calculated in an univariate and multivariate analysis. Of all investigated parameters, the mode of tumour invasion and lymphangio-invasive growth were independent prognostic factors. If these unfavourable prognostic signs are present, post-operative radiotherapy has to be intensified to at least curative doses of 66 Gy or more to the areas at risk.

Key words: Head and neck neoplasms; Radiotherapy; Surgery; Prognosis.

Introduction

A combination of radiotherapy and surgery is the therapy of choice for the majority of advanced tumours in the head and neck. There is no convincing evidence that one of the two possible modalities of combination, i.e. pre- or post-operative irradiation, is superior to the other. The often quoted study of Vandenbrouck *et al.* (1977), by which pre-operative radiotherapy can be criticized, was interrupted before the study was completed. Two prospective studies of the R.T.O.G. (Snow *et al.*, 1980; Kramer *et al.*, 1987), in which the two modalities were compared, failed to demonstrate an improved survival for one of the modalities. Since treatment planning can be based on histological parameters investigated in the surgical specimen and post-operative complications cannot be enhanced by previous irradiation, many Institutes nowadays prefer post-operative radiotherapy (Mantravadi *et al.*, 1981; Arriagada *et al.*, 1983; Van den Bogaert *et al.*, 1984). Several recent studies showed that some of the indications for post-operative radiotherapy were independent factors for prognosis (Table I). The mode of tumour invasion was not an issue encountered in one of these studies. Since mode of invasion is an indication for post-operative radiotherapy in our Institute, we wanted to evaluate its significance in relation to local and regional cure together with the other indications for post-operative radiotherapy.

Patients, methods of analysis

The indications for post-operative radiotherapy were evaluated retrospectively for their significance in relation to local and regional cure in 80 consecutive, clinical-radically, operated patients (55 males, 25 females, mean age 60 years) with a squamous cell carcinoma of the oral cavity (n = 29, cancer of the lip excluded), oropharynx (n = 22) and laryngo-hypopharynx (n = 29; classification to region of origin, larynx or hypopharynx, was in these advanced cases often a matter of debate). In our head and neck group indications for post-operative radiotherapy were: advanced local disease (pT3, pT4), poorly differentiated or undifferentiated squamous cell carcinoma (G3, G4), tumour thickness of more than 5 mm, specific pat-

TABLE I

LITERATURE REVIEW ON INDEPENDENT PROGNOSTIC FACTORS IN HEAD AND NECK CANCER, RADICALLY OPERATED AND POST-OPERATIVELY IRRADIATED

Published by	Patients	Independent prognostic factors
Geoffray *et al.*, 1987	96	Surgical margins; pN– vs pN+
Lewis *et al.*, 1989	58	Oral cavity/oropharynx vs other sites; N0N1 vs N2N3
Franchin *et al.*, 1989	258	Performance state; oral cavity vs other sites
Amdur *et al.*, 1989	139	Surgical margins; oral cavity vs other sites; N0N1 vs N2N3; Indications Index
Stell, 1990	765	Number of invaded lymph-nodes; extra capsular rupture

pN–: no metastasis detected in the surgical specimen.
pN+: histological proven neck node metastasis in the surgical specimen.

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Accepted for publication: 30 September 1992.

tern of tumour invasion (diffuse tumour invasion with strands and solitary cell nests: Jakobsson, grade 3 and 4) (Jakobsson *et al.*, 1973), lymphangio-invasive tumour growth, three or more positive lymph nodes or lymph node metastasis with extranodal spread, microscopically tumour positive surgical margins (tumour within 5 mm of the surgical margin or carcinoma *in situ*/invasive carcinoma in the surgical margin) and those cases in which occult lymph node metastasis may be expected but in which no elective neck dissection was performed (in our clinic with T3–T4N0 glottic laryngeal carcinoma). Though verified retrospectively for their completeness, all indications were reproduced as noted down in the original pathological reports, operation charts or patients files. In 32 patients (32/80; 40 per cent) two or three indications for post-operative radiotherapy were present. In the other 48 patients the number of indications for post-operative radiotherapy were in the range from 4 to 7. Post-operative irradiation was delivered in all cases by a linear accelerator (6–10 megavolt). The whole operation field and the neck was irradiated to 50 Gy. On certain strict indications (microscopic positive surgical margin and/or extranodal spread), a higher dosage (60–66 Gy) was delivered on the areas at risk. All courses of radiotherapy were delivered as a continuous course of five fractions of 1.8–2 Gy per day, five days a week. The interval between surgery and start of radiotherapy varied from 3 to 10 weeks.

The cumulative probability of freedom of local-regional tumour recurrences was estimated according to Kaplan and Meier. Univariate statistical analysis was performed with a chi-square test or, in the case of small expected cell frequencies, Fisher's exact test (a test result leading to a p value less than 0.05 was considered significant). The (multivariate) Cox proportional hazards regression analysis was used to investigate prognostic factors for the time until tumour recurrence (BMDP statistical software, California 90025, version 1987).

Results of treatment

Follow-up was done in a combined clinic. Minimal follow-up was 36 months; there were no patients lost to follow-up. In 16 patients (16/80, 20 per cent) local/regional recurrent tumour growth was detected: local recurrences in nine patients; local and regional recurrences in five; and regional recurrences only in two patients. All local and regional recurrences were localized within the treatment field. The vast majority of recurrences (12/16) were detected in the first two years after therapy. The longest interval between initial treatment and the moment of detection of recurrent tumour growth was 42 months. Cumulative probability to be tumour free after two years is 84 per cent (SE = 4 per cent), after 3½ years is 79 per cent (SE = 5 per cent).

Indications for combined therapy and their prognostic significance

In this uniformly treated group of advanced head and neck cancer patients, the significance of the various indications for combined therapy were analysed with univariate and multivariate analysis. In this analysis the indications for post-operative radiotherapy were regarded as either tumour-related indications or therapy-related indications.

TABLE II
TUMOUR RELATED FACTORS

Factors		Local failure		U.V.A.	M.V.A.
Oral cavity		6/19	(21%)		
Oropharynx		5/22	(23%)	n.s.	n.s.
Laryngohypopharynx		5/29	(17%)		
pT1, 2		1/12	(8%)		
pT3, 4		15/68	(22%)	n.s.	n.s.
G1, G2		9/57	(16%)		
G3, G4		7/23	(30%)	n.s.	n.s.
'Diffuse'	yes:	15/43	(35%)		
growth	no:	1/37	(3%)	$p<0.005$	$p<0.0005$
Perineural	yes:	9/33	(27%)		
spread	no:	7/47	(15%)	n.s.	n.s.
Lymphangio-	yes:	5/10	(50%)		
invasive growth	no:	11/70	(16%)	$p = 0.001$	$p = 0.005$
Depth of	≤5 mm:	2/17	(12%)		
invasion	>5 mm:	14/63	(22%)	n.s.	n.s.
No		3/17	(18%)		
pN–		4/20	(20%)	n.s.	n.s.
pN+		9/43	(21%)		

M.V.A. = multivariate analysis; U.V.A. = univariate analysis; pT/N = tumour staging in the surgical specimen.

Tumour-related indications (Table II)

Pathological staging (pT3/pT4), histological grading (G3/G4) as well as depth of tumour invasion did not bear prognostic significance. The presence of lymph node metastasis, a well known prognostic factor, did not have prognostic significance either. Pattern of tumour invasion (diffuse tumour growth, $p<0.0005$), and lymphangio-invasive tumour growth ($p = 0.005$), on the other hand, were highly prognostic significant signs for a larger probability of recurrent tumour growth. These are independent prognostic factors since significance is expressed in the univariate as well as in the multivariate analysis.

Treatment-related indications (Table III)

In 40 patients the surgical margins had to be considered as tumour positive. A microscopically irradical operation however was not a distinct unfavourable prognostic sign. Division in the 'sub' categories tumour free, tumour within 5 mm of the surgical margin (seven patients, one local recurrence), carcinoma *in situ* of the margins (seven patients, two local and regional recurrence) and microscopically invasive carcinoma in the margin of the surgical specimen (26 patients, eight local/regional recurrences) also could not reveal a clear prognostic significance. The localization and number of positive margins however did reveal prognostic significance. If deep surgical margins were positive, more local regional recurrences were detected (8/21), and if more than one deep surgical margin was positive, prognosis was very poor (7/10 versus 1/11; $p = 0.008$). There was no influence on

TABLE III
TREATMENT RELATED FACTORS

Factors		Local failure		U.V.A.	M.V.A.
Surgical	Negative	5/40	(12%)	n.s.	n.s.
margins	Positive	11/40	(27%)	($p = 0.105$)	
Indication	≤3:	1/32	(3%)		
Index	>3:	15/48	(31%)	$p = 0.002$	n.s.

M.V.A. = multivariate analysis; U.V.A. = univariate analysis.

https://doi.org/10.1017/S0022215100123369 Published online by Cambridge University Press

the treatment outcome when the interval between operation and start of radiotherapy was observed.

Indication index

Amdur (1989) introduced the 'indication-index' for post-operative radiotherapy. This index is a summation of all indications present. In the univariate analysis an index of four or more appeared to be an unfavourable prognostic sign. It was not an independent prognostic factor in the multivariate analysis due to the correlation with mode of invasion of the primary tumour.

Discussion

The purpose of this retrospective study was to consider the significance of various standard indications for post-operative radiotherapy for local and regional recurrences. Should one or more of these presently accepted indications be found to bear a clearly unfavourable prognosis, adjustment of our standard protocol for post-operative radiotherapy will have to be reconsidered. There is much debate on the prognostic significance of the histological differentiation of tumours. Jakobsson *et al.* (1973) proposed a sophisticated system for tumour grading. In Jakobssons' grading system, several patterns of invasive growth are distinguished. Loose bands, small tumour nests and solitary dispersed tumour cells had to be regarded as prognostically unfavourable as was already pointed out by McGravan *et al.* (1961). The unfavourable prognosis of patients with tumours with this particular pattern of tumour growth was again stressed by Crissman *et al.* (1984) and Yamamoto *et al.* (1984) in which studies the 'diffuse-spread' decreased the probability to survive to 30–40 per cent in contrast to the 80–90 per cent survival in patients with tumours with 'pushing' borders. In our study the diffuse and poorly demarcated tumour invasion appeared to be a major unfavourable prognostic sign. As a reflection of the biological behaviour of the tumour, lymphangio-invasive growth as well as this 'diffuse'-spread showed a very close relation to the occurrence of local/regional tumour growth.

The localization of the primary tumour was of no importance for the prognosis in this group of patients selected for combined therapy. Though this is in accordance to recent studies of the R.T.O.G. (1987), other studies which can be compared to ours came to different conclusions. Due to the relationship between pathological staging (pT3–pT4) and occurrence of local recurrent tumour growth, Fletcher (1984) proposed post-operative irradiation for these advanced head and neck tumours. This could not be confirmed in this study. Depth of invasion is another known prognostic factor. The method of documentation of the depth of the tumour invasion in mm after which prognosis becomes worse, does vary however in several studies. Prognosis deteriorates for tumours in the oral cavity if the depth of tumour invasion is 5 mm or more. For tumours of the mobile tongue the prognosis changed when tumour thickness exceeded 2 mm and for tumours in the buccal mucosa 6 mm seemed the important landmark (Platz *et al.*, 1983; Spiro *et al.*, 1986; Urist *et al.*, 1987; Nathanson *et al.*, 1989). We compared tumours in all localizations with a depth of infiltration of 5 mm or less with deeper infiltrating tumours. It was not found to be an important parameter.

TABLE IV
INTERRELATION BETWEEN SURGICAL MARGIN, PATTERN OF TUMOUR GROWTH AND THE PRESENCE OF LOCAL/REGIONAL RECURRENCES

	'Diffuse' growth local failure/number		'Pushing border' local failure/number
Tumour positive surgical margin	10/25	← S→ (p = 0.03)	1/15
Tumour negative surgical margin	5/18	← S → (p = 0.013)	0/22

Lymph node metastases is an important independent prognostic variable in many studies (Snow *et al.*, 1982). In this study however none of the different parameters to lymph node involvement (NO versus N+, pN− versus pN+, solitary versus multiple nodes and extranodal tumour spread yes/ no) were of significance for local and regional recurrences. The prevention of regional recurrences by post-operative radiotherapy to less than 10 per cent is a possible explanation for the absence of any prognostic significance (Snow *et al.*, 1982).

Severe dysplasia and carcinoma *in situ* is reported to be present in the surgical margins in about 2 per cent. In our patients it is observed more often, probably due to the meticulous examination of the surgical specimen by our pathologist. The same explanation probably accounts for the high percentages of invasive carcinoma found within 5 mm of the surgical margin or within the surgical margin. The reported presence of microscopically irradical operations varies from 3 to 60 per cent, probably due to the differences in interpretation and the mode of investigation of the surgical margins. The occurrence of local recurrent tumour growth is around 30–40 per cent in the reported series (Looser *et al.*, 1978; Snow *et al.*, 1980; Chen *et al.*, 1987). By the combination of surgery and post-operative radiotherapy in our series the prognostic significance for local or regional recurrence of a positive microscopical surgical margin is not present. The precise localization of the positive surgical margin (deep surgical sections versus mucous membrane margins) and the number of positive surgical margins do however bear prognostic significance. The significance of the mode of tumour invasion is lucidly expressed when the interrelation between the surgical margin (tumour positive versus tumour free) and the pattern of tumour growth (diffuse versus pushing) is observed (Table IV). The difference between the occurrence of recurrent tumour growth is, regardless of the quality of the surgical margin, statistically significant if the mode of tumour invasion is observed.

The summation of the various indications (Indication Index) present for post-operative radiotherapy appeared to be an important parameter to predict local/regional cure. Due to the close interrelation with the pattern of invasive growth however the Indication Index is not an independent prognostic factor in the multivariate analysis. If the Indication Index and 'diffuse' growth are observed together, this can be explained. If the Indication Index was four or more (48 patients) a significant difference (p = 0.039) in occurrence of local/regional recurrent tumour growth was found between those with (13/34) and those without (1/14) 'diffuse' infiltrating tumours.

Conclusion

In 80 patients with advanced head and neck cancer the

https://doi.org/10.1017/S0022215100123369 Published online by Cambridge University Press

various indications for post-operative radiotherapy were retrospectively analysed for their significance in predicting local/regional cure. Since all patients were irradiated post-operatively (50 Gy, some with even higher doses (60–66 Gy) in certain risk areas, several well known prognostic factors, like the neck node status and positive surgical margins, apparently lost their prognostic significance. Of all eight indications, only mode of tumour invasion ('diffuse' versus 'pushing borders') and lymphangio-invasive tumour growth (present yes or no) appeared to be independent factors. This study does emphasize that technique and dosage of post-operative radiotherapy have to be adjusted in the case of 'diffuse' tumour invasion or in the case of lymphangio-invasive tumour growth. Since high dosage radiotherapy (66–70 Gy) has to be delivered in the treatment field in these cases, brachytherapy has to be considered.

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