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IS IT POSSIBLE TO PREDICT THE OUTCOME OF RADIATION THERAPY OF HEAD AND NECK CANCER?

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Abstract

Methods for predicting the outcome of radiation treatment are discussed. The correlation of tumour decrease during irradiation with recurrence-free survival is poor. A reliable method for predicting the long-term result of radiation therapy is urgently needed. Methods using flow cytometry, electron microscopy and positron emission tomography with short-lived radiopharmaceuticals are under investigation.

Key words: Cancer, head and neck, radiation therapy, prediction of recurrence.

The early response of a malignant tumour to radiation treatment does not necessarily correlate to its radiocurability. The tumour may decrease rapidly during treatment and even clinically disappear, but nevertheless recur within some months. On the contrary, the tumour may persist all through the treatment and still disappear some weeks later never recurring (1, 2). In head and neck cancer there is a great need for methods that with some degree of reliability can predict both the radioresponsiveness and the final radiocurability of the tumour. Such methods should be useful for choice of therapy and for planning of combined treatment. As head and neck cancer often remains locoregional for a long time, adequate treatment of the primary tumour and neck node secondaries is of great importance for the final outcome.

The significance of rapid response

The behaviour of a tumour during radiation therapy hinges on several factors: the growth fraction, the cell cycle time, the amount of stroma and oedema in the tumour, and cell loss. To elucidate the significance of the response of the irradiated tumour, 123 patients with head and neck cancer were collected from two hospitals in Finland and carefully followed during and after treatment (2). Tumour response was evaluated at the midpoint and the end of radiation treatment with 50 to 70 Gy in 5 to 7 weeks. The findings were correlated with local freedom of recurrence during two years. Thirteen patients died from distant metastases or intercurrent diseases within two years. The follow-up of the remaining 111 cases was at least two years.

Patients with early stage tumours (T1–2, N0) with a rapid regression observed at the midpoint of treatment were significantly more often recurrence-free at 2 years than patients with tumours with slow response (Table 1). There was no correlation between the status at the end of therapy and recurrence-free survival at two years (Table 2). In the advanced cases the situation was different: a complete response of the tumour at the midpoint of therapy did not at all correlate to the outcome at two years of observation (Table 3). On the other hand, a complete response at the end of treatment was significantly correlated to local freedom of recurrence at two years in these patients (Table 4). Our conclusion was that the early, individual response of a head and neck cancer during radiation treatment should not lead to a change of treatment schedule.

There have been controversial findings in tumours at other locations. For example, in cervix cancer an early response predicted local curability according to Marcial & Bosch (3). The high single doses of intracavitary applications may have influenced the speed of the response in

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Table 1

Recurrence of T1–2N0 head and neck carcinoma in relation to tumour regression at the midpoint of radiation treatment

Tumour size at the midpoint of treatment	n	No recurrence within 2 years		Recurrence within 2 years	
Disappeared	17	14	(82%)	3	(18%)
			p = 0.02		
Diminished by more than 50%	22	12	15 (50%)	10	15 (50%)
Diminished by less than 50%	4	2		2	
No change	4	1		3	
Incomplete information	14	10		4	
Total	61	39		22	

Table 2

Recurrence of T1–2N0 head and neck carcinoma in relation to tumour regression at the end of treatment

Tumour size at the end of treatment	n	No recurrence within 2 years		Recurrence within 2 years	
Disappeared	49	32	(65%)	17	(35%)
			p = 0.8		
Diminished by more than 50%	8	6	6 (67%)	2	3 (33%)
Diminished by less than 50%	–	–		–	
No change	1	0		1	
Incomplete information	3	1		2	
Total	61	39		22	

Table 3

Recurrence of T1–2N1–3 and T3–4N0–4 head and neck carcinoma in relation to tumour regression at the midpoint of treatment

Tumour size at the midpoint of treatment	n	No recurrence within 2 years		Recurrence within 2 years	
Disappeared	9	4	(44%)	5	(56%)
			p = 0.18		
Diminished by more than 50%	17	5	9 (24%)	12	28 (76%)
Diminished by less than 50%	16	3		13	
No change	4	1		3	
Incomplete information	3	1		2	
Total	49	14		35	

Table 4

Recurrence of T1–2N1–3 and T3–4N0–3 head and neck carcinoma in relation to tumour regression at the end of treatment

Tumour size at the end of treatment	n	No recurrence within 2 years		Recurrence within 2 years	
Disappeared	28	12	(43%)	16	(57%)
			p = 0.02		
Diminished by more than 50%	9	2		9	16 (89%)
Diminished by less than 50%	8			6	
No change	1			1	
Incomplete information	3			3	
Total	49	14		35	

cervical cancer or there may be differences in the vascularity of the malignant tissue. It is interesting to note that Denekamp (4) in animal experiments, found a clear correlation between early response and tumour curability. Here, however, the fractionation used was different from the usual practice in head and neck cancer. According to Dawes (5), a correlation between tumour response and local curability cannot be observed earlier than one month after the end of radiation treatment.

Immune functions and prognosis of cancer patient

Methods for predicting the outcome of radiation therapy of head and neck cancer may concern either the host organism or the tumour itself. During the 1970s several studies concerned the possible immunosuppressive effect of radiotherapy (6). Nordman et al. (7) studied the immunosuppressive effect of radio- and chemotherapy but found no correlation between immunosuppression (determined with mitogen response to PHA, Con A and PPD) and the long-term survival of the patients with some common cancer forms. After postoperative irradiation of breast cancer patients an obvious decrease in the mitogen responses was detected, but there was no significant difference between patients with and without recurrence (8). In gastrointestinal cancer, however, a correlation was found between immune functions and survival. In head and neck tumours, a correlation between the number of NK cells and the radiation response was seen (Table 5), but there was no correlation between the number of NK cells and recurrence-free survival (Nordman & Toivanen, to be published).

^{18}F-deoxyglucose, flow cytometry and electron microscopy

In the Radiotherapy Department of the University Central Hospital in Turku, a multidisciplinary project has been

Table 5

The response of lymphocytes to PHA, Con A, PPD and NK cell activity in patients with head and neck cancer in correlation to response to radiotherapy

	PHA net counts ±SD	Con A net counts ±SD	PPD net counts ±SD	NK cells 50 : 1
Before radiotherapy				
Tumour disappeared during irradiation	63 500 ± 23 700	50 300 ± 33 700	13 200 ± 15 700	59.89–15.27 (n = 9)
n = 17	n.s.	n.s.	p < 0.001	p < 0.005
Tumour persisted during irradiation	54 800 ± 36 700	33 500 ± 20 900	7 000 ± 9 300	38.5–7.61 (n = 6)
n = 9				
After radiotherapy				
Tumour disappeared during irradiation	36 100 ± 17 200	32 700 ± 13 200	9 200 ± 15 000	52.44–11.67 (n = 9)
n = 17	n.s.	n.s.	n.s.	p < 0.01
Tumour persisted during irradiation	31 600 ± 16 500	24 300 ± 13 000	10 600 ± 17 000	31.4–14.33 (n = 5)
n = 9				

conducted since 1983 for studies of patients with head and neck cancer treated with radical radiotherapy (9). The aim has been to find predictive tests concerning potential tumour radiocurability. To be of clinical value, such tests should have high true positive and low false negative predictive power as to the local curability, making it meaningful to modify the treatment strategy during the early course of treatment. Finally it should, of course, lead to improved survival.

Scintigraphy with ^{18}F-fluorodeoxyglucose (FDG) (10), determination of DNA content with flow cytometry (FCM) (11), and electron microscopy (EM) (12) have been the methods investigated. FDG accumulates in tissues with a high demand for glucose like the brain, the heart, and malignant tumours. The radiotherapy of our head and neck patients was delivered to a total dose of 60 to 70 Gy (2 Gy/fraction, 5 fractions weekly). The FDG imaging was performed with a gamma camera before therapy and after a tumour dose of 20 to 40 Gy. Samples for DNA, FCM, EM and light microscopy were obtained from fresh biopsies before radiotherapy and after a tumour dose of 10 or 30 Gy.

A close correlation ($r = 0.86$, $p < 0.001$) between pretherapeutic FDG uptake and the percentage of S + G2/M-phase cells in FCM was found to indicate that enhanced glycolysis is associated with increased proliferative acitivity. In radioresponsive, regressing tumours the FDG uptake decreased, whereas clinically progressive tumours showed unchanged or increased uptake. Radioresponsiveness was not a consistent characteristic of tumours with a high percentage of S-phase cells. In three cases DNA aneuploidy was found before therapy, and the aneuploid stemline disappeared during irradiation in all cases. During treatment the number of S-phase cells tended to decrease and the G2/M-phase cells to increase, indicating a radiation-induced block in mitosis.

In the light microscopy and EM evaluation, the following parameters were studied: nuclear grade, invasion, fibrosis, number of mitoses, keratinization, lymphocytes and neutrofils. All parameters changed during irradiation in the direction of differentiation in these patients. Especially in cases with complete response for 1 to 5 years the filaments and desmosomes had a trend to increase. The findings are in concert with the report of Glucksman (13), who found a change to greater degree of differentiation in cases with favourable prognosis. The detailed results of the FCM and EM studies are presented in other articles in this issue.

In order to further elucidate the relationship between malignant glycolysis and tumour proliferative activity, studies with positron emission tomography are in progress. The positron emission tomography (PET) camera recently installed at the University Central Hospital in Turku enables quantitative determination of the glucose metabolic rate in vivo (14), and it seems to be useful in follow-up studies during and after radiotherapy (15). The decrement of FDG uptake in radioresponsive tumours is probably due to both the cell-killing effect of irradiation and regression of tumour volume. The nuclear DNA content analysis performed by FCM repeatedly from fine-needle biopsy aspirates may be a suitable technique for clinical routine. Further studies are clearly indicated before its clinical value can be determined. Ultrastructural and morphometrical analyses are too laborious for routine practice, but in selected cases they may be valuable for assessing radiation response and radiocurability.

Several other methods have been investigated concerning their ability to predict the outcome of radio- and chemotherapy such as clonogenic cell assay, micronuclei assay and subrenal capsule assay. The predictability of long-term prognosis by these methods has yet to be confirmed.

The most useful method at present for predicting the local cure of a tumour seems to be the computer method presented recently by RTOG (16), which takes into account several clinical parameters such as age, sex, TNM, size of tumour, histology, degree of differentiation and infiltration, and Karnofsky's index.

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