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Doxorubicin in Advanced Breast Cancer: Influence of Schedule on Response, Survival and Quality of Life

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The influence of scheduling of doxorubicin on response, survival and quality of life was assessed in a randomised trial in patients with advanced breast cancer, none of whom had previously received cytotoxic chemotherapy for advanced disease. 28 patients received 75 mg/m² doxorubicin every 3 weeks for four courses (arm 1) and 31 patients received 25 mg/m² weekly for 12 courses (arm 2). Response rates and median time to progression were similar in the two arms and median survival was 8 months in both arms. However, amongst patients receiving treatment every 3 weeks, psychological distress measured using the Rotterdam symptom checklist fell significantly over the course; no such change was observed in those treated weekly. Physical symptoms related to cancer improved during treatment similarly for both groups.
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INTRODUCTION

THE MANAGEMENT of patients with metastatic breast cancer is essentially palliative in intent. Breast cancer is moderately sensitive to several cytotoxic agents, of which doxorubicin is generally considered to be the most active, with response rates between 40 and 57% when given at doses of 60–75 mg/m² every 3 weeks to previously untreated patients [1, 2]. The optimum dose and schedule of administration for doxorubicin has, however, not been established [3]. The importance of dose was shown in a randomised study, in which patients who received 70 mg/m² doxorubicin every 3 weeks had a higher response rate and a longer median survival than those receiving 35 mg/m² every 3 weeks [4]. Dose intensification has recently been investigated as a possible way of increasing the efficacy of treatment [5–9]. Response rates up to 85% have been reported for patients receiving doxorubicin at doses between 75 and 135 mg/m², given at monthly intervals [6]. These high doses of doxorubicin are associated with marked toxicity including severe myelosuppression, stomatitis and potential cardiotoxicity, but there is no definite evidence that such high dose intensity treatment prolongs survival.

Although doxorubicin is conventionally given every 3 weeks, weekly treatment is also effective and may reduce the incidence of cardiotoxicity [10]. The efficacy and toxicity of weekly and every 3 weeks doxorubicin treatment given at equal planned dose intensities (mg/m²/week) have not, however, been compared in a prospective trial. In this study patients with metastatic breast cancer who had not previously received cytotoxic chemotherapy for advanced disease were randomised between two regimens with the same planned dose intensity: doxorubicin 25 mg/m² weekly or 75 mg/m² every 3 weeks. The efficacy of the two treatment schedules was compared using the standard parameters of response and survival. An important feature of this trial was an attempt to compare the quality of life for patients receiving the two different schedules. At present there is no single agreed approach to the measurement of quality of life [11]. For the purposes of this study, assessment of quality of life involved patients' reports of psychological symptoms, physical symptoms, levels of physical activity, practical difficulties associated with treatment and a global evaluation of quality of life. In this paper, aspects of the Rotterdam symptom checklist (RSCL) [12] concerning psychological adjustment and physical symptoms are presented. Full results of the quality of life assessments will be reported elsewhere. Pharmacokinetic studies were undertaken during the first cycle of treatment in a subset of these patients [13].

PATIENTS AND METHODS

Between July 1987 and June 1989, 59 patients were entered into this randomised phase III study at Guy's Hospital and the Christie Hospital. All patients had histologically proven breast cancer with either metastatic (n = 53) or locally recurrent disease which was not considered curable (n = 6). None had received previous cytotoxic chemotherapy for advanced disease. Patients who had received prior adjuvant chemotherapy were eligible provided this had not included an anthracycline. Other eligibility criteria were as follows: age less than or equal to 75 years; measurable or evaluable disease; a life expectancy of at least 3 months and a performance score of 0–2 on the WHO scale [14]. Patients with a performance score of 3 due solely to immobility resulting from the presence of bone metastases were also eligible. Approval was obtained from local committees on ethical practice and all patients gave informed consent.

Patients with a peripheral white blood count (WBC) $< 3.0 \times 10^9$/l or a platelet count $< 70 \times 10^9$/l were excluded as were those with a serum bilirubin > 25 μmol/l or

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an aspartate transaminase level greater than twice the upper limit of normal. Other exclusion criteria were as follows: symptomatic cerebral metastases confirmed by computer tomography (CT) or MRI; prior or concomitant malignancy (with the exception of adequately treated carcinoma *in situ* of the cervix or non-melanomatous skin cancer); any condition preventing adequate follow up or weekly attendance at the hospital; active uncontrolled infection; a history of congestive cardiac failure, significant arrhythmias or bifascicular bundle branch block.

Treatment

Patients were randomly allocated to receive either four courses of doxorubicin 75 mg/m^2 given by slow intravenous bolus injection every 3 weeks (arm 1) or 12 courses of doxorubicin 25 mg/m^2 given weekly (arm 2). For patients in arm 1, the second, third and fourth cycles of chemotherapy were given only if the blood count on day 21 showed WBC $> 3.0 \times 10^9$/l and platelets $> 100 \times 10^9$/l. If the blood counts had not recovered to these levels, treatment was delayed until these values were reached. During the first cycle of chemotherapy a nadir blood count was measured on day 10 and the dose of doxorubicin was modified for subsequent courses according to these results. For patients in arm 2 of the study no such dose reductions were made. Treatment was given each week if the WBC was $> 2.0 \times 10^9$/l and platelets were $> 70 \times 10^9$/l on the day chemotherapy was due. If the blood count was below these levels treatment was deferred for one week or until these values were attained.

At the completion of planned treatment patients who had stable disease or had responded were observed without specific therapy until there was objective evidence of disease progression. Treatment on relapse varied, but patients who had shown a good response to doxorubicin generally received this again.

Investigations and assessment of relapse

Before starting treatment a full medical history was taken from each patient and a clinical examination was performed. Performance status was graded by WHO criteria [14]. The dimensions for all measurable sites of disease were recorded and all visible lesions were photographed. A full blood count, biochemical screen, chest radiograph, ECG and radionuclide bone scan were performed on all patients. Plain radiographs were taken of all suspicious lesions detected on bone scan. Ultrasound or radionuclide liver scans were undertaken in patients with hepatomegaly or abnormal liver biochemistry.

Responses were assessed according to UICC criteria [15]. Clinical assessment of response was made every 3 weeks. In patients with pulmonary or pleural disease, chest radiographs were repeated at 6 week intervals. Plain radiographs of evaluable bone lesions were performed every 3 months and at the time of clinical progression. Liver metastases were also reassessed radiologically at 3 month intervals.

Quality of life assessment

Quality of life was assessed using a 30 item version of the RSCL [12]. Each item is scored between 0 (not at all) and 3 (very much). Seven of the items within the RSCL are concerned with psychological symptoms. These are: worrying; feeling irritable; feeling nervous; feeling depressed; feeling anxious; feeling tense; feeling despondent about the future. Possible scores on this 7 item psychological subscale range from 0 to 21. The RSCL was administered before treatment, at the midpoint of treatment and at the completion of treatment. Providing there were no delays in therapy, the second and third assessments were performed 6 weeks and 12 weeks after starting treatment. Toxicity for each cycle of treatment was graded according to WHO criteria [14].

Statistical analysis

Response to the two treatments was compared using the χ^2 test. Time to progression and survival from the date of first treatment with doxorubicin were calculated by the Kaplan and Meier method [16], the treatments being compared by the log-rank test. Quality of life scores for patients in the two arms of the study at individual time points were compared using the Wilcoxon rank sum test. Changes in quality of life scores over time in each arm of the study were assessed by Friedman's 2-way analysis of variance. Quality of life data were analysed on an intention to treat basis.

The expected interval until recovery of blood counts was used to calculate received dose intensity (i.e. 3 weeks after the final injection for patients in arm 1 and 1 week after the final injection for those in arm 2). For patients receiving the protocol as planned, the total time period used for these calculations was, therefore, 12 weeks for patients in either arm.

RESULTS

A total of 59 patients were entered into the study. The median age was 52 years (range: 34–74 years). 28 were randomised to

Table 1. Patients' characteristics

	Treatment arm	
	75 mg/m^2 every 3 weeks (n = 28)	25 mg/m^2 weekly (n = 31)
Age		
Median (years)	54	53
Range	32–69	34–74
Previous adjuvant chemotherapy	3	2
Previous endocrine therapy		
Adjuvant	3	11
Advanced	21	17
Metastatic disease at first presentation	2	1
Locoregional relapse only	3	3
Metastatic disease following relapse	23	27
Disease free interval*		
Median (months)	24	27
Range	4–100	5–271
Time from relapse to start of study*		
Median (months)	8	8
Sites of disease		
Breast	7	7
Lymph nodes	18	21
Cutaneous	11	14
Bone	21	22
Lung	10	9
Liver	5	8
Pleura	11	9
Other	1	2
Number of sites of disease		
1	2	3
2	9	6
3	6	13
≥4	11	9

* For patients with relapsed disease only.

Table 2. Response to treatment

	75 mg/m² every 3 weeks (n = 28)		25 mg/m² weekly (n = 31)	
Best response				
CR	0	(50%)	1	(58%)
PR	14		17	
SD	9		10	
PD	5*		3	
Status at 12 weeks				
CR	0	(71%)	1	(71%)
PR	13		15	
SD	7		6	
PD	5		6	
Dead	3		3	

* Includes 2 patients with early death (see text).

arm 1 (3 weekly schedule) and 31 to arm 2 (weekly schedule). Patient characteristics at the time of entry to the study are shown in Table 1. The two groups were well balanced for exposure to previous adjuvant chemotherapy, disease free interval, time from relapse to first treatment with doxorubicin and extent of disease. More patients in arm 2 had received adjuvant endocrine therapy ($P = 0.03$), but the total number of patients who had received endocrine therapy at any time prior to the study was similar for the two arms.

Response and survival

Response to treatment and disease status 3 months after starting treatment, when planned chemotherapy should have been completed, are shown in Table 2. The response rate with 3 weekly treatment (50%) did not differ significantly from that for weekly treatment (58%: $P = 0.6$). 2 patients receiving treatment every 3 weeks died within 6 weeks of starting treatment (1 from a cerebrovascular accident, one following a surgical pleurodesis) and have been included as treatment failures. An equal proportion (71%) of women in the two arms of the study were either in remission or had stable disease 3 months after starting treatment. Median time to progression was similar for the two groups (4 months and 5 months; $P = 0.4$). Median survival was 8 months in both arms ($P = 0.25$; Fig. 1).

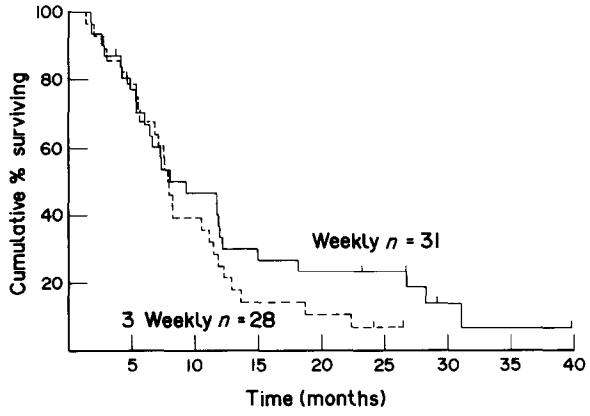

Fig. 1. Survival for patients treated with doxorubicin 75 mg/m² every 3 weeks (----) or doxorubicin 25 mg/m² weekly (———).

Table 3. WHO toxicity grading

	Every 3 weeks (n = 28) WHO grade		Weekly (n = 31) WHO grade	
	3	4	3	4
Haemoglobin	0	0	1	0
White blood count	4	1	9	1
Platelets	0	0	0	0
Stomatitis	2	0	4	0
Nausea/vomiting	4	1	5	0
Alopecia	23	0	19	0
Infection	1	0	0	1

Toxicity

The number of patients in each arm who experienced grade 3 or 4 toxicities (WHO scale) at any time during treatment is shown in Table 3. 23 (82%) of the patients receiving treatment every 3 weeks experienced grade 3 alopecia, compared with 19 (61%) in the weekly arm. Apart from alopecia, 10 patients (36%) in the weekly arm and 14 patients (45%) in the weekly arm experienced at least one episode of grade 3/4 toxicity of some type. No significant differences were observed between the groups with respect to nausea and vomiting, stomatitis or neutropenia. No clinical evidence of cardiotoxicity was observed in this study.

Dose reductions and delays

The proportion of the planned total dose that was administered was similar for the two groups (means 85 and 87%, respectively) (Table 4). The dose–time intensity (mg/m²/week) was also calculated, as the criteria for dose modifications differed for the two arms of the study. Mean received dose–time intensity for the two groups (89 and 86% of that planned, respectively) did not differ significantly.

Table 4. Received doses and dose intensity

	75 mg/m² every 3 weeks (n = 28)	25 mg/m² weekly (n = 31)
Doses received (% of planned total dose)		
Mean	85	87
Range	33–100	42–100
Received dose intensity (% of planned dose intensity)		
Mean	89	86
Range	50–100	53–100
No. receiving full planned dose	15 (54%)	20 (65%)
No. receiving full planned number of cycles (with or without dose reductions)	24 (86%)	20 (65%)
No. receiving all planned treatment without delays or dose reduction	15 (54%)	9 (29%)

Table 5. Scores on psychological subscale of the Rotterdam symptom checklist

		Pre-treatment	Midpoint	Post-treatment
Treatment every 3 weeks				
(n = 21)	Mean	8.2	5.0	5.4
	Median	8	4	6
	Range	2–21	1–19	0–16
Weekly treatment				
(n = 21)	Mean	8.1	7.7	7.8
	Median	10	8	8
	Range	1–18	0–19	0–18

Scores for 13 patients who only completed one or two of the three planned assessments are omitted from this table.

24 (86%) of the women in arm 1 received the planned four cycles. The other 4 women either died early (2) or had progressive disease while on treatment (2). Only 15 (54%) of the patients in this arm received all four courses without any delay or dose reduction. The major reasons for dose modifications were neutropenia (7 patients) and stomatitis (2 patients).

20 of the 31 (65%) patients in arm 2 received the planned 12 courses. There was one septic death and 7 patients stopped treatment early because of progressive disease. A further 3 stopped treatment because of toxicity. 2 of these found treatment non-specifically intolerable and 1 had severe stomatitis. Treatment was delayed on at least one occasion in 20 of the patients receiving weekly therapy. The commonest indication for deferring treatment was neutropenia (9 patients), followed by specific requests by the patient (5) and stomatitis (4). Pulmonary embolism, pathological fracture, pleurodesis, laparotomy and herpes zoster led to delays in 4 patients. Only 9 (29%) of the patients received the full 12 cycles of weekly treatment without any delays.

Quality of life (Table 5 and Fig. 2)

55 of the 59 patients entered into the trial underwent initial quality of life assessment. The remaining 4 patients were either not requested to complete the quality of life assessments due to an oversight (2 patients), declined to participate in this part of the study (1 patient) or spoke no English (1 patient). 42 patients completed all three quality of life assessments (pre-, mid- and post-treatment), 21 in each arm of the study.

As described in the methods section, seven of the items in the RSCL constitute a psychological subscale. When all 55 patients who completed a pre-treatment RSCL were considered, no significant difference was observed in median psychological scores between the two arms of the study (P = 0.7). Psychological scores for the 21 patients in each arm who completed all three RSCL assessments are shown in Table 5 and Fig. 2. No significant difference was observed between the median pre-treatment psychological scores for the patients in each of the two treatment groups (P = 0.9). For patients receiving treatment every 3 weeks, psychological scores improved significantly over the course of treatment (Fig. 2a: P = 0.001, analysis of variance). No such change was observed in the weekly treatment group (Fig. 2b: P = 0.48).

For patients receiving treatment every 3 weeks, changes in psychological scores between the first two assessments ranged from a decrease (or improvement) of 13 points to an increase (or deterioration) of 3 points (median decrease: 4 points). For those receiving weekly treatment equivalent changes ranged from a decrease of 10 points to an increase of 6 points (median decrease: 1 point). Comparison between the two arms showed that the median improvement in psychological score observed in the 3 weekly group was significantly greater than that for the weekly group (P = 0.01, Mann–Whitney). At the end of the study, a difference in improvement of psychological scores was still observable, but did not achieve statistical significance (P = 0.11).

The components of the RSCL related to physical symptoms were considered separately. At the pre-treatment assessment more than one third of the patients reported moderate or high levels of breathlessness and pain. These two symptoms were therefore considered to be predominantly cancer related. In contrast, significant vomiting or diarrhoea were reported by less than 10% of patients before treatment and none reported hair loss. These symptoms were therefore considered to be treatment related. Amongst the 21 patients in each arm of the study who completed all three assessments, both pain and breathlessness improved with treatment, whilst vomiting and diarrhoea scores increased at 6 weeks and reverted to pretreatment levels after completion of chemotherapy. These changes were similar in both arms of the study.

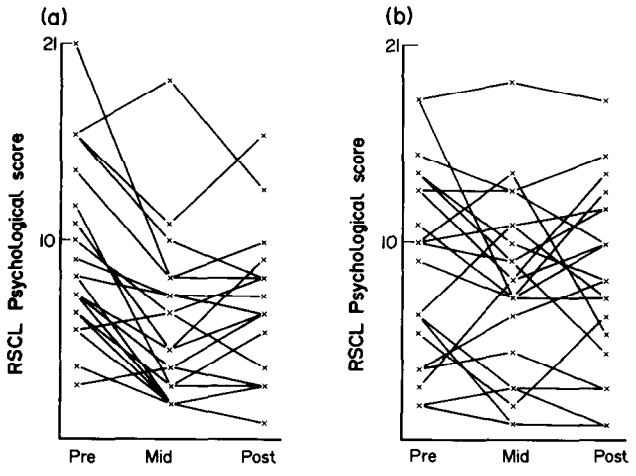

Fig. 2. Changes in psychological scores over the course of the study. (a) Patients receiving 3 weekly treatment. (b) Patients receiving weekly treatment.

DISCUSSION

Bielack and coworkers recently reviewed the literature concerning the effect of different schedules of doxorubicin administration on toxicity and anti-tumour efficacy [3]. They concluded that there are surprisingly few prospective randomised trials comparing different methods of doxorubicin administration. In a study reported by Knight *et al.* [17] patients were randomised to receive doxorubicin 70 mg/m^2 given either every 3 weeks or every 5 weeks. Response rates and survival did not differ significantly, but the 3 weekly schedule was associated with more leukopenia. Creech *et al.* [18] compared 'low dose' doxorubicin (20 mg/m^2, day 1 and 8, every 28 days) with conventional dose therapy (60 mg/m^2, every 21 days). Again no difference in outcome was observed. Importantly, in neither of these trials did the treatments being compared have the same planned dose intensity.

In view of the probable impact of dose intensity on response [5] and of the influence of response on performance status, symptomatic improvement and general well being [19–22] we have compared two doxorubicin schedules of equal and moderately high planned dose intensity (25 mg/m^2/week). Both treatment schedules have been extensively used in patients with breast cancer [2, 10, 23]. No major differences in response rate or survival were expected with this trial design. However, the main reason for undertaking the study was to compare the toxicities of the two schedules and in particular to examine the patients' own reports of their symptoms.

The optimum duration of chemotherapy for advanced breast cancer is still uncertain. In two relatively small studies no differences in relapse rates were observed between patients who received continuous chemotherapy and those who stopped treatment after either 6 months [24] or 9 weeks [25]. We planned to give brief initial treatment followed by further therapy at the time of progression. After the initiation of our study, a larger trial examining duration of therapy was reported by Coates and coworkers [26]. In that trial, continuous chemotherapy was associated with a small but significant improvement in time to progression (median 6 vs 4 months, $P < 0.001$), improved quality of life and a trend towards longer survival ($P = 0.07$) than intermittent therapy.

The response rates observed in the current study were satisfactory and similar to those reported in other studies of doxorubicin used either as a single agent or in combination with other drugs. Time to progression and survival were, however, poor. While this may possibly reflect the use of brief initial therapy, it is also probably due to extensive disease at the start of treatment (median 3 sites), a factor which has previously been shown to be associated with poor survival [27]. In addition, our policy has been to use chemotherapy relatively late in the natural history of the disease, after failure of endocrine therapy in the large majority of cases.

As we expected, no significant differences were observed in response rate, time to progression or survival between the two schedules. Both treatment schedules were, however, associated with considerable toxicity. The mean total dose received and the mean received dose intensities appear high in comparison to the planned total dose and planned dose intensity (Table 3). However, only 54% of those receiving treatment every 3 weeks and 29% of those receiving weekly treatment completed all treatment as planned. The major cause of dose reductions (arm 1) or delays (arm 2) was neutropenia. In addition, a relatively large number of patients on the weekly schedule suffered complications relating to their disease, some of which required surgical intervention and thereby delayed treatment. No imbalance in pre-treatment characteristics was identified to account for an excess of complications in those patients receiving weekly treatment.

One of the major end points for this study was the comparison of quality of life between the two treatment groups. A major problem in quality of life studies in advanced cancer is that data are frequently incomplete, either because patients become too unwell to complete the assessments or because they may die before the end of the study. In this study, response and survival were similar for the two treatment groups as was the proportion of patients who were able to complete all three quality of life assessments. Thus, comparisons of quality of life between the two groups are unlikely to be biased.

Although pre-treatment psychological scores from the Rotterdam symptom checklist were similar for the two groups, important differences in psychological distress were identified between the two patient groups over the course of the study. Doxorubicin delivered every 3 weeks was associated with a significant reduction in psychological distress, whilst no such change was observed with the weekly treatment. These differences in psychological parameters cannot be explained by differences in objective measures of disease response or by the patients' or physicians' ratings of the severity of physical toxicity. They may, however, reflect differences in the pattern of these toxicities, with the patients on weekly treatment experiencing more continuous nausea and malaise than those receiving treatment every 3 weeks. Interestingly, in a pharmacokinetic study conducted in a subgroup of the patients in this trial, aggregate exposure to doxorubicin was greater in patients treated weekly than in those treated every 3 weeks [13].

In conclusion, the two doxorubicin schedules used in this study were of equal dose intensity and efficacy. However, psychological adjustment was better in those receiving the treatment every 3 weeks.

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Radiation Therapy, an Important Mode of Treatment for Head and Neck Chemodectomas

Didier A. Verniers, Ronald B. Keus, Paul F. Schouwenburg and Harry Bartelink

Between 1970 and 1990, 22 patients with 44 chemodectomas in the head and neck region were seen at the Netherlands Cancer Institute in Amsterdam. All patients were treated with radiation therapy (17 patients with radiation therapy only and 5 in combination with surgery). One patient was treated two times with an interval of 12 years at each side of the neck. Standard dose was 50 Gy in 25 fractions over 5 weeks. A radiation portal arrangement with oblique fields with paired wedges was used most frequently. The follow-up period ranged from 1 year to 20 years. Two recurrences at 2 and 9 years after treatment were observed. The actuarial local control rate was 88% at 10 years follow-up. Comparison of the results of surgery and radiotherapy demonstrates that radiation therapy is an effective treatment modality without mutilation or severe late morbidity for chemodectomas in the head and neck region.
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INTRODUCTION

CHEMODECTOMAS OR glomus tumours are slowly growing tumours originating in the chemoreceptor bodies [1, 2]. The glomus bodies are responsive to changes in blood oxygen, carbon dioxide tensions and pH. They belong to the APUD system (amine precursor uptake and decarboxylating system), that embryologically originates from the neural crest cells [3–8], and are composed of neurovascular structures. It is a very rare tumour type, with an incidence of 2/100 000. There is a female predominance with a sex ratio of 3 and the peak age range is 50–60 years [9]. The incidence is higher in patients with chronic hypoxia, such as long standing hypoxemia in chronic heart diseases, or living at high altitude [7]. Because of the indolent clinical course, a long follow-up period is necessary to evaluate the treatment [5].

Chemodectomas can occur in multiple sites in the head and neck region in the same patient. Frequent localisations are the middle ear, the mastoid air cell system (glomus tympanicum), the jugular bulb (glomus jugulare), the carotic bifurcation (glomus caroticum) and the hypopharynx (glomus vagale tumour) [7, 9–13]. In the early stages of the disease, each of these localisations gives different clinical symptoms. In late stages the symptomatology is less specific. Although their clinical progression is slow and indolent, in advanced cases cranial nerve palsies and bone destruction can cause important morbidity. Therefore, treatment is to be considered at an early stage.

A controversy, however, about the treatment of choice exists. These tumours have been treated by surgery alone, radiation therapy alone, embolisation or a combination of these treatment modalities. The debate about irradiation arises because of the slow tumour regression after radiotherapy. The purpose of this paper is to study the value of radiation therapy in the treatment of head and neck chemodectomas in the Netherlands Cancer Institute.

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