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Response to Preoperative Concomitant Radio-chemotherapy with Mitomycin C and 5-Fluorouracil in Advanced Head and Neck Cancer

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Abstract—*Advanced head and neck tumours have a poor prognosis due to the high frequency of local recurrence. Multimodality treatment has been shown to be effective in decreasing local recurrence. In this study, 51 patients with advanced oral and oropharyngeal carcinoma were entered in a trial of preoperative radio-chemotherapy. After exclusion of 10 protocol violations (no surgery or no chemotherapy), 41 patients remained evaluable.*

Chemotherapy consisted of 15 mg mitomycin C/m² given intravenously (bolus) on day 1. 5-Fluorouracil (750 mg/m²/24 h) was infused during days 1–5 (continuous infusion for 120 h). Radiotherapy was performed simultaneously with chemotherapy beginning on day 1. A total dose of 50 Gy to the primary tumour and neck region was delivered over 5 weeks.

Treatment was well tolerated. Side-effects were mainly of local character (mucositis). No severe systemic toxicity was seen. Some delayed wound healing was noted at the operation (4 weeks after irradiation).

The CR rate of the primary tumours was 56% (23/41). In 39% (16/41) only histological residual tumour was found. Two patients had minor response (categorized as NR) of their tumour (macroscopic residual tumour). None had tumour progression. The response rates considering lymph node metastases were 59% (22/37) CR, 35% (13/37) PR and 5% (2/37) NR.

After a follow up of 18–30 months, analysis of local recurrent disease and survival was performed. The loco-regional recurrence rate was 32% (13/41) and the survival rate 63% (26/41). All deceased patients, except two, died of tumour progression. Patients with T4 tumours showed inferior prognosis whereas no significant difference in survival of T2 and T3 patients was found. Patients with CR of tumour and lymph nodes (including N0) have all survived and are without evidence of disease.

INTRODUCTION

ADVANCED CANCERS of the head and neck region have a poor prognosis due to loco-regional failure. By combining surgery, radiotherapy and chemotherapy, efforts are made to increase local tumour control and survival. Though aggressive preoperative chemotherapy exhibits high response rates, a major ultimate benefit has seldom been reported. A high grade of toxicity also marred the efficacy of potent drug combinations and even chemotherapy-related deaths have been reported.

By combining a less toxic chemotherapy with concomitant irradiation preoperatively, we expected a therapeutic benefit without more severe side-effects. A combination which has proven very effective in squamous cell cancer in different sites is mitomycin C, 5-fluorouracil and irradiation. Especially in anal cancer, this treatment modality has widespread acceptance [1, 2]. Reports on treatments with similar regimens have been published on oesophagus [3], uterine cervix [4–6] and head and neck cancers [7], showing encouraging results.

This report evaluates the interim results on the first patients followed for 18–30 months and discusses the response to preoperative radio-chemotherapy by determination of the histological examination of the operative specimen.

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PATIENTS AND METHODS

In 1985 a non-randomized trial with preoperative radio-chemotherapy in advanced head and neck cancer was initiated. Forty-one patients (four female, 37 male) aged 29–77 years (median age 53 years) were treated according to the protocol. All patients treated had a histologically proven squamous cell carcinoma. Initially 51 patients were entered into this study containing preoperative radiotherapy and concomitant chemotherapy with mitomycin C and 5-fluorouracil. Due to protocol violations (no chemotherapy or no surgery) ten patients had to be excluded from this analysis (see Table 5). This report includes patients treated between May 1985 and May 1986, assessed by November 1987, so that patients have been followed 18–30 months. All patients treated presented advanced stage (III or IV) cancer of the oral cavity or oropharynx and had a Karnofsky performance of at least 50%. Distribution of tumour site and tumour staging are in Tables 1–3. Stage of disease was determined by clinical examination (inspection, palpation), as well as sonography and computed tomography. Patients also had regular blood tests (CBC and SMA 12), chest X-ray and a liver sonogram.

Table 1. Distribution of patients by tumour site

Oral cavity	
Floor of the mouth	15 (2)
Retromolar trigone	10 (3)
Tongue (mobile part)	5 (2)
Buccal mucosa	— (1)
Oropharynx	
Base of tongue	5
Tonsil	6 (2)
	41 (10)

( ) excluded patients.

Table 2. Staging of tumour according to the TNM system, UICC 1987

Primary (T)	
T1	Tumour diameter 2 cm or less
T2	Tumour diameter more than 2 cm, but not more than 4 cm
T3	Tumour diameter more than 4 cm
T4	Tumour infiltration into neighbouring structures (such as bone, skin, paranasal sinuses)
Lymph nodes	
N0	Not clinically positive
N1	Single clinically positive lymph node 3 cm or less in diameter
N2	Clinically positive ipsilateral single lymph node more than 3 cm but not more than 6 cm in diameter, or multiple positive ipsilateral lymph nodes none more than 6 cm in diameter, or bilateral or contralateral lymph nodes no more than 6 cm in diameter
N3	Clinically positive lymph node(s) more than 6 cm in diameter

Table 3. Stage distribution of oral cavity and oropharyngeal cancer (n = 41) according to UICC 1987

	N0	N1	N2	N3
T1				
T2		2 (3)	12	1
T3	4	6 (3*)	10 (1)	
T4		2 (1)	4 (2)	

( ) excluded patients.
*One patient M1.

Treatment consisted of simultaneous radiotherapy and chemotherapy with mitomycin C and 5-fluorouracil. Chemotherapy was administered during the first 5 days of irradiation. On day one a single dose of 15 mg mitomycin C/m^2 was applied intravenously before the first irradiation. During the first 5 days of treatment 750 mg 5-fluorouracil/m^2/24 h was given by continuous infusion for 120 h. A total dose of 50 Gy (single dose 2 Gy, 5 fractions weekly) was irradiated to the primary tumour and the neck nodal regions. The irradiation was performed with a 42 MeV Betatron (Siemens) or with cobalt-60 (Gammatron, Siemens). Three to five weeks following radiotherapy patients had surgery (tumour resection and lymph node extirpation) choosing conservative non-mutilating surgery and avoiding radical neck dissection.

All operative specimens were evaluated considering histologic residual tumour. When no microscopic residual tumour was detectable, this was considered a complete response (CR). When only microscopic residual tumour was seen in the operative specimen the response was classified a partial response (PR). All cases where macroscopic residual tumour was found were determined as no response (NR) to preoperative therapy.

RESULTS OF COMBINED PREOPERATIVE THERAPY

The interim results of therapy were assessed by November 1987 so that the time following therapy is 18–30 months. Treatment tolerance, response to preoperative therapy, survival and loco-regional recurrence rates have been evaluated. For results of excluded patients, see Table 5.

Of 41 primary tumours 23 did not show any residual histological tumour (56%). In 16 cases only microscopical residual tumour could be found (39%). This reveals an overall response rate of 95% (39/41). Only two patients had macroscopic tumour at the operation (NR 5%).

Thirty-seven patients clinically presented with lymph node metastases prior to therapy. The response rates in these patients are 22/37 (59%) complete response, 13/37 (35%) partial response and 2/37 (5%) no response. None of the patients

experienced a tumour progression or progression of lymph node metastases during preoperative therapy. Table 4 shows the response to preoperative combined therapy due to the tumour stage. According to the table, the overall response rate in T2 and T3 is 100%. Thirteen patients (32%) experienced local or regional recurrence (in seven cases a local recurrence, in four cases a regional lymph node recurrence and in two patients a combined locoregional recurrent disease was found). None of these patients had a histological complete response to preoperative therapy. These recurrences were noted 1–13 months (median 5.5 months) after therapy.

The chemotherapeutic regime used has not caused any severe side-effects. Only minor bone marrow depression, never requiring therapy or interruption of planned treatment, occurred. Only one patient showed a platelet count of less than 100,000/mm^3, the nadir was 78,000/mm^3. All other patients had platelet counts of more than 150,000/mm^3 and white blood cell counts above 3500/mm^3 during and following therapy.

The mucosal reaction to irradiation started earlier than we would expect from irradiation without concomitant chemotherapeutic treatment. In most cases a pronounced mucositis was observed after a dose of 20 Gy. Conservative treatment with analgesics, antiphlogistics, mechanical soft diet and nasogastric tube feeding relieved all patients who suffered from increased mucositis. The skin reaction did not exceed erythema as seen after 50 Gy without chemotherapy. Patient acceptance of preoperative therapy was excellent. Due to the dramatic tumour shrinkage, onset of pain relief in initially painful patients was effective and early. During the 3–5 weeks following irradiation the local reaction diminished. At surgery, a slightly increased tendency for bleeding was noted as well as some delayed wound healing. These differences were not thought to be clinically significant. Two cases of osteoradionecrosis occurred.

Twenty-six patients (63%) have survived 18–30 months following treatment. Out of 15 patients who died only two patients were without evidence of recurrent disease, all others died with tumour progression.

The mean survival according to the primary tumour was significantly lower in T4 patients than T2,3 patients. In T4 patients the mean survival was 12.5 months versus 24 months in T2 and T3 patients (Breslow $P = 0.0089$ Mantel–Cox $P = 0.0011$). Analysing the mean survival in T2 versus T3 (23 months versus 22 months), no significant difference was found. Disease free survival (mean) according to the tumour stage was 22 months in T2, 22 months in T3 and 5 months in

Table 4. Response to preoperative combined therapy

Tumour stage	Patients (No.)	No histological residual tumour (CR)	Microscopical residual tumour (PR)	Macroscopic residual tumour (NR)
T2	(15)	73%	27%	
T3	(20)	55%	45%	
T4	(6)	17%	50%	33%
Total:	(41)	56%	39%	5%

Table 5. Reason for exclusion and outcome in 10 patients

Tumour site	Stage	Age	Reason for exclusion	Survival (months)
Retromolar trigone	T4N2	68	Refused op—reirradiation	11
Buccal mucosa	T4N1	81	No chemotherapy*	16
Floor of mouth	T3N1	51	Incomplete chemotherapy†	NED 3
Tongue	T2N1	49	Refused operation recurrence (9 mo): op	NED 25+
Tonsil	T3N1	58	Incomplete chemotherapy†	NED 25
Floor of mouth	T3N1M1	67	No op: radiation‡	26
Tonsil	T2N1	50	Refused op—recurrence: op	6
Tongue	T2N1	68	Refused op—recurrence: op	8
Retromolar trigone	T4N2	72	Refused op—recurrence: chemo	5
Retromolar trigone	T3N2	85	No chemotherapy*	10

*Excluded because of age.
†Interruption of administration—lacking cooperation.
‡M1, only radiation therapy.

T4. The T4 patients have a significant lower disease free survival ($P = 0.0001$, Breslow = Mantel–Cox). Comparing the survival in N0,1 patients (25 months) with N2,3 patients (20 months) no statistically significant difference was found.

DISCUSSION

A major advantage of preoperative radiation therapy is the opportunity it affords to use histological response as an indicator of treatment efficacy. Which dose to deliver preoperatively is an important question. The dose chosen should at least be capable of eradicating subclinical disease but should not increase perioperative complications. The dose of 50 Gy delivered in 5 weeks in 25 fractions is tolerable to the patient and postoperative morbidity is acceptable. Based on experience from squamous cell cancer in other sites [1–7] with the simultaneous administration of mitomycin C and 5-fluorouracil, we expected an increased tumour clearance without major systemic side-effects, for cancers of the head and neck region.

In considering the timing of administration we chose to administer mitomycin C shortly before irradiation on the first day of treatment. This decision was based on experimental observations by von der Maase and Overgaard [8], who suggested a greater radiation enhancement than when the drug was given after radiation. The use of 5-fluorouracil by infusion was based on suggested benefits from the work of Byfield *et al.* [9] and Calabro-Jones *et al.* [10]. Administering 5-fluorouracil by infusion also has shown lower bone marrow toxicity compared to bolus-administration as reported by Seifert *et al.* [11].

The side-effects noted were mainly due to the early onset of mucositis, though never leading to treatment interruption. The systemic side-effects were negligible. We believe the acceptability of this regimen is important for this group of patients, many of whom have poor performance status and who are unsuitable for more toxic regimens [12–14].

We believe that the rate of complete histológical response (56%) of the tumour cannot be explained by any of the two modalities alone. Knöbber *et al.* [15] irradiated oral and oropharyngeal cancers with 50 Gy without chemotherapy and still found tumour in 2/3 of all patients despite 13% of patients having T1 tumours and 44% T2 tumours. According to data obtained from the extensive overview of radiation therapy in head and neck cancers published by Withers *et al.* [16], doses corresponding to 62–68 Gy (single fractions of 2 Gy) show local control in 34–56% of T2–T4 oral cavity or oropharyngeal cancer. Mitomycin C and 5-fluorouracil with addition of hydroxyurea has also been used to treat squamous cell cancer of the head and neck region. The authors of this EORTC study stated that this regimen had low antitumour activity and substantial toxicity which precluded further evaluation of the regimen [17]. The ultimate way these drugs and irradiation interact still remains unclear and needs further clarification.

Although reports on similar combinations with chemotherapy and irradiation have been used in treatment of squamous cell cancer in the head and neck region with apparently good results [3, 7] only one randomized trial using this combination has been published [18]. Keane *et al.* [18] found no difference in their study on advanced laryngeal and hypopharyngeal squamous cell cancer, comparing irradiation ± MMC and 5-FU. Their two treatment arms consisted of 50 Gy/20 fractions/4 weeks versus split course treatment, 50 Gy/20 fractions/8 weeks plus chemotherapy days 1–5 and 42–45. Even though no difference was found between the two treatment arms, the addition of MMC and 5-FU simultaneously to irradiation was able to compensate for a split of 4 weeks duration. Overgaard *et al.* [19] suggested that each week of split course may be equivalent to a 'loss' of a dose of 4 Gy.

It is very important to stress the role of surgery. Following initial treatment, tumours may show rapid shrinkage and clinically often completely disappear. Yet when surgery is performed vital tumour can still be found in some of these cases. Clinical examination is insufficient to determine whether there is residual tumour or not. Knöbber *et al.* [15] found clinically 80% complete responders whereas the histological complete response only was achieved in 33% of cases. It is also important that the operating surgeon has seen the patient at the beginning of the preoperative therapy and is aware of the initial tumour extent.

Though all patients entering the trial gave consent to the planned treatment, five decided not to undergo surgery. This reflects one of the 'problems' with this approach; tumour shrinkage, which often is clinically complete, may convince some patients that surgery is unnecessary.

The overall survival in our series is 63% (after 18–30 months follow up) and quite comparable with data found by others such as Knöbber *et al.* [15], though the latter had more earlier stages in their study. Weller *et al.* [20] achieved a 2 year survival of less than 50% in oropharyngeal cancers (all stages) after radiotherapy as the only treatment. Similar results have recently been published from the RTOG study 73–03 [21], comparing pre- and postoperative irradiation.

In our trial, patients who showed a complete response (histologically proven), never recurred in this site. All patients who achieved a complete response to pretherapy (primary as well as lymph nodes) are alive without any evidence of disease, suggesting that no additional treatment is necessary

for this group of patients. However, patients with microscopic or macroscopic residual tumour may benefit from additional postoperative treatment. Since 1987 patients with histologically confirmed residual tumour have been treated by additional postoperative irradiation of 26 Gy/3 weeks. This postoperative local radiotherapy is well tolerated. Future evaluation will show if the local recurrence rate can be decreased by additional irradiation. Furthermore, a randomized trial in advanced head and neck cancer was initiated in 1988, comparing 76 Gy (50 Gy–2 weeks–26 Gy) with and without concomitant administration of MMC and 5-FU.

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