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Waiting times for radiotherapy: consequences of volume increase for the TCP in oropharyngeal carcinoma

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Abstract

Background and purpose: Waiting lists for radiotherapy have become longer over the past years. Apart from the psychological distress for the patient we are concerned about tumour growth during this waiting time, which may worsen prognosis. The purpose of this pilot study was to investigate tumour growth in the waiting time and to obtain an indication of its clinical consequences for patients with oropharyngeal carcinoma. A tumour control probability (TCP) model was applied to evaluate consequences for outcome.

Methods and materials: Increase in tumour volume was measured for 13 patients with oropharyngeal carcinoma by outlining the tumour on the diagnostic as well as on the treatment planning CT scan. Waiting time was defined as time between histopathological diagnosis and start of radiotherapy. For each tumour we calculated the increase in tumour volume and the tumour doubling time. The potential increase in TCP was calculated for each tumour for the situation without treatment delay.

Results: The mean increase in tumour volume was 70%. The mean waiting time was 56 days. Expected TCP with incorporation of delay was 47%, without delay it might have been 63–66%.

Conclusion: This study shows tumour progression during the time between the diagnostic CT scan and the treatment planning CT scan in oropharyngeal cancer. As a consequence of waiting time, which allows tumour volume increase, there may be an average control loss of 16–19 % for these tumours during the total waiting time before radiotherapy.

Keywords: Radiotherapy; Tumour growth; Oropharyngeal carcinoma; Waiting time; TCP

1. Introduction

The present continuous increase in the number of cancer patients exerts a strong pressure on the necessary facilities for diagnosis and treatment, which in many parts of the world does not match this necessity [3]. Therefore, waiting lists for radiotherapy have become longer over the past years in many countries [1,13,14,18]. This problem has been reinforced by the fact that treatment schedules for radiotherapy have improved and become more refined, but require more preparation and are therefore more time consuming [19]. In our clinic for head and neck tumours, Brouha et al. already reported a median time period of 43 days between the date of histopathological diagnosis and the start of radiotherapy in patients with early laryngeal carcinoma treated between 1980 and 1996 [1]. Although little is known about the clinical consequences, we regard this situation as undesirable.

Since oropharyngeal carcinomas mostly presents at an advanced stage and many of these tumours are treated by radiotherapy, we started a pilot study in which we investigated possible tumour growth during the waiting time by measuring tumour volume on the diagnostic CT scan as well as on the treatment planning CT scan. This last CT scan is carried out in treatment position in addition to the scan for diagnostic purpose. Thereby we also wanted to estimate the clinical consequences of the volume difference between the diagnostic scan and the planning scan.

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A survey by Dubben et al. showed a clear correlation between tumour volume and treatment response [2]. In the evaluation of new irradiation techniques, and especially intensity modulated radiotherapy (IMRT), the use of tumour control probability (TCP) models is well accepted [14,16,17]. With these models we can estimate control rates for a tumour with any given number of clonogenic cells and thus estimate the clinical consequence of tumour growth during the waiting period.

2. Methods and materials

2.1. Patients

All the patients with oropharyngeal carcinoma treated in our radiotherapy department between 1996 and 2001 were selected. Inclusion criteria were primary, squamous cell carcinoma, without distant metastases. All the patients were treated with primary radiotherapy or combined radio- and chemotherapy with curative intent. Altogether 46 patients with oropharyngeal carcinoma had been treated with primary radiotherapy. In 23 cases a CT planning had been performed. A further selection was done based on the requirement that both the diagnostic and the planning CT scan were made in our clinic to avoid a different acquisition technique of CT. As many patients were referred with CT scans performed in other hospitals, we had to exclude another 10 patients. Finally, 13 patients with oropharyngeal cancer were eligible for this study.

2.2. CT technique and volume measurements

To observe tumour growth during the waiting time we evaluated each patient for diagnostic CT scan (CT1) and the planning CT scan (CT2). To determine the tumour volume we outlined the tumour manually on the individual CT slices. Tumour volume was calculated by multiplying each cross-sectional area by the inter-slice distance and subsequently adding slices together (summation of areas technique). CT scans made for diagnosis had an inter-slice distance of 2 mm and a slice thickness of 3 mm. CT scans made for planning of radiotherapy had an inter-slice distance of 3 or 5 mm with a similar slice thickness of 3 or 5 mm. Contrast infusion was given in 1.5 ml/sec during 60 s with a fixed scan delay of 30 s in all cases.

Three observers, a resident and two experienced radiation oncologists, delineated each tumour. For each case the diagnostic and planning scan were evaluated successively in order to discriminate developing lymph nodes. When there was doubt about tumour delineation we asked for an opinion from an experienced radiologist. User defined magnification as well as adaptation of window/level setting of the images was possible. The delineation of tumour volume on CT scans was performed with the software used for this purpose at the radiotherapy department (PLATO IPS v 2.7, Nucletron, The Netherlands).

Volume increase was expressed as the difference between the volume on CT2 and the volume on CT1 as an average of three observations. For each patient the absolute increase in volume and the percentage increase were calculated. Knowing the time between CT1 and CT2, the tumour doubling time could be estimated.Waiting time was defined as time between the histopathological diagnosis and the start of radiotherapy.

Neck nodes were considered positive if their largest diameter was >1 cm. In that case their volume was measured the same way as the primary tumour. We classified each patient according to the TNM classification at the time of CT1 and CT2, respectively, on the basis of the CT scan.Clinical examination under general anaesthesia was not repeated.

2.3. TCP analysis

To obtain an impression of the clinical consequences of tumour growth we made use of a tumour control probability (TCP) model. According to Webb and Nahum the TCP in radiotherapy can be calculated starting with the number of clonogenic cells (N_0) [21]. The number of clonogenic cells surviving fractionated radiotherapy (N) can be estimated by the formula $N = N_0 e^{-\alpha D}$, where α is the sensitivity and D the total dose. The tumour control probability is given by $\mathrm{TCP} = e^{-N}$.

A doubling of the number of surviving tumour cells directly translates into a decrease of the TCP. Assuming the characteristics of the tumour do not change, the starting number of clonogenic cells after one doubling of the tumour volume becomes $N = 2N_0$. This results in a clonogenic cell survival after radiotherapy of $N = 2N_0 e^{-\alpha D}$, which results in $\mathrm{TCP}(2N_0) = \mathrm{TCP}(N_0)^2$. After a waiting period of m doubling times the tumour control is equal to $\mathrm{TCP}(N_m) = \mathrm{TCP}(N_0)^{2^m}$. According to this formula the effect of the treatment delay is independent of α, assuming that the tumour characteristics do not change in this short interval. To achieve clinical information about the TCP only populations can be considered. Therefore, a certain spread (σ) of the value for α is assumed.

For our analysis we used a clonogenic cell density of 10^7 per cm^3, an $\alpha = 0.30\ \mathrm{Gy}^{-1}$ with a spread $\sigma = 0.02$ [7]. The dose was 66 Gy. We analysed the TCP according to $\alpha = 0.30\mathrm{Gy}^{-1}$ and according to $\alpha = 0.30(\sigma)\mathrm{Gy}^{-1}$ for the whole population. The relation between TCP and volume is given in Fig. 1 for $\alpha = 0.30\mathrm{Gy}^{-1}$, $\alpha = 0.30 \pm 0.02\mathrm{Gy}^{-1}$ and the average.

The volume of the tumour at the time of diagnosis and the volume at the beginning of radiotherapy were estimated using the volumes at CT1 and CT2 and the tumour doubling times. The resulting differences in TCP were quantified by means of the TCP formula.

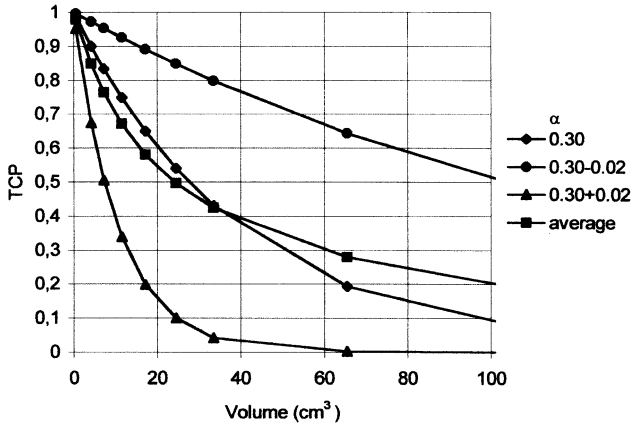

Fig. 1. Relation between TCP and tumour volume. The TCP was calculated for $\alpha = 0.30\text{Gy}^{-1}$ and for $\alpha = 0.30(\pm\sigma)$ where $\sigma = 0.02\text{Gy}^{-1}$.

3. Results

In this study there were 10 men and three women, aged 47–102 years (mean 68). Two tumours were stage II, four tumours stage III and seven were stage IV.

Table 1 shows the classification according to the diagnostic CT scan for each tumour and according to the treatment planning CT scan. In three cases, progress of T stage could be determined. In eight cases an increase in the number of lymph nodes between CT1 and CT2 was observed. As a consequence of these changes three patients (nos. 2, 6 and 8) progressed up to another stage according to the UICC classification [20].

Increase in tumour volume between CT1 and CT 2 was observed in all patients (Table 2). Two lymph nodes were included in the analysis to illustrate lymph node progression as well as tumour progression. The increase is shown as absolute volume increase and as a percentage of the volume on the diagnostic scan. The absolute volume increase ranged from 0.8 to 149 cm^3 (mean 22 cm^3). The percentage change of tumour volume ranged from 11 to 235% (mean 70%). The mean time between the planning CT scan and the diagnostic CT scan was 34 days (median 35, range: 12–47). Figs. 2 and 3 illustrate the growth of the tumour for patient no. 6.

Table 1
Patient characteristics

No	TNM-classification 1st scan	Tumour localisation	TNM-classification 2nd scan
1	T2N1	Tonsillar fossa	T3N1[a]
2	T2N1	Vallecula	T2N2b[b]
3	T3N0	Vallecula	T3N0
4	T4N1	Vallecula	T4N2a[c]
5	T4N2b	Pharynx wall	T4N2b
6	T3N0	Tonsillar fossa	T4N2b[b]
7	T4N2	Tonsillar fossa	T4N2
8	T2N0	Tonsillar fossa	T3N1[d]
9	T2N0	Palatum molle	T2N0
10	T1N2	Vallecula	T1N0[e]
11	T4N2	Tonsillar fossa	T4N2
12	TxN3	Tonsillar fossa	TxN3
13	T4N2c	Tonsillar fossa	T4N2c

[a] Progress in T classification only.
[b] Tumour progress from stage III to IV.
[c] Progress in N classification only.
[d] Tumour progress from stage II to III.
[e] This patient underwent neck dissection during the waiting time

The inter-observer differences we found were small compared to the measured differences in volume between CT1 and CT2. The paired sample *t*-test was applied to evaluate the significance of the difference in volume between CT1 and CT2 and this appeared to be statistically significant ($P < 0.02$). The different settings of the diagnostic and planning CT scans made it easy to discriminate them but did not influence our measurements.

The volume doubling time was calculated for each tumour, which varied from 21 to 256 days. The mean waiting time between histopathological diagnosis and start of radiotherapy was 56 days (median 54, range 45–69). Waiting time, expressed in doubling times, was calculated by dividing the waiting time between histopathological diagnosis and start of radiotherapy by the tumour doubling time. In nine cases the waiting time was more than one doubling time and in four cases it was even two doubling times.

Using the volumes at CT1 and CT2 and the tumour doubling time, we calculated the initial volume at diagnosis, the volume at the start of radiotherapy and the related TCPs for $\alpha = 0.30\text{Gy}^{-1}$ and according to $\alpha = 0.30(\sigma)\text{Gy}^{-1}$. TCP analysis revealed large differences in TCP at the time of diagnosis and TCP at the start of radiotherapy (Table 3). A

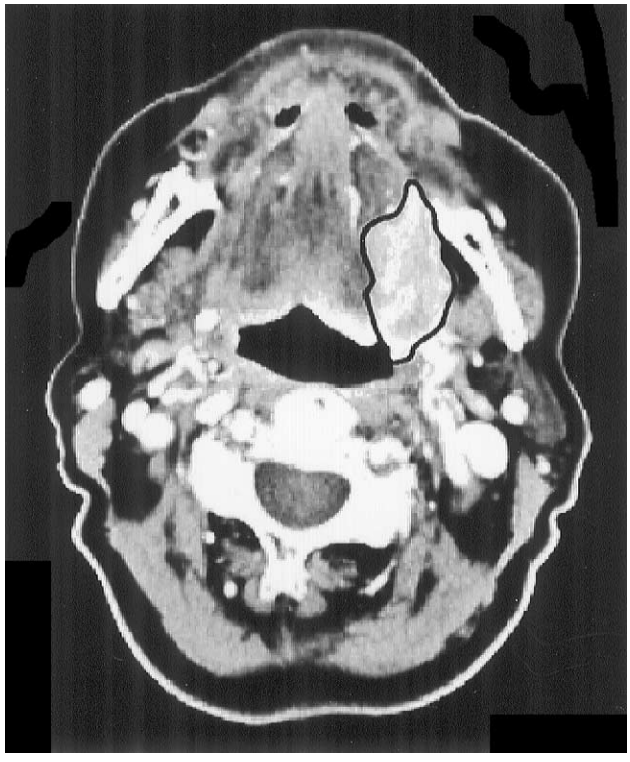

Fig. 2. Case 6. Patient with oropharyngeal cancer, the tumour delineated at time of diagnostic scan.

Table 2
Waiting time expressed as number of volume doubling times per tumour, on basis of the calculated tumour volume increase between the two CT scans

Patient	Tumour volume CT1 (cm^3)	Tumour volume CT2 (cm^3)	Tumour volume increase (cm^3)	Tumour volume increase (%)	Time between CT1 and CT2 (day)	Tumour doubling time (day)	Time between PA-RT (day)	Waiting time in tumour doubling time
1	15	26	11	77	21	26	69	2.7
2	10	11	1.1	11	35	233	62	0.3
3	8.5	10	1.9	22	26	89	49	0.5
4	5.6	13	7.3	130	47	39	60	1.5
5	61	69	8.1	13	41	229	63	0.3
6	20	66	46	235	37	21	50	2.4
7	49	103	55	112	28	26	54	2.1
8	5.1	11	5.5	107	32	30	60	2.0
9	4.1	6.2	2.1	51	35	59	63	1.1
10	1.3	2.1	0.8	62	43	62	60	1.0
11	55	65	9.8	18	12	51	54	1.1
12	8.6	9.5	0.9	11	37	256	48	0.2
12[a]	121	269	149	123	37	32	48	1.5
13	38	60	23	61	39	57	53	0.9
13[a]	14	16	1.8	13	39	229	53	0.2
Average	**28**	**49**	**22**	**70**	**34**	**96**	**56**	**1.2**

CT1, CT scan made for diagnosis; CT2, CT scan made in treatment position for planning of radiotherapy; PA, date of histopathological diagnosis; RT, date of start of radiotherapy.
[a] Lymph node.

maximum absolute TCP decrease of 53% was observed in patient no. 6. The estimated TCP with incorporation of waiting time was 47%, without any waiting time it might have been 63–66%.

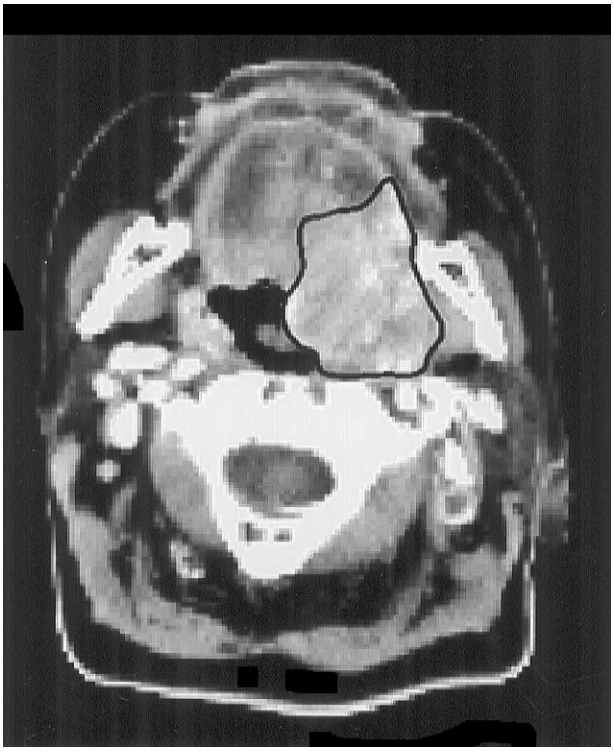

Fig. 3. Case 6. Treatment planning CT of the same patient prior to treatment (37 days later). Growth of the tumour is clear; the tumour is extending to the midline and infiltrates the m. pterygoideus medialis.

4. Discussion

Waiting times for primary radiotherapy treatment of cancer increased during the last years [1,12,13,18]. At our institution there was an increase from 43 to 54 days median time between the date of histopathological diagnosis and start of radiotherapy in patients with laryngeal carcinoma treated between 1980 and 1996. Apart from the fact that treatment delay will bring important psychological distress for the patient, there is also the possibility that tumour growth during this time diminishes treatment results. This study was initiated as a pilot study to evaluate tumour growth during the waiting time and to obtain an indication of it's clinical consequences.

We evaluated 13 patients with advanced stage oropharyngeal cancer and concluded that tumour growth could be substantiated. The mean waiting time was 56 days, tumour growth, however, was measured over a shorter period; the mean time between the diagnostic and planning CT scan was 34 days. In three cases there was progression to a more advanced stage because of developing lymph node metastases. The mean volume increase was 22 cm^3 (70%).

Literature findings concerning waiting time and its consequences are inconsistent. Brouha et al. could not show a negative influence on local outcome for early stage laryngeal carcinoma as a consequence of waiting time [1]. There is, however, a significant negative relation between tumour volumes in advanced stage head and neck carcinoma and outcome [6,9]. This negative relationship seems to be stronger for larynx carcinoma [5,10]. For oropharyngeal carcinoma T stage as well as volume are important prognostic factors [8,15].

Recently, one study demonstrated a decrease in survival

Table 3
TCP decrease during the waiting time

Patient			Individual patient $\alpha = 0.30\ Gy^{-1}$		Whole population $\alpha = 0.30\ (0.02)\ Gy^{-1}$	
	V-PA	V-RT	TCP: V-PA	TCP: V-RT	TCP: V-PA	TCP: V-RT
1	7.0	46	0.84	0.32	0.77	0.36
2	9.4	11	0.79	0.75	0.71	0.67
3	7.6	11	0.83	0.76	0.75	0.68
4	6.5	19	0.85	0.62	0.78	0.56
5	56	68	0.24	0.18	0.31	0.27
6	13	66	0.72	0.19	0.64	0.28
7	30	128	0.47	0.04	0.45	0.15
8	3.7	14	0.91	0.70	0.86	0.62
9	3.5	7.3	0.92	0.83	0.87	0.76
10	1.1	2.2	0.97	0.95	0.96	0.91
11	38	79	0.39	0.14	0.40	0.24
12	8.6	9.7	0.81	0.78	0.73	0.71
12[a]	121	341	0.05	0.00	0.16	0.03
13	38	71	0.39	0.17	0.40	0.26
13[a]	14	17	0.70	0.65	0.62	0.58
Average	24	59	0.66	0.47	0.63	0.47

V-PA, volume calculated at the time of histopathological diagnosis; V-RT, volume calculated at the time of start of radiotherapy;
[a] Lymph node.

for patients who have a delay of more than 40 days [4]. A study from Glasgow reported about volume increase during the waiting time (median increase of 19%, mean increase of 56%) for radiotherapy of lung cancer [18]. That study demonstrates that 21% of the patients on the waiting list became incurable during the waiting period (mean: 54 days between the CT scans made for diagnosis and planning).

Our data are in line with these findings. We revealed tumour volume increase up to 235% and progression of staging in one-third of our study group during the time between the diagnostic scan and the planning scan. However, the true waiting time is more than 50% longer because of the additional time between the diagnostic CT scan and the histopathological diagnosis and by waiting time between the planning CT scan and the start of radiotherapy. When we regard the complete waiting time, one can hypothesize that the increased tumour volume is even larger. These results are consistent with the findings of theoretical models as well as clinical observed data [4,11] and must therefore be taken seriously.

Although the patients we studied constitute a relatively small group, we think it is a realistic reflection of the treated population in our clinic.

The TCP analysis gives some insight into the clinical consequences of this treatment delay as estimated for radiotherapy treatment alone. Mean TCP with incorporation of delay was 47%. Without delay because of waiting time between PA and start of therapy we estimate a TCP of 63–66%. Problems arise if we try to identify the TCP for individual patients. We can only consider the whole population; these TCP's are distributed via the less steep average TCP curve defined by the spread in α. This also implies that patients in a very heterogeneous population, in which there are very high and low TCP values, are only slightly affected by the treatment delay and that results for individual patients must be considered with care. However, for oropharyngeal carcinoma the spread in α is considered small [7]. We analysed for $\alpha = 0.30\mathrm{Gy}^{-1}$ and $\alpha = 0.30(\sigma)\mathrm{Gy}^{-1}$ and found that the results are consistent. Our results confirm the findings by Mackillop et al. who investigated the effect of tumour growth on local control without taking into account the heterogeneity in α [11].

This study indicates that the waiting period is of great importance for those tumours where local control defines the treatment outcome. However, we must consider the fact that it will be impossible to start treatment at the time of histopathological diagnosis. In our clinic, patients are being seen by a clinician who, when there is the suspicion of malignancy, first makes a diagnostic CT scan to evaluate tumour extent, then secondly the patients go through biopsy combined with examination under anaesthesia. Within 1 week treatment options will be discussed in a multidisciplinary team. When primary radiotherapy is the treatment of choice, the planning CT scan has to be made before treatment can finally start. This implies that without waiting time the minimum time between histopathological diagnosis and start treatment will be at least 2 weeks.

5. Conclusion

This is the first study that shows relevant tumour progression during the waiting time for radiotherapy in oropharyngeal carcinoma. Mean volume increase was 70% and we revealed progression of stage in three cases in a time

span shorter than the true waiting time. The TCP analysis indicates that tumour progression during the waiting time constitutes a serious risk for our patients. We regard this as an important finding with direct consequences for the organisation of our clinic. Further investigations will be performed.

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