International Journal of Gynecology & Obstetrics 57 (1997) 295–303

International Journal of GYNECOLOGY & OBSTETRICS

Article

Radiation therapy duration influences overall survival in patients with cervical carcinoma

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Received 31 July 1996; revised 5 February 1997; accepted 21 February 1997

Abstract

Objective: This article analyses the influence of treatment duration on survival in patients with invasive carcinoma of the cervix treated by radical radiation therapy. *Method:* Three hundred and sixty patients with FIGO stage IB-IIIB carcinoma of the cervix were treated in Lausanne (Switzerland) with external radiation and brachytherapy as first line therapy. Median therapy duration was 45 days. Patients were classified according to the duration of the therapies, taking 60 days (the 75th percentile) as an arbitrary cut-off. *Results:* The 5-year survival was 61% (S.E. = 3%) for the therapy duration group of less than 60 days and 53% (S.E. = 7%) for the group of more than 60 days. In terms of univariate hazard ratio (HR), the relative difference between the two groups corresponds to a 50% increase of deaths (HR = 1.53, 95% CI = 1.03–2.28) for the longer therapy duration group ($P = 0.044$). In a multivariate analysis, the magnitude of estimated relative hazards for the longer therapies are confirmed though significance was reduced (HR = 1.52, 95% CI = 0.94–2.45, $P = 0.084$). *Conclusion:* These findings suggest that short treatment duration is a factor associated with longer survival in carcinoma of the cervix.

Keywords: Treatment time; Overall survival; Radiation therapy; Cervical carcinoma

1. Introduction

Carcinoma of the uterine cervix can be effectively treated with definitive radiation therapy [1–3]. External irradiation and brachytherapy are combined in order to increase local control and hence survival. Both treatment modalities may be applied. One of the unanswered questions is how to combine these two radiotherapeutic modalities. Should they be given sequentially or concomitantly? Overall treatment time will depend upon the choice of the treatment sequence.

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0020-7292/97/$17.00
PII S0020-7292(97)02888-X

Recently the importance of overall treatment time has been highlighted in large series of patients treated by radiation therapy for cervical cancer [4–7]. The importance of this particular prognostic factor for the outcome is supported by in vivo evidence of a short potential doubling time (T_{pot}) in cervical cancer [8]. This T_{pot} value, measured prior to treatment, is probably closely related to the kinetics of proliferative clonogenic cells during treatment, which is generally thought to be at the origin of failure to control the disease locally. To check the intrinsic importance of the sequencing of both treatment modalities and hence treatment duration, we decided to retrospectively analyze a consecutive series of patients, treated by external radiation and brachytherapy.

2. Methods

2.1. Patients population

From January 1971 to December 1992, 612 consecutive patients with primary FIGO stage IB-IIIB carcinoma of the cervix were treated with radiation therapy. Only 360 of them received both external radiation and brachytherapy, and were considered for the current study. Of the 252 patients excluded, 114 received either external radiation or brachytherapy alone, 40 had been diagnosed too recently or had incomplete baseline data, and 98 had undergone total hysterectomy. Patients characteristics are summarized in Table 1. The median age was 60 years (range 20–90 years). Baseline evaluation included physical and pelvic examination, cervical biopsies, complete blood count, chemistry profile, chest X-ray, intravenous pyelogram or computerized tomography, cystoscopy and rectoscopy. Treatment variables are described below and summarized in Table 2.

2.2. Radiation therapy

External radiation therapy was delivered initially with a betatron (45 MeV) and later with a linear accelerator (6–18 MeV). The pelvic volume was approached using a four-field box technique. The dose per fraction generally was 180–200 cGy/fraction, 5 days per week. Patients with stage IB-IIA received 45 Gy to the whole pelvis. Patients with advanced stage IIB-IIIB received 45 Gy to the pelvic volume and a 10–15 Gy boost to the involved parameter(s). Intracavitary brachyther-

Table 1
Patients characteristics

	Patients	%
Decade		
1971–1979	184	51.1
1980–1989	137	38.0
1990–1992	39	10.9
Age (years)		
≤ 39	29	8.1
40–49	49	13.6
50–59	81	22.5
60–69	105	29.2
≥ 70	96	26.6
FIGO stage		
IB	21	5.8
IIA	17	4.7
IIB	165	45.8
IIIA	6	1.7
IIIB	151	42.0
Histology		
Squamous	327	90.8
Adenocarcinoma	28	7.8
Other	5	1.4

Table 2
Treatment characteristics

	Patients	%
Intracavitary curietherapy		
Radium	172	47.8
Cesium	188	52.2
Mode of therapy		
Concomitant (Con)	291	80.8
Sequential (Seq)	69	19.2
Treatment duration		
≤ 60 days	271	75.3
> 60 days	89	24.7
Total effect		
≤ 1164 Gy[2]	87	24.2
> 1164 Gy[2]	273	75.8

apy delivered a boost of 30 Gy to point A in 1–3 fractions for LDR and in 3 or 4 fractions over 3 or 4 weeks for HDR. In the first decade (1971–1979), low dose-rate brachytherapy (LDR: 90 cGy/h at point A) was systematically used, whereas from the second decade on, all patients were submitted to high dose-rate (HDR: 30 cGy/min at point A). The isotope used for LDR was radium, and the isotope used for HDR was cesium. The rectal dose was measured during the insertion of the source and the total rectal dose for the whole period of brachytherapy was computed. External radiation therapy and intracavitary brachytherapy were performed concomitantly (Con) or sequentially (Seq). Sequential curietherapy was given at weekly intervals, 5–20 days following completion of external radiation. From 1990 to 1993 radiation therapy was Seq in 92% of the patients.

2.3. Total effect

In 1980, when HDR curietherapy was introduced, the original Nominal Standard Dose (NSD) from Ellis and the modification proposed by Orton were used to calculate the biological equivalence of HDR vs. LDR [9,10]. For the present analysis the treatment related factors (total dose, number of fractions) were introduced in the linear quadratic model modified according to the proposal of Fowler in order to calculate the Total Effect (TE) [11]. For the curietherapy a correction for the TE was introduced with the continuous repair model from Thames [12]. No corrections were made for overall treatment duration because no individual data are available either on pre-treatment potential doubling time, or on time of kick-off repopulation as suggested by Withers [13,14]. To facilitate the discussion, all doses will be expressed as TE in Gray squared (Gy^2) for both external and brachytherapy treatments (see addendum). One should be aware that this TE is different from the real dose given at point A. It is a measure of the radiobiological effectiveness of the treatment for tumor tissue. For these calculations some assumptions have been made concerning repair half-time ($T_{1/2}$) and related continuous repair factor (g-factor). A $T_{1/2}$ of 1.5 h has been considered and the corresponding g-factor has been extrapolated according to the exposure time for both HDR and LDR. Moreover, the choice of the α/β factor, required for calculation of TE, does not really influence the results because the same value has been chosen for HDR as for LDR. This factor is merely a measure of the intrinsic sensitivity of the tumor tissue to a change in fraction size and is unrelated to the dose-rate. Total effect could not be calculated for 14 patients due to incomplete information on radiotherapy doses administered. Median total effect was 1283 Gy^2. For the purpose of this analysis patients were classified according to whether they had received treatment with rather low total effect, taking 1164 Gy^2 (the 25th percentile) as an arbitrary cut-off.

2.4. Therapy duration

This included the duration of external radiation therapy, the time interval between the former and brachytherapy, and the duration of brachytherapy. Therapy duration was calculated in days. Median therapy duration was 45 days. For the purpose of the analysis, patients were classified according to whether they had rather long therapies, taking 60 days (the 75th percentile) as an arbitrary cut-off.

2.5. Statistical methods

The primary endpoint of this study was overall survival (OS), which was defined as time from beginning of radiation therapy to death. For the purpose of this analysis, survival status for all patients was updated during the summer of 1993.

Statistical analyses were carried out by means of the software package Stata [15]. Survival percentages over time have been calculated by the Kaplan–Meier method [16] and their corresponding standard errors (S.E.) with Greenwood's formula [17]. For univariate analysis of OS the *P*-values from the log-rank test are reported for each comparison considered [18]. Estimated hazard ratios (HR) of death, with respect to the indicated reference group, their 95% confidence intervals (95% CI) and *P*-values were calculated with pro-

portional-hazard regression with appropriate binary variables to identify each group of interest [19]. For the multivariate analysis, some categories of variables have been collapsed to allow for small numbers of deaths in the respective subgroups. Values of HR greater than unity indicate increased rates of death with respect to the chosen reference category. For analyses other than on OS, chi-squared tests (for categorical variables) or Kruskall–Wallis tests (for continuous variables) have been used [20]. All probability values are for two-sided tests. For the purpose of the analyses of survival and unless otherwise indicated, observations have been censored at 5 years in order to limit the effect of competing causes of mortality and also to avoid having only patients registered during the earlier periods contribute to the right tail of the survival curves. Five-year survival is also considered a relevant endpoint for cervical cancer patients.

3. Results

3.1. Total effect and therapy duration

Among patients treated with the sequential modality, median total effect was 1183 Gy^2 as opposed to 1283 Gy^2 in the group treated with the concomitant modality ($P < 0.001$). Similarly, as concerns therapy duration, the sequential and concomitant groups had a median duration of 72 and 44 days, respectively ($P < 0.001$).

The association among type of therapy on the one hand and total effect and duration on the other was also visible in terms of the percentage of patients in each therapy group with a total effect less than 1164 Gy^2 (namely 38% for Seq and 21% for Con, $P = 0.004$) or with a therapy duration longer than 60 days (namely, 74% for Seq and 13% for Con, $P < 0.001$). In addition, of the therapies of more than 60 days, 32% had a total effect of less than 1164 Gy^2, as opposed to 22% of the therapies of less than 60 days ($P = 0.064$).

FIGO stage I was more frequently treated with shorter therapies ($P < 0.038$) and with lower total effect ($P < 0.001$). No other associations between therapy descriptors and other clinical characteristics were identified.

3.2. Survival analysis

Median follow-up for the studied patients was in excess of 12 years. Median survival for the whole group was 7.5 years and the 5-year survival was 59% (S.E. = 3%). Fig. 1 displays the survival experience of the whole group. For the following analyses, survival has been censored at 5 years, as explained in the Statistical Considerations. When considering sub-groups, the 5-year survival for the Con and Seq groups was 60% (S.E. = 3%) and 58% (S.E. = 8%), respectively ($P = 0.226$). Similarly, for the total effect groups less than 1164 Gy^2 and more than 1164 Gy^2, the 5-year survival was 47% (S.E. = 6%) and 63% (S.E. = 3%), respectively ($P = 0.010$), while for the therapy duration groups of less than 60 days and more than 60 days we observed a 5-year survival of 61% (S.E. = 3%) and 53% (S.E. = 7%), respectively ($P = 0.044$). In terms of univariate hazard ratio (HR), the relative difference between the two therapy duration groups corresponds to an increase in hazard of death of about 50% (HR = 1.53, 95% CI = 1.03–2.28) for the more than 60 days group with respect to the less than 60 days group. These and additional univariate results are displayed in Table 3. Figs. 2–4 display the survival experience of the sample, according to type, duration and total effect of therapy.

In light of the associations observed among the various descriptors considered, which may also have an important effect on survival, a multivariate analysis has been performed to establish the residual effect of each of the variables studied after simultaneous adjustment of all other factors considered. The results are displayed in Table 4 and confirm the association in magnitude of longer therapies with increased risk of death. The estimated relative hazard for longer therapies is as in the univariate analysis (HR = 1.52, 95% CI = 0.94–2.45) but with only borderline significance ($P = 0.084$). The indication of the univariate analysis concerning a possible role of total

Table 3
Five-year overall survival and univariate analysis

	5-year survival			Log-rank	Univariate Cox regression	
	Deaths	%	S.E.	*P*-value	HR	95% CI
Age (years)						
≤ 39	11	60	9		Reference	
40–49	21	52	7		1.14	0.55–2.38
50–59	28	63	5	0.227	0.95	0.47–1.92
60–69	33	67	5		0.82	0.41–1.62
≥ 70	43	47	6		1.37	0.71–2.67
FIGO stage						
IB	3	85	7		Reference	
II	56	66	4	< 0.001	2.51	0.78–8.03
III	77	47	4		4.86	1.53–15.42
Histology						
Squamous	122	59	3		0.81	0.47–1.41
Other		51	7.6	0.475	Reference	
Decade						
1970–1970	69	63	4		Reference	
1980–1989	61	53	4	0.341	1.29	0.91–1.82
1990–1992	6	65	13		1.02	0.43–2.38
Type of therapy						
Sequential	21	58	8		Reference	
Concomitant	115	60	3	0.226	0.74	0.46–1.18
Total effect						
≤ 1164 Gy^2	42	47	6		1.62	1.12–2.33
> 1164 Gy^2	94	63	3	0.010	Reference	
Therapy duration						
≤ 60 days	104	61	3		Reference	
> 60 days	32	53	7	< 0.044	1.53	1.03–2.28

effect of therapy is not confirmed. Stage is still a strong predictor of survival. An exploratory analysis has been performed considering the whole of the follow-up available on each patient (no censoring at 5 years). A multivariate regression confirms the effect of longer therapies (HR = 1.52, 95% CI = 1.03–2.26, $P = 0.037$).

4. Discussion

The main issue of this study was to determine whether overall treatment time was an authentic prognostic factor, as it was already reported [4–6]. Differing from other reports, besides clinical description we have studied the role of this factor together with that of total dose (expressed in total effect) and type of therapy (concomitant and sequential) which may be acting as confounders of the association of interest. Strong associations among treatment descriptors were observed.

The univariate analysis showed that overall treatment time and total effect are of prognostic significance. The multivariate analysis confirmed the prognostic importance of overall treatment time and FIGO stage, but not the role of total effect. The relative risk of death increased significantly when overall treatment time exceeded 60 days. The possible influence of overall treat-

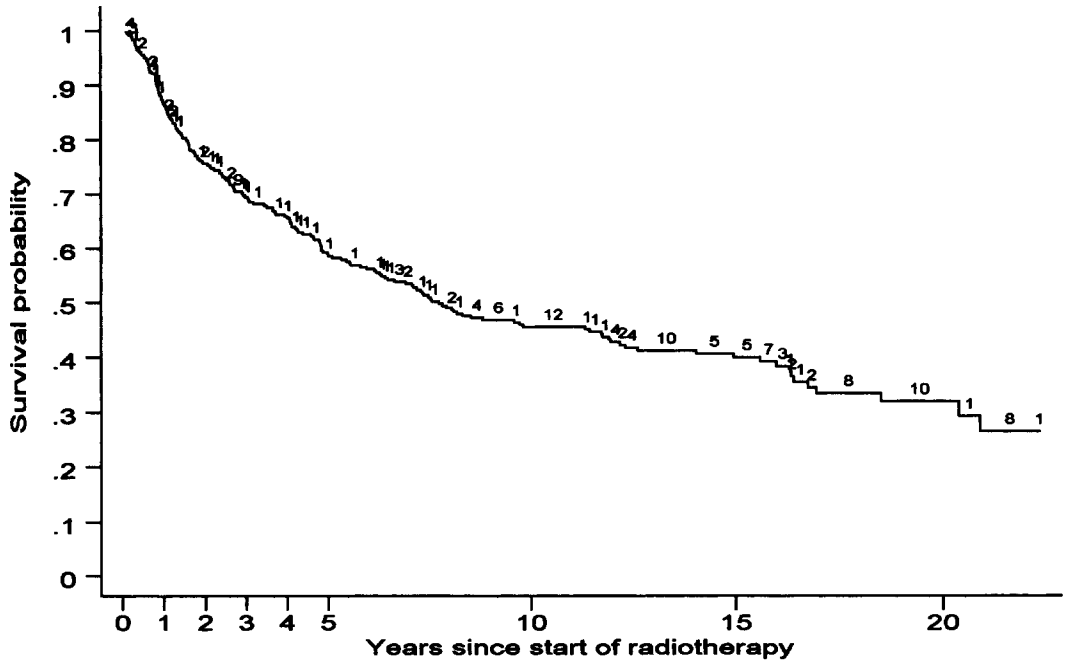

Fig. 1. Overall survival in all patients.

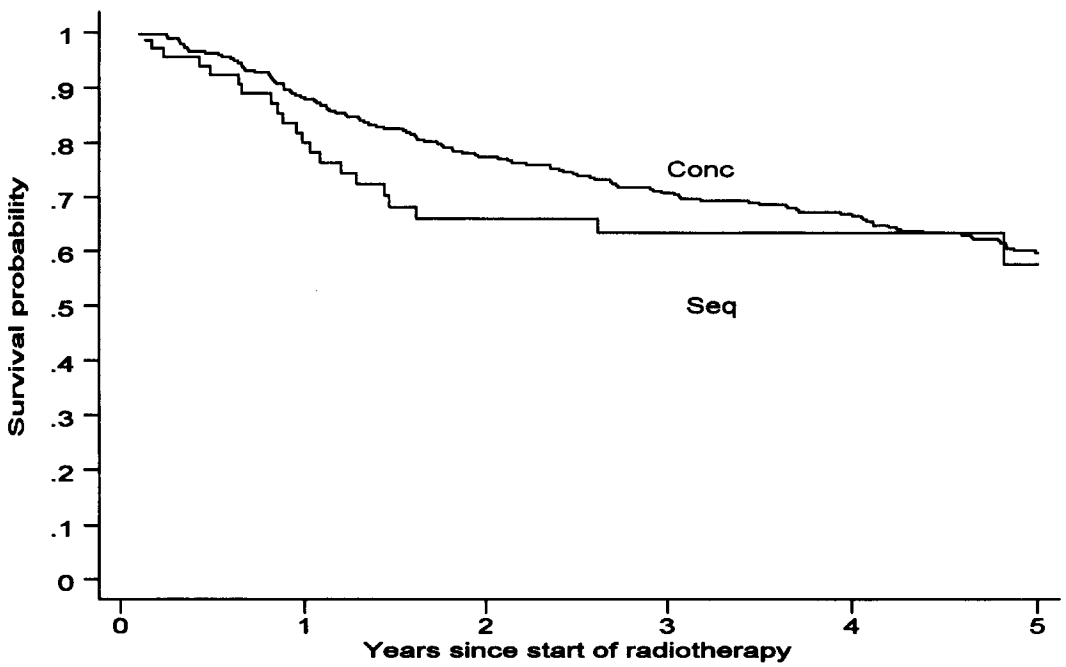

Fig. 2. Overall survival according to type of therapy: concomitant (Conc) or sequential (Seq).

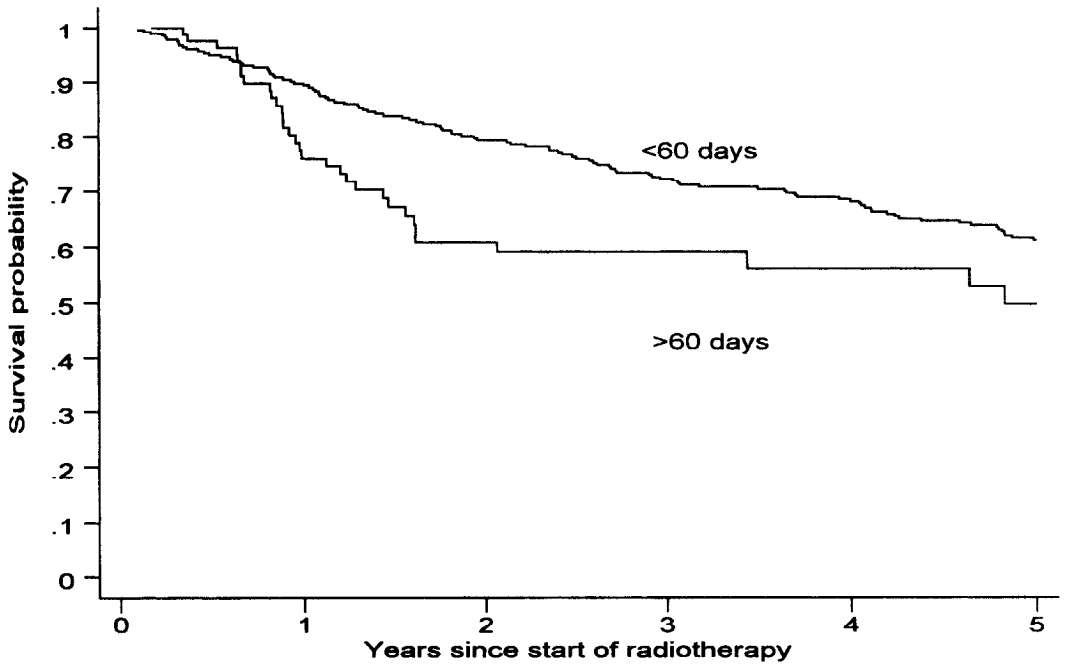

Fig. 3. Overall survival according to duration of therapy: > 60 days or ≥ 60 days.

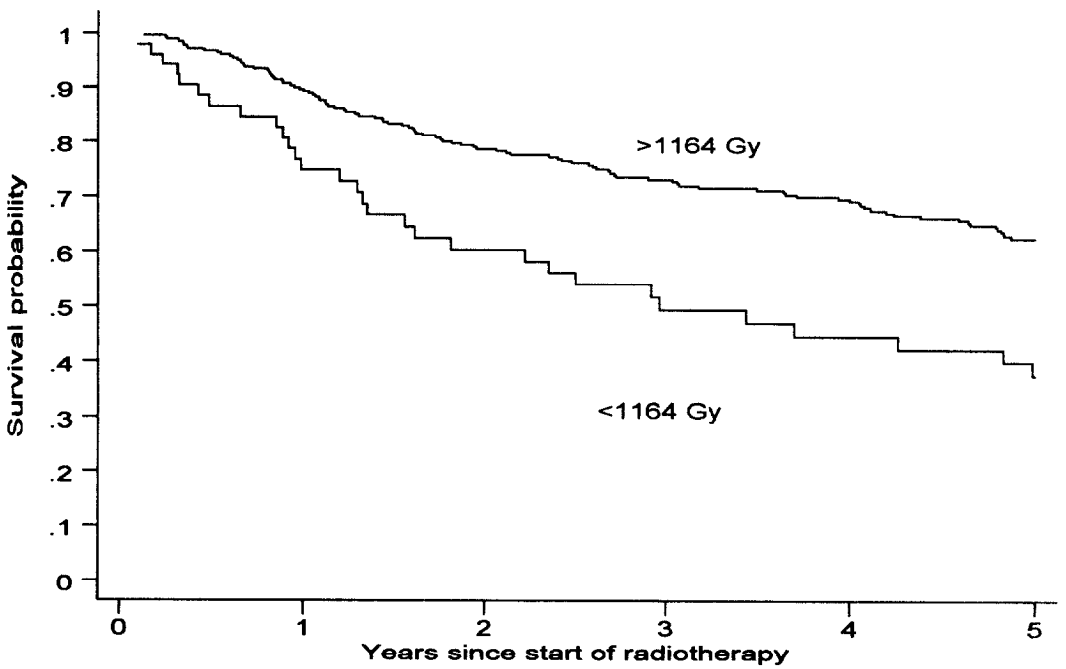

Fig. 4. Overall survival according to total effect: > 1164 Gy^2 or ≤ 1164 Gy^2.

Table 4
Multivariate analysis of survival censored at 5 years

	HR	95% CI	*P*-value
Age (years)			
≤ 49	Reference		
50–59	0.65	0.38–1.10	0.108
60–69	0.62	0.38–1.02	0.061
≥ 70	1.03	0.64–1.65	0.913
FIGO stage			
IB–II	Reference		
III	2.03	1.41–2.91	0.001
Histology			
Squamous	0.78	0.45–1.36	0.378
Other	Reference		
Decade			
1970–1979	Reference		
1980–1992	0.58	0.22–1.53	0.274
Type of therapy			
Sequential	Reference		
Concomitant	0.88	0.49–1.58	0.661
Total effect			
≤ 1164 Gy^2	1.23	0.83–1.82	0.299
> 1164 Gy^2	Reference		
Therapy duration			
≤ 60 days	Reference		
> 60 days	1.52	0.94–2.45	0.084

ment time on outcome after radiation therapy has been extensively studied in head and neck cancer [11]. Any prolongation of radiation treatment is potentially deleterious for local control and survival. Fowler calculated a median rate of loss of local control of 14% (range 3–25%) per week of extra overall time [11]. In cervical cancer, Girinsky et al. [6] reported a loss of local control of approximately 1% per day, when treatment time exceeded 52–62 days. Lanciano et al. [5] showed that total treatment time duration was predictive for both local control and survival especially for FIGO stage III. Fyles [4] also showed a highly significant association between pelvic control and treatment duration. The hypothesis of a rapid proliferation of clonogenic cells during the course of radiation therapy was highlighted by Withers [13,14]. We hypothesized that potential doubling time (T_{pot}) was shorter in cervical cancer than in head and neck cancer, pointing to rapid proliferating tissue potentially escaping the treatment when gaps or unnecessary delays are introduced. The multivariate analysis in our series confirmed therapy duration as a significant prognostic factor.

Several sources of bias may have affected the results of this retrospective analysis. Chronologic time (more than 20 years have elapsed since the first patient was registered), patient selection, diagnostic accuracy, tailoring of total dose according to stage and response during treatment, or data quality might have acted as confounders. There are no obvious reasons to suggest that these factors would not have similarly affected all subgroups. However, other considerations may also contribute to the strength of the observed results. In particular, our patients have been treated by a single institution, where traditionally, treatment choices have been dictated primarily by the therapeutic philosophies of successive teams of clinical staff. Despite this, we have considered in the multivariate analysis, most of the prognostic factors which may also have affected treatment choice. In addition, we have simultaneously been able to address the issues of treatment duration and total effect in patients treated with either the concomitant or sequential modalities and allowing for the effect of surgery, thus accounting for most of the variation in survival attributable to treatment. Our study does not allow us to conclude that treatment time must be less than 60 days, since this threshold was arbitrarily chosen as a cut-off. Based on our results, we decided to apply brachytherapy (30 Gy to point A) concomitantly with the external irradiation (45 Gy to the pelvic volume and a boost of 10–15 Gy to the involved parameters). In order to optimize the geographical distribution of the dose within the tumor, this brachytherapy is applied at the end of the external treatment. This therapy schedule therefore reduces overall duration to less than 60 days.

5. Addendum

Calculation of total effect (TE) expressed in Gy^2

For HDR or LDR treatment

$TE_1 = (\alpha/\beta + d \times g)n \times d$

d = dose per application

n = number of applications

g = continuous repair factor

$\alpha/\beta = 10$ Gy

g-values, assuming a repair half-time of 1.5 h (obtained by extrapolation from tabulated values) [12]

$g_{HDR} = 0.88$ (application duration $\pm$ 20 min)

$g_{LDR} = 0.16$ (application duration $\pm$ 24 h)

For external radiation therapy

$TE_2 = (\alpha/\beta + d)n \times d$

d = dose per fraction

n = number of fractions

$\alpha/\beta = 10$ Gy

Cumulative total effect (TE_C)

$TE_C = TE_1 + TE_2$

Examples:

1. HDR (4×10 Gy)

$TE_1 = (10\text{ Gy} + 10\text{ Gy} \times 0.88)4 \times 10\text{ Gy} = 752\text{ Gy}^2$

2. External radiation therapy (25×1.8 Gy = 45 Gy)

$TE_2 = (10\text{ Gy} + 1.8\text{ Gy})25 \times 1.8\text{ Gy} = 531\text{ Gy}^2$

$TE_3 = TE_1 + TE_2 = 1283\text{ Gy}^2$

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