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Importance of the Time Interval Between Radiotherapy and Surgery in Oral Cancer

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From 1969 to 1985, 62 patients with squamous cell carcinoma of the oral cavity received preoperative radiotherapy (RT) 40–50 Gy before radical surgery. The time interval between the end of the RT and surgery varied from 4 to 49 days (median 19 days). The cancer specific survival rate was significantly lower for the 32 patients with intervals longer than or equal to 19 days compared with patients with shorter intervals ($P = 0.001$). The reason for choosing a longer interval between the treatment modalities was not related to stage or performance status, however, a possibility that patients in poor condition were preferentially allocated to the long intertreatment interval group cannot be ruled out. This study suggests that when using combined modalities any effort should be exercised to reduce the time interval between the modalities.

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INTRODUCTION

SEVERAL STUDIES have shown that local tumour control rate of head and neck cancers is reduced during a prolonged course of radiotherapy time [1, 2]. This is thought to be caused by repopulation of surviving tumour cells. A similar effect may be expected when combining treatment modalities. In a retrospective study of advanced head and neck cancer Schiff *et al.* [3] found that a prolonged time interval between surgery and postoperative radiation had a negative impact on the locoregional control if the radiation dose was less than 60 Gy, but no impact was seen if the radiation dose was higher than 60 Gy. We have performed a retrospective analysis to see whether the time interval between preoperative radiotherapy and radical surgery influenced the local control rate and the survival for patients with oral cancer.

PATIENTS AND METHODS

Since the middle of the 1960s all cases of oral cancer in a geographically well-defined area in Denmark (Funen and the Southern part of Jutland) have been treated at the Department of Oncology and the Department of Plastic Surgery at Odense University Hospital. From 1969 to 1985 the standard treatment policy was preoperative radiotherapy followed by radical surgery, although, however at the end of the period more cancers tended to be treated with surgery alone.

A total of 72 patients with squamous cell carcinoma (SCC) of the oral cavity were treated by preoperative radiotherapy (RT) and radical surgery. Of these, 62 patients received 40–50 Gy with an interval between the end of RT and surgery of less than 50 days. They form the population studied in this paper. The treatment time of RT ranged from 28 to 50 days with a median fraction size of 1.96 Gy (1.65–2.14 Gy) (Table 1). The median age of the group was 63.6. All patients have been followed-up for more than 5.8 years or until the time of death. The median follow-up time was 12.2 years. The ratio of males/females was 1 : 1. All patients were restaged according to UICC 1987. 35 patients were stage I–III, 27 patients were stage IV (Table 2).

Table 1. Treatment characteristics

	All	Interval between end of RT and surgery		
		4–18 days	19–49 days	
No. of patients	62	30	32	
Surgery				
Resection	5 (8%)	1 (3%)	4 (12%)	
Hemiglossectomy	22 (36%)	14 (47%)	8 (25%)	
Amputation of tongue	3 (5%)	0 (0%)	3 (9%)	
Excision of alveololaris inf.	3 (5%)	2 (7%)	1 (3%)	
Mandibulectomy	16 (26%)	9 (30%)	7 (22%)	
Hemi-mandibulectomy	12 (19%)	4 (13%)	8 (25%)	
Maxillectomy	1 (2%)	0 (0%)	1 (3%)	
Neck dissection	50 (81%)	27 (90%)	23 (72%)	ns†
Radiation				
Dose (Gy)	45 (40–50)	45 (45–47)	45 (40–50)	ns*
Fractions	23 (21–26)	23 (22–24)	23 (21–26)	ns*
Field size (cm^2)	115 (60–189)	113 (64–168)	117 (60–189)	ns*
Fraction size (Gy)	1.96 (1.65–2.14)	1.96 (1.96–2.05)	1.96 (1.65–2.14)	ns*
Duration (days)	33 (28–50)	38 (31–50)	31.5 (28–43)	ns*

*Wilcoxons test: Short intertreatment interval group vs. long interval group.
†Fishers exact test between the groups as above.

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Table 2. Patients' characteristics

	All	Interval between RT and surgery		P
		4–18 days	19–49 days	
No. of patients	62	30	32	
Age	63.6 (27.7–87.9)	60.0 (27.7–73.1)	66.9 (46.0–87.9)	0.001*
Year of 1st visit	1979 (1969–1985)	1982 (1970–1985)	1977 (1969–1985)	0.002*
Haemoglobin (mmol/l)	8.7 (6.9–10.8)	9.0 (7.1–10.4)	8.5 (6.9–10.8)	0.027*
LDH§	335 (132–491)	336 (207–439)	325 (132–491)	ns*
Sex				
Female	31 (50%)	17 (57%)	14 (44%)	ns†
Male	31 (50%)	13 (43%)	18 (56%)	
Stage				
I	15 (24%)	5 (17%)	10 (31%)	ns‡
II	10 (16%)	8 (27%)	2 (6%)	
III	10 (16%)	6 (20%)	4 (13%)	
IV	27 (44%)	11 (37%)	16 (50%)	
T-status				
T1	17 (27%)	7 (23%)	10 (31%)	ns‡
T2	19 (31%)	12 (40%)	7 (22%)	
T3	2 (3%)	1 (1%)	1 (3%)	
T4	24 (39%)	10 (33%)	14 (44%)	
Nodal status				
N0	36 (58%)	19 (63%)	17 (53%)	ns‡
N1	18 (29%)	9 (30%)	9 (28%)	
N2	6 (10%)	2 (7%)	4 (13%)	
N3	2 (3%)	0 (0%)	2 (6%)	
Location				
Tongue	26 (42%)	12 (40%)	14 (44%)	ns†
Floor of mouth	18 (29%)	10 (33%)	8 (25%)	
Alveolaris inf.	15 (24%)	8 (27%)	7 (22%)	
Alveolaris sup.	2 (3%)	0 (0%)	2 (6%)	
Inside of cheek	1 (2%)	0 (0%)	1 (3%)	

*Wilcoxons test: Short intertreatment interval group vs. long interval group.
†χ^2 for $2 \times n$ tables in groups as above.
‡χ^2 for trend in a 2×4 tables in groups as above.
§Values for 55, 28, and 27 patients only.

Before irradiation all tumours were tattooed with ink by the plastic surgeons in order to be able to respect the whole of the initial tumour area with a margin of at least 1 cm after the radiotherapy.

RESULTS

The median interval from radiotherapy to surgery was 19 days ranging from 4 to 49 days. The median dose was 45 Gy. The 5 year crude survival rate was 53.2%, the corrected 5 year survival rate was 68.0%.

The study population was divided into two groups, one consisting of the patients with an interval between radiotherapy and surgery shorter than the median interval, and one of the patients with a longer interval. The short interval was thus from 4 to 18 days, the longer interval from 19 to 49 days. A total of 19 failures were observed (Table 3). A highly significantly better corrected survival rate (logrank, $P=0.001$) was seen for the patients with the short intertreatment with a corrected 5 year survival rate of 88.7 and 49.1 in the two groups

Table 3. Treatment failures

	All	Interval between end of RT and surgery	
		4–18 days	19–49 days
Local*	11 (18%)	3 (30%)	8 (25%)
Nodal	9 (15%)	2 (7%)	7 (22%)
Distant metastasis	1 (2%)	0 (0%)	1 (3%)
Total failures†	19 (31%)	5 (17%)	14 (44%)

*Including 1 patient in the group 19–49 days who never became free of tumour.
†Failures at more than one site for 2 patients in the long interval group.

(Fig. 1). An analysis of recurrence free survival using loco-regional failures among patients who became free from tumour (Fig. 2) gave a similar result with significant better recurrence free survival for patients in the short interval group (logrank, $P<0.04$).

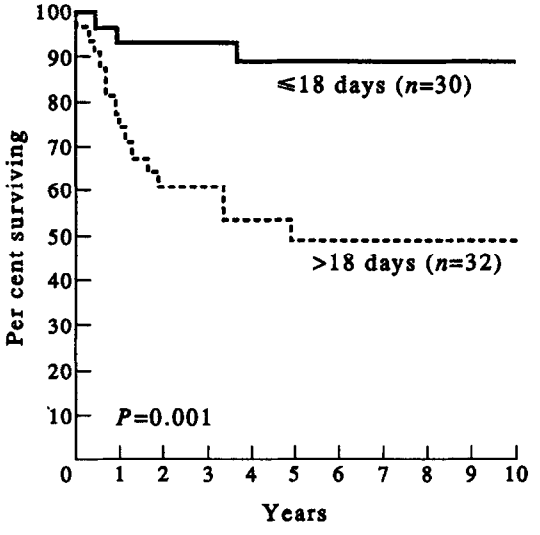

Fig. 1. Kaplan–Meier plot: corrected survival. (a) Interval between end of RT and surgery of 4–18 days. (b) Interval between end of RT and surgery of 19–49 days.

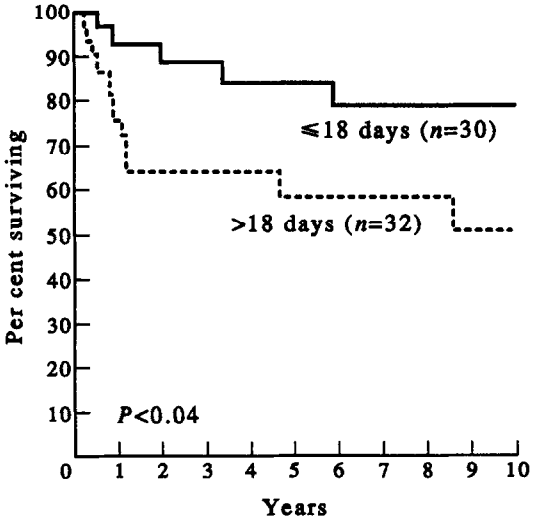

Fig. 2. Kaplan–Meier plot: loco-regional recurrence-free survival. (a) Interval between end of RT and surgery of 4–18 days. (b) Interval between end of RT and surgery of 19–49 days.

In a further sub-analysis of the data according to stage, pooling stage I–III in one group, and stage IV in another group, it was seen that the difference between patients with long and short interval between the end of RT and the surgery persisted in both of the sub-groups (Fig. 3).

The median time interval from the beginning of RT to the surgery was 54 days ranging from 39 to 80 days. An analysis of the data dividing the patients into two groups, one consisting of the 30 patients with an interval from start to RT to surgery of 39–53 days and one consisting of the 32 patients with an interval of 54–80 days showed a similar result as studying the time interval from the end of RT to surgery with a significant better corrected survival rate in the short interval group (logrank, $P<0.02$). An analysis of the recurrence free survival as above failed to show a statistical significant difference between the two groups.

No obvious connection existed between choosing a long intertreatment interval, and the patients stage or the patients condition. Male/female ratio, and the distribution of stages were similar in the two groups. However, the median age for the patients in the group with the longer interval were higher compared with the short interval group, but this had no influence on the corrected survial. The median value of haemoglobin was slightly but statistically significantly higher in the longer interval group. No difference was observed between measurements of lactate dehydrogenase (LDH) in the two groups.

In a sub-analysis excluding the youngest (less than 45 years) and the oldest patients (older than 75 years) two homogeneous groups appear. This subset of data then consisted of 52 patients. Still a significant difference appeared in the corrected survival rates for patients with a long and a short treatment interval (Fig. 4).

In a Cox regression model including stage, intertreatment interval, sex, haemoglobin, age, and year of diagnosis, only the time interval came out as a significant factor for the corrected survival (Table 4).

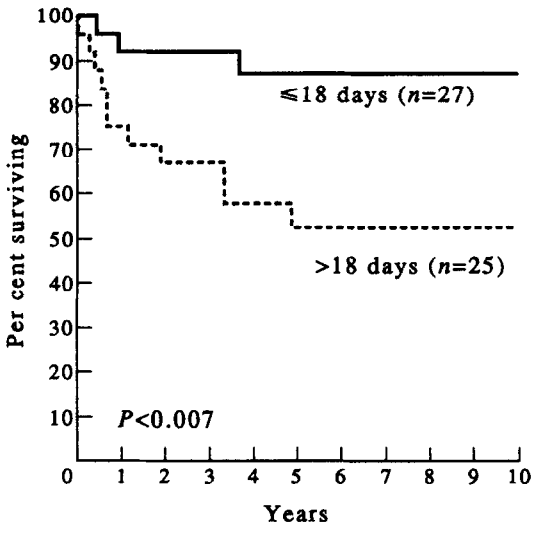

Fig. 3. Kaplan–Meier plot: corrected survival according stage. (a) Interval between end of RT and surgery of 4–18 days, stage I–III. (b) Interval between end of RT and surgery of 4–18 days, stage IV. (c) Interval between end of RT and surgery of 19–49 days, stage I–III. (d) Interval between end of RT and surgery of 19–49 days, stage IV.

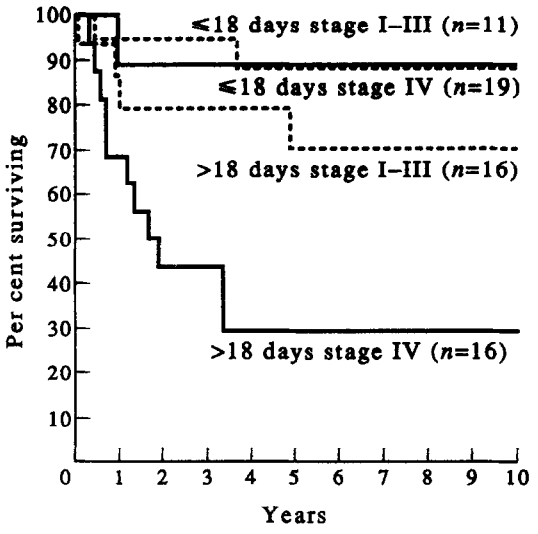

Fig. 4. Kaplan–Meier plot: corrected survival: age 45–75 years. (a) Interval between end of RT and surgery of 4–18 days. (b) Interval between end of RT and surgery of 19–49 days.

Table 4. Cox regression analysis. Relative risk and 95% confidence limits

Covariate	RR	95% conf. RR	*P* value
Time interval (days)	1.059	1.006–1.115	0.0277
Stage (IV/I–III)	2.152	0.770–6.017	0.1439
Sex (male/female)	1.755	0.669–4.602	0.2530
Age (years)	1.029	0.972–1.089	0.3283
Haemoglobin (mmol/l)	1.142	0.613–2.125	0.6761
Year of treatment (years)	0.995	0.878 – 1.127	0.9338

RR = relative risk.

DISCUSSION

The reduced survival and local control in the group of patients with a long interval between the initial radiotherapy and the subsequent radical surgery may be explained by at least two hypotheses. The first is that during the long interval between the 1st and the 2nd treatment the clonogenic tumour cells had proliferated thus increasing the risk of spreading of tumour cells beyond the area for the surgical resection. This area was marked before radiation, and all surgical specimens except one had margins free of tumour cells in the microscopic analysis. Schiff *et al.* [3] found an effect of the interval between radical surgery and radiotherapy only in the group of patients that had less than 60 Gy. In this study all patients had between 40 and 50 Gy and by far the largest proportion of the patients had 45 Gy. This dose represents about 2/3 of the dose sufficient to cure macroscopic visible tumour, and the "insufficient" radiation doses therefore is likely to induce repopulation of clonogenic tumour cells.

The reason for the large variation in the time interval between radiotherapy and surgery was basically a lack of capacity in the surgical department due to other surgical tasks such as extensive wound surgery, burns and other cancer surgery, combined with public holidays and vacations. It was therefore not possible to reduce the interval between radiotherapy and surgery even though an intertreatment interval of 1–2 weeks was considered to be the optimal interval with regard to the surgical procedures and reduction of the risk of metastasising.

The other hypothesis that may explain the result of the study is that patients in poor condition were preferentially allocated to the long intertreatment interval group. No reason was given in the patients' files for choosing a specific date of surgery. The modest but significant differences in the haemoglobin and in the age profiles between the two groups indicated that a selection of people in poorer condition to the long intertreatment interval group hazard taken place. On the other hand no difference in the LDH-measurements was found. It is however likely that some sort of selection has occurred, but it is remarkable that when you compensate for this selection bias the significant impact of the time interval remains.

In conclusion: this study suggests that in the treatment of oral cancer a long interval between preoperative therapy and surgery reduces the survival rates. When using combined modalities every effort should be exercised to reduce the time interval between the modalities.

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