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Time factors in breast carcinoma: influence of delay between external irradiation and brachytherapy

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Summary

From 1971 to 1983, 398 (33 T_1, 309 T_2, 56 T_3) biopsy-proven breast adenocarcinomas were treated conservatively at Hôpital Henri Mondor by an initial course of external irradiation (45 Gy, 25 fractions, 5 weeks) followed by interstitial iridium-192 implant for a further 37 Gy to the tumor. The mean interval between external irradiation and brachytherapy was 5.9 weeks (S.D. 1.7, range 1–18). Seventy-seven local failures were observed at 10–148 months (median 34.5). The actuarial probabilities (S.E.) of local control at 5 and 10 years were 0.86 (0.02) and 0.74 (0.03), respectively. The follow-up for patients free of local recurrence was 4–205 months (median 95). Multivariate analysis showed an increasing probability of local failure with longer interval between external irradiation and brachytherapy (Relative Risk [R.R.] 1.23 [95% confidence limits: 1.07, 1.41] per week, $p = 0.005$), and a lower risk of failure in case of complete tumor regression after external irradiation (R.R. 0.47 [0.25, 0.90], $p = 0.022$), and higher brachytherapy dose rate (R.R. 0.13 [0.02, 1.02] per Gy/h, $p = 0.053$). No influence of tumor size and total dose (possibly because only limited variations in total dose were observed), or histological grading (not performed in 140 [35%] patients) was found. Because of the lack of dose-control relationship, quantification of the effects of delay between external irradiation and brachytherapy (in terms of compensatory dose) and of dose rate (Incomplete Repair Model) was not possible. The present analysis suggests that the implant dose rate should be high (but no extrapolation can be made above 1 Gy/h) or that total dose should be increased to compensate lower dose rate. However, our data do not indicate how much extra dose is necessary, since no dose-control relationship was elicited. In addition, the treatment duration should remain as short as possible in order to maximize local control.

Introduction

Mazeron et al. recently reported on a series of 398 breast adenocarcinomas treated conservatively by external irradiation followed by brachytherapy. They evaluated 340 two-plane applications and observed an increase in local control with higher dose rate [10]. In the present paper, it is assumed that the initial course of external radiotherapy is likely to have triggered an accelerated proliferation of the clonogenic tumoral cells. Therefore, a protracted interval between external irradiation and brachytherapy should translate into a lower control probability. We present a complementary analysis of Mazeron et al. data, addressing the influence on local control of the delay between external irradiation and brachytherapy. The clinical relevance of repopulation in breast cancer is discussed.

Material and methods

Patients

Between 1971 and 1983, 398 adenocarcinomas of breast were treated conservatively by an association of external irradiation and brachytherapy at Hôpital Henri

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TABLE I

Distribution of patients according to the TNM UICC 1979 classification.

	T_1	T_2	T_3	Total
N_0	23	208	32	263
N_1	9	99	24	132
N_2	0	2	0	2
N_3	1	0	0	1
Total	33	309	56	398

Mondor (Tables I and II, Figs. 1 and 2). Histological diagnosis was obtained either by drill biopsy or tru-cut. There was 33 (8%) T_1, 309 (78%) T_2 and 56 (14%) T_3. Mean age was 56 years (S.D. = 12), with 165 (41%) premenopausal versus 233 (59%) postmenopausal patients. Follow-up duration for patients free of local recurrence was 4 to 205 months (median 95).

Treatment modalities

The initial course of external irradiation delivered 45 Gy in 25 fractions over 5 weeks with cobalt-60. It was followed by an additional electron therapy to the internal mammary chain (15 Gy, 7 fractions, 1.5 week) and the lower axilla (25 Gy, 11 fractions, 2.5 weeks).

Interstitial implant of iridium-192 was used to deliver a further 37 Gy to the tumor. The dose was prescribed at the 85% level of the basal dose, calculated in the central plane of the application (Paris system [2]). The implanted volume was adapted to the tumor extent by varying the number of sources and their active length. Rigid needles were secured by templates in single- or double-plane geometry, depending on tumor

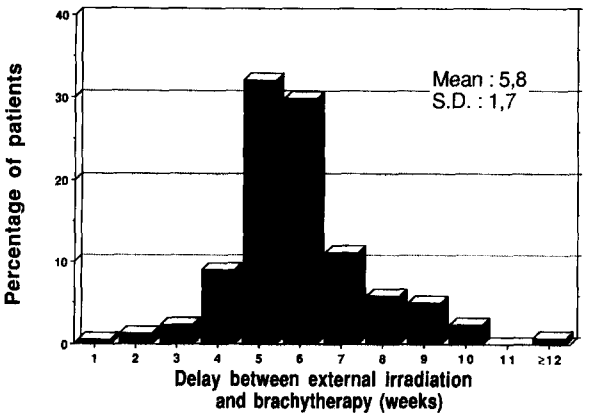

Fig. 1. Histogram of delay between external irradiation and brachytherapy.

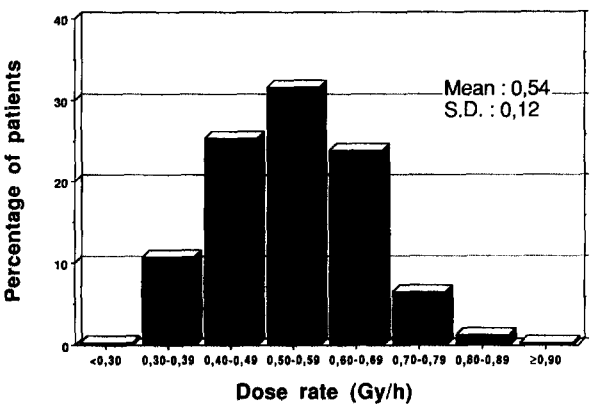

Fig. 2. Histogram of brachytherapy dose rate.

TABLE II

Clinical characteristics (means and standard deviations).

	All patients	Controlled tumors	Failures	*p* (*t*-test)
Age (years)	56.2	56.6	54.1	0.11
	(12.3)	(12.2)	(12.6)	
Tumor size (cm)	3.9	3.8	4.1	0.12
	(1.3)	(1.3)	(1.2)	
External irradiation:				
Total dose (Gy)	45	45	45	
	(0)	(0)	(0)	
Duration (weeks)	5.1	5.1	5.1	0.74
	(0.4)	(0.4)	(0.6)	
Dose per fraction (Gy)	1.81	1.82	1.80	
	(0.11)	(0.12)	(0)	
Delay between external irradiation and brachytherapy (weeks)	5.9	5.8	6.1	0.19
	(1.7)	(1.7)	(1.7)	
Brachytherapy:				
Total dose (Gy)	37.0	37.1	36.8	0.37
	(2.2)	(2.2)	(2.4)	
Dose rate (Gy/h)	0.54	0.54	0.52	0.08
	(0.11)	(0.12)	(0.10)	

and breast volumes. Intersource spacing varied from 1.5 to 2.0 cm (mean 1.95, S.D. 0.11). In the present work, dose rate was computed as the ratio of the delivered dose to the duration of the application.

No dose adaptation was made according to initial tumor size, tumor response to external irradiation, or dose rate. Actually, no selection of linear activity, and therefore dose rate, was possible since, at any time, only one activity was on stock in the department.

Statistical analysis

The raw data were kindly provided by Dr. Mazeron, stored and processed on a DEC VAX computer in the Department of Biomathematics, at M.D. Anderson Cancer Center. All statistics were performed by means of a SAS statistical package (SAS Institute Inc., Cary, NC, USA).

The **endpoint for analysis** was time to recurrence in the brachytherapy volume. Possible predictive variables were age, menopausal status, tumor T stage and size, external irradiation parameters (total dose, dose per fraction and duration), time interval between external irradiation and brachytherapy, tumor response to external irradiation (complete versus non-complete regression), and brachytherapy characteristics (total dose and dose rate). Histological grading (according to Scarf, Bloom and Richardson) was performed in only 258 (65%) patients.

Numbers of patients and means of quantitative variables were compared by Chi-square test and variance analysis. In order to take into account the patients lost for follow-up without recurrence, actuarial probabilities of recurrence were calculated according to the life-table method and compared by the log-rank test.

For **multivariate analysis** of time to local recurrence, an ascending stepwise Cox Proportional Hazards model was used. On the first step, the program measures the association between each of the variables cited in the statistical methods, the strongest association with tumor failure yielding the lowest p-value. Then, the most significant variable is entered into the model and the variables remaining out of the model are once again individually assessed. The process is reiterated until all the variables are entered or none of those remaining has a p-value lower than 5%. Two or more variables might be correlated and therefore carry a very similar information regarding the outcome. The entry in the model of one variable is then likely to result in a loss of significancy (the p-value becomes larger than 5%) for the others. The latter are called "close alternative" in Table III, since they might have been entered into the model, had the selected variable been omitted from the study. The effect of categorical variables (menopausal status, T stage, and response to external irradiation) was modeled with a set of zero-or-one indicators. Age, tumor size, irradiation parameters and time intervals were modeled as continuous variables.

Results

Seventy-seven local failures were observed at 10–148 months (median 34.5 months). Actuarial probabilities of local control at 5 and 10 years were 0.86 (0.02) and 0.74 (0.03), respectively.

Bivariate analysis (Table I) showed no significant differences between failing and controlled patients in terms of age, menopausal status, tumor size, histological grading and response to external irradiation, delay between external irradiation and brachytherapy, external irradiation and brachytherapy parameters.

Multivariate analysis (Cox Proportional Hazards model) was first performed without any patients excluded (Table III). The probability of tumor recurrence increased with longer intervals between external irradiation and brachytherapy (Relative Risk [R.R] of failure 1.23 [95% confidence limits: 1.07, 1.41] per week of delay, $p = 0.005$), and decreased when regression after external irradiation was complete (R.R. 0.47 [0.25, 0.90], $p = 0.022$), and with increasing dose rate (R.R. 0.13 [0.02, 1.02] per Gy/h, $p = 0.053$).

TABLE III

Multivariate analysis of recurrences (Proportional Hazards model).

Step no.	Variable	Relative risk [95% confidence limits]	P	Close alternative
1	Delay (weeks) between external irradiation and brachytherapy	1.23 [1.07, 1.41]	0.005	Size
2	Complete regression after external irradiation	0.47 [0.25, 0.90]	0.022	Size
3	Brachytherapy dose rate (Gy/h)	0.13 [0.02, 1.02]	0.053	

Tumor size was a close alternative for delay between external irradiation and brachytherapy and, to a lesser extent, for response after external irradiation. It is noteworthy that shorter intervals between external irradiation and brachytherapy were observed for smaller tumors, with a significant but low linear correlation (Pearson's coefficient 0.21, $p = 10^{-4}$). In addition, tumor size was smaller when a complete regression was achieved after external irradiation (mean 3.53 [S.D. 0.15] cm versus 3.95 [0.07], $p = 0.006$). When tumor size was forced into the model [with a non-significant p-value, both the interval between external irradiation and brachytherapy and the complete regression after external irradiation remained significant, and the confidence intervals for the dose rate parameter were reduced (R.R. 0.10 [0.01, 0.82] per Gy/h, $p = 0.03$)]. This suggests a predominant and size-independent effect of interval between irradiation and brachytherapy and tumor response to external irradiation. No effect of dose, delivered either by external irradiation or by brachytherapy, could be elicited, but the range of doses was very small. The exclusion of three patients with very long intervals between external irradiation and brachytherapy (12, 13 and 18 weeks) did not alter the above results.

Discussion

We report a complementary analysis of a series of 398 breast adenocarcinomas treated by an initial course of external irradiation followed by interstitial implantation of iridium-192. Multivariate analysis showed that longer intervals between external irradiation and brachytherapy, lack of complete regression of the tumor after external treatment beam, and lower dose rates yielded poorer local control rate.

A decrease in local control with longer intervals between surgery and radiotherapy was also observed in a series of 436 T_1–T_2 breast carcinomas treated at Institut Gustave Roussy [1]. The other prognostic factors (multivariate analysis) were histological grading and Nominal Standard Dose (N.S.D.) to the tumor bed. The N.S.D. effect was attributed to treatment protraction, since there was little variability in total dose and fraction size. In another series of 221 operable breast carcinomas treated by irradiation alone, Van Limbergen et al. found a lower local control for larger tumors, longer treatment times and smaller doses [20,21]. These data and our present analysis suggest that treatment protraction does worsen the local outcome in breast cancers, as observed in head and neck, for instance, [4,7,9,12–15,22,23], bladder [8] or skin tumors [5].

The harmful effect of treatment protraction has been related to tumor cell proliferation [16,18,19]. Accelerated repopulation is believed to occur after such a cytotoxic insult as surgery or chemotherapy [19,23]. In the present series, it is possible that the initial course of irradiation triggered accelerated proliferation of tumor cells, making it easier to elicit a detrimental effect of prolonged intervals on local control.

The influence of treatment protraction can be quantified either in terms of R.R. of failure per unit of time (Proportional Hazards model), or in terms of dose increase necessary to compensate the treatment split. The latter may have immediate clinical application but implies the demonstration of a dose-control relationship. From Van Limbergen's data, the additional dose to counterbalance irradiation protraction can be estimated to be 0.45 Gy per day in 2-Gy fractions [20], i.e. two thirds of the dose suggested for head and neck tumors [23]. No dose-control relationship could be established on our present series, because of the low variability in the dose patterns. We estimated the R.R. of failure to be 1.23 [1.07, 1.41] per week of delay between external irradiation and brachytherapy. For a given patient, this relative risk translates into a 23% increase in the actuarial probability of failure each time the brachytherapy is delayed by one week. Similar increases have been observed in head and neck tumors recently reviewed in [7]. Our data do not provide direct evidence that accelerated repopulation is of clinical importance after surgical excision. However, keeping short the delay between surgery and radiation therapy seems to be a reasonable precaution since Clarke et al. estimate of R.R. of failure was 3.3 for interval between surgery and radiotherapy longer than 7 weeks [1].

The significance of tumor regression after external irradiation remains an open issue. Tumor regression is generally accepted as an indicator of good prognosis in many other tumor locations. However, we do not know whether tumors disappeared because they were particularly radiosensitive or just smaller.

From experimental data, a decrease in biological effect is expected when the dose rate is reduced [3]. Clinical data however yield contradictory results in terms of either local control or complication rate (see review in [3,10]). These studies were all retrospective and the statistical methods suboptimal according to the modern standards. Many factors may have confounded the analyses. For instance, technical aspects are of tantamount importance in brachytherapy: careful determination and homogenous coverage of the target volume are critical because of the very steep dose gradient within and around the application. Over the years, striking progress in medical imaging and computer do-

simetry has been made. In addition prognostic factors of tumor control, as well as factors predisposing to complication (age, vascular condition, etc.), are likely to have influenced the treatment modalities and confounded the analyses.

The results of a randomized trial comparing two dose rates (0.4 and 0.8 Gy/h) for preoperative brachytherapy in uterine cancers have been recently presented [6]. The treated volume was determined before randomization and the total dose kept constant. A total of 204 women with operable cervical cancer (stage I–II) and 107 women with operable endometrial carcinoma (stage I–II) were included between January 1985 and September 1988. The median follow-up time was 33 months. For corpus carcinoma, no difference in local control, early and late effects were observed. For cervical cancer, there was no difference in local control and short-term tolerance, but complications after 6 months were more frequent in the higher dose rate group ($p < 0.01$). As opposed to our series, brachytherapy (actually plesiotherapy) represented the initial part of the treatment, and all patients underwent secondary surgery. Possibly more important, the brachytherapy dose (60 Gy to the isodose encompassing the tumor volume) was much higher than ours. One may therefore assume a larger dose rate effect when a relatively small total dose is delivered (steep portion of the dose-control curve) than with a large total dose (asymptotic portion of the dose-control curve).

The absence of a dose-control relationship prevented us from fitting an Incomplete Repair model [17] to our data. Therefore, we are still missing in vivo quantification of the dose-rate effect in human tumors. In addition, since no data is available regarding the kinetics of tumor repopulation in breast adenocarcinomas, we do not know whether proliferation can be considered as negligible during a brachytherapy application [3].

Conclusion

Our retrospective analysis of 398 breast adenocarcinomas suggests a significant effect of dose rate on local control, but does not allow extrapolation to dose rate larger than 1 Gy/h. This finding is not supported by the only randomized trial addressing the influence of dose rate on local outcome [6]. This trial, however, was performed in a different clinical context (preoperative plesiotherapy of uterine cancer) and at a much higher total dose level.

In any case, the time period between the initial part of the definite treatment (surgery or external irradiation) and the complementary modality (brachytherapy in our data) should be kept short, as observed in other sites. This should be kept in mind when alternate treatment regimens are considered, which may result in protraction of overall treatment time.

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