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Papers

Carcinoma of the Cervical Stump: A Review of 213 Cases

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From 1970 to 1987, 213 cases of carcinoma of the cervical stump were accrued in a multi-institutional prospective cooperative study. This group accounted for 5.5% of cervical carcinoma diagnosed during the same period. 13 had *in situ* carcinoma and 200 had invasive carcinoma (96% squamous cell carcinoma, 4% adenocarcinoma). Radiotherapy alone (external and brachytherapy) was given to 77%, brachytherapy and surgery to 15% and surgery alone to 8%). FIGO stage distribution was: I (31%), IIa (15%), IIb (27%), IIIa (5%), IIIb (17%) and IV (5%). Five-year locoregional control per stage was 100% in Ia, 85% in Ib, 82% in IIa, 71% in IIb, 45% in IIIa, 54% in IIIb and 30% in IV. Corrected 5-year survival per stage was 82% in Ib, 78% in IIa, 73% in IIb, 69% in IIIa, 38% in IIIb and 0% in IV. The diameter of disease in stage II strongly influenced the 5-year locoregional control (81% for tumours of less than 3 cm vs. 68% for tumours more than 3 cm). Lymphangiogram was associated with a 44.5% 5-year locoregional control when positive vs. 74% when non-positive. Brachytherapy was advantageous in obtaining locoregional control in patients receiving external irradiation and brachytherapy: 81.5% vs. 38.5% in patients treated with external radiotherapy alone. Surgery was performed only for *in situ* carcinoma and for part of stages Ia, Ib and IIa. There is no significant difference in locoregional control at equal stage between radiotherapy alone and treatment schemes including surgery. However, lethal complications were observed in 6% of the patients of the surgical group as compared to 0.6% of the patients treated with radiotherapy alone. Radical radiotherapy seems to provide similar results of locoregional control and survival at equal stages in carcinoma of the cervical stump compared to carcinoma developed on an intact uterus. The rate of severe complications reported with the French–Italian glossary is 13% for G3 and 3% for G4, which is close to the observed rate during the same period in our series of radical radiotherapy to the intact uterus.
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INTRODUCTION

TWO MAJOR controversies still remain linked with the prevention and treatment of carcinoma arising on the cervical stump: should subtotal hysterectomies be banished from the treatment modalities of benign gynaecological conditions? Are there new arguments favouring either radiotherapy alone or combined radiotherapy and surgery in carcinoma of the stump?

This paper reports on the outcome of treatment of 213 patients with cervical stump carcinoma treated in a prospective non-randomised study over nearly two decades. The technical and

Table 1. French cooperative study group: participating institutions

Participating institutions	Responsible radiotherapist(s)	No. of patients
CHU Jean Minjoz, Besancon	S. Schraub	21
Fondation Bergonie, Bordeaux	J. Pigneux	57
Centre J. Perrin, Clermont-Ferrand	R. Rozan	13
Centre G.F. Leclerc, Dijon	J.C. Horiot	76
CHU La Tronche, Grenoble	C. Vrousos, M. Bolla	9
CHR Bon Secours, Metz	E. Achille, E. Barthelmé	6
Centre P. Lamarque, Montpellier	H. Pourquier	13
Hospices Civils, Strasbourg	R. Keiling	9
Centre C. Regaud, Toulouse	P. Combes, N. Daly	9

dosimetric improvements of radiotherapy that occurred during this period may help in answering the second question.

Since the early seventies, a French Cooperative Group for treatment of gynaecological malignancies nicknamed "Groupe des 9" has been tackling the development of radiotherapy techniques in the treatment of carcinoma of the cervix. The aim was not to substitute radiotherapy alone for combined radiotherapy and surgery in all cases, but only to document prognostic factors, locoregional control and complication rates in patients of all stages treated with radiotherapy alone. Although the majority of patients were treated with radiotherapy alone, a group of patients with either early disease or unfavourable anatomy for brachytherapy was treated with a classical strategy of combined surgery and radiotherapy.

PATIENTS AND METHODS

From 1970 to 1987, 2747 patients with cervical carcinoma were registered by the nine participating institutions. According to the general guidelines described by G.H. Fletcher at the M.D. Anderson Hospital at Houston [12, 13] 1532 previously untreated cases with an intact uterus were treated with radiotherapy alone. Treatment protocols, data collection, radiotherapy techniques and results were previously reported [8, 10, 16]. During the same period, 213 cases of carcinoma arising on the cervical stump were accrued, registered and treated in the "Groupe des 9".

The distribution of the 213 patients over participating centres is presented in Table 1. Minimum, maximum and mean ages at the time of diagnosis were 29, 84 and 60 years, respectively. The mean time between subtotal hysterectomy and the diagnosis of cancer was 18 years. Patients with a time shorter than 3 years were considered to have an incorrect initial diagnosis: they probably had a carcinoma left on the stump and not a carcinoma that developed later on the stump. Therefore, they were excluded from this study. Minimum, maximum and mean follow-up were 4, 20 and 10 years, respectively.

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The prevalence of carcinoma of the cervical stump in patients with subtotal hysterectomy was not evaluable due to the specialisation of the participating institutions in that they all are tumour institutes or hospitals with a special interest in gynaecological oncology. This explains the rather large accrual of this type of patient, while in most cases the subtotal hysterectomy was performed elsewhere.

Similarly, the relative incidence of carcinoma of the stump compared to the incidence of carcinoma on an intact uterus varied widely from one participating centre to another, the only reliable figure being obtained from the largest contributor (Centre G.F. Leclerc, Dijon) with 76 patients (5.5%) with carcinoma of the stump compared to 1362 patients with carcinoma of cervix accrued during the same period.

Work-up

Once the diagnosis was established from biopsy specimens, the work-up included gynaecological examination under general anaesthesia and cystoscopy, intravenous pyelogram, small bowel contrast series, lymphangiography when not contra-indicated, chest X-rays and routine laboratory investigations. Although pelvic computed tomography (CT) scan and ultrasonography are now performed routinely, most of the patients included in this series did not undergo these examinations since they were treated up to 20 years ago.

Patients were staged according to two staging systems, UICC-FIGO and MDAH modified sub staging [11–13, 20]. UICC-FIGO staging is used in this paper. The major criticism of the international staging being the lack of evaluation of the tumour volume, a clinical estimate of the maximum macroscopic diameter of the tumour was registered and obtained in 75.5% of the cases. Table 2 represents the distribution of patients according

Table 2. Distribution per UICC-FIGO stages

UICC-FIGO stage	No. of patients (%)
Carcinoma *in situ*	13 (6%)
Ia	7 (3.4%)
Ib	55 (25.7%)
IIa	30 (14%)
IIb	54 (25.4%)
IIIa	10 (4.7%)
IIIb	34 (16%)
IV	10 (4.7%)

Table 3. Distribution per tumour size and stage

UICC-FIGO stage	Size of the cervix < 3 cm	3–5 cm	> 5 cm
I	39 (58%)	25 (37%)	3 (5%)
II	26 (41%)	36 (57%)	1 (2%)
III	4 (14%)	18 (64%)	6 (22%)
IV	2	4	1

to UICC-FIGO stage and Table 3 represents the distribution according to the tumour diameter per stage.

Treatment methods and protocols

External irradiation was delivered using high energy photon beams (25 mV photons) and brachytherapy with Caesium 137. In some cases, transvaginal 150 kV X-rays filtered with 1.5 mm Cu were used to boost central disease with transvaginal cones of different sizes. Treatment strategy with radiotherapy alone followed the guidelines described by Gilbert H. Fletcher [12, 13] consisting, in the majority of cases, of external irradiation delivering 20–50 Gy in 2–5 weeks and 10–25 fractions depending upon the volume of disease, delivered through two or four portals [anteroposterior–posteroanterior (AP–PA) and lateral]; and on completion of external irradiation, one or two brachytherapy applications using, whenever possible, a short intracervical radioactive line and a vaginal colpostat. Vaginal cylinders and a longer vaginal source line were used when vaginal disease extended beyond the upper third of the vagina.

When combined radiotherapy and surgery was planned, most patients (87%), had brachytherapy first to a dose of about 60 Gy in 6 days. The 60 Gy isodose curve encompassed fornices and stump on computer dosimetry. This was followed 6 weeks later by a colpectomy and lateral lymphadenectomy. Postoperative external beam radiation was given only when positive nodes were found.

Surgery alone was delivered in cases of *in situ* carcinoma localised to the cervix in patients in good general condition. The distribution of treatment strategies per stage is shown in Table 4. *In situ* carcinomas are excluded from this table.

Follow-up

All patients have been regularly followed up three times per year until the second year and twice a year thereafter. Data were gathered in a 600-item computerised form with a yearly update of locoregional control, survival, signs and symptoms of complications. 174 patients were available for follow-up at 5 years and 86 at 10 years.

Table 4. Distribution per treatment strategy and stage

Treatment strategy	UICC-FIGO stage I	II	III	IV
RT alone (n = 163 cases)				
RTE + BT + intracavitary	7	53	25	1
RTE alone	1	16	17	8
BT alone	2	3	0	0
RT + surgery (n = 33 cases)				
BT + surgery	8	5	0	0
BT + surgery + RTE	10	6	0	0
RTE + surgery	2	2	0	0
Surgery alone (n = 17 cases)				
13 carcinoma *in situ*	2	1	0	1

RTE = external radiotherapy, BT = brachytherapy.

Table 5. Pelvic recurrences (cumulative failure rate with and without metastatic failures): distribution per UICC-FIGO stage

UICC-FIGO stage	No. of patients	Central M0	Central M1	Regional M0	Regional M1	Massive M0	Massive M1
Ia	7	0	0	0	0	0	0
Ib	55	5	1	0	0	0	2
IIa	30	1	4	0	0	0	0
IIb	54	7	3	0	1	4	4
IIIa	10	1	0	0	0	1	1
IIIb	34	1	1	2	0	3	9
IV	10	0	0	0	0	5	5

RESULTS

Pathology

Well or moderately well differentiated squamous cell carcinoma was found in 174 patients (82.5%), anaplastic carcinoma or grading unspecified carcinoma in 6% and adenocarcinoma in 5.5%.

Nodal status

Lymphangiogram was performed in 63.5% of the cases (63% of stage I, 72% of stage II, 63.5% of stage III and 60% of stage IV). It was interpreted with the criteriae described by Wallace and Piver [27] and was found positive in 23% of all cases (2.5% of stage I, 19.5% of stage II, 43% of stage III and in all stage IV).

Locoregional control (independently of treatment strategy)

The analysis of loco regional control is based upon the occurrence of central failures (cervix and proximal structures), regional failures (distal pelvic structures and/or pelvic nodes), and/or massive pelvic failures (central and regional). Table 5 summarises this pelvic recurrence (cumulative failure rate with and without metastatic failures and unlimited follow-up). Due to the large variation in follow-up time, an actuarial estimate of local control rate gives a better display of the incidence and of the time of occurrence of locoregional failures per FIGO stage (Fig. 1).

High locoregional control rates (beyond 80%) are observed in

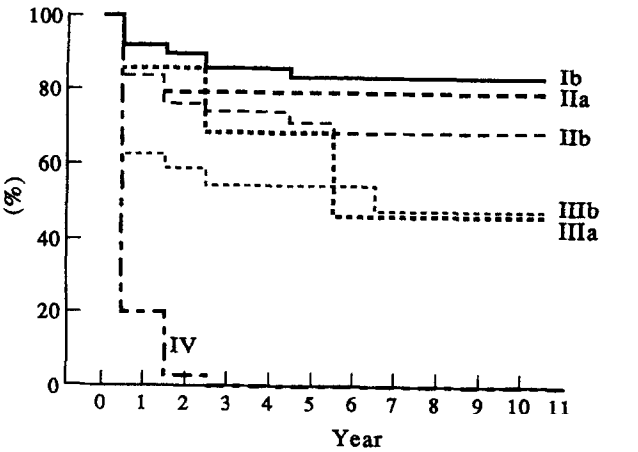

Fig. 1. UICC-FIGO staging: locoregional control.

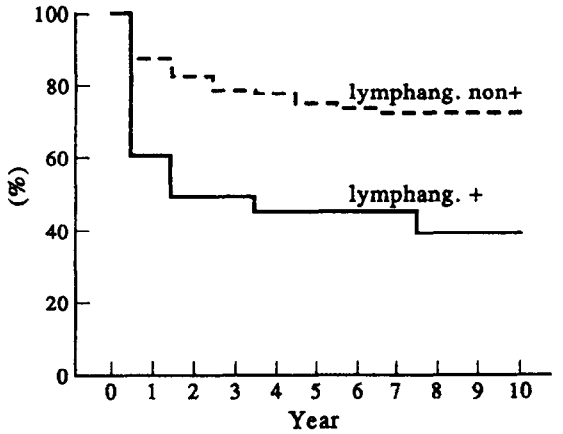

Fig. 2. Locoregional control according to results of lymphangiogram.

stage I and stage IIa. Stages IIb and IIIa show rather high and similar 5-year locoregional control figures of about 70% whereas in stage IIIb locoregional control rates are of 55%. Locoregional control remains stable beyond 5 and 10 years in stage I only; they continue to deteriorate slightly in stage IIb and above, reaching a plateau after 7 years. A 100% locoregional control was obtained in *in situ* carcinoma (which is not represented in this figure).

Metastatic spread

Distant metastases occurred in 19% of patients and occurred without associated pelvic failures in only 6% of this series. The lung was the site of distant spread in 2 out of 3 metastatic cases.

Locoregional control and lymphangiogram

The presence or absence of positive nodes on the lymphangiogram was found to be the most significant factor predicting locoregional failure using a univariate analysis (Fig. 2) and of better prognostic significance than the stage itself (72% 5-year locoregional control all stages together in non-positive lymphangiogram vs. 43% in positive lymphangiogram; P value = 0.01).

Survival (Fig. 3)

Survival was calculated using the Kaplan–Meier method and corrected for intercurrent death. Small differences in specific survival are observed between stages Ib (85% 5-year survival), stages IIa (80%) and stages IIb (76%).

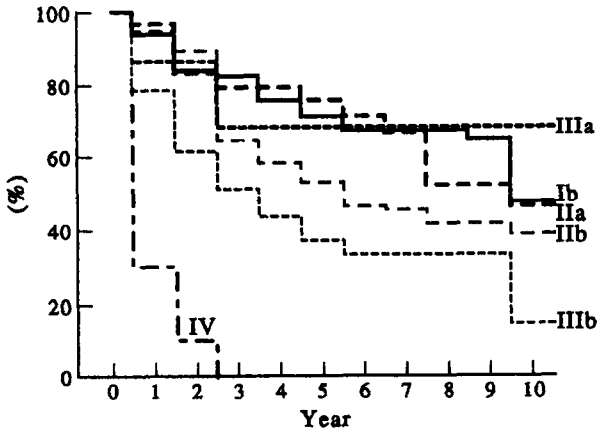

Fig. 3. UICC-FIGO staging: survival.

Results of treatment according to tumour size

Five-year actuarial locoregional control was 78% in stages II less than 3 cm diameter vs. 68% in stages II greater than 3 cm. Five-year actuarial survival was of 72% in stages I (less than 3 cm) vs. 56% (more than 3 cm), and of 76% in stages II (less than 3 cm) vs. 58% (more than 3 cm).

Although these differences were not considered significant due to the small sample size, they seem to suggest that the volume of tumour may be a better prognostic factor than the stage of disease.

Analysis of results according to treatment strategy

Early stages I and II were treated in 77% of the cases with radiotherapy alone. When compared to similar cases treated with surgery, no difference was found with locoregional control and survival. However, the surgical group is of a much smaller size and this did not provide the basis for a good statistical comparison.

External radiotherapy alone vs. external radiotherapy and brachytherapy

External irradiation alone was performed in stage IV disease and in 22% of stage II and 40% of stage III disease. The most frequent reason for not performing brachytherapy was poor anatomical conditions (mostly vaginal atrophy) which did not provide good geometry for brachytherapy. A highly significant difference in locoregional control ($P < 0.001$) was observed in stage II disease according to whether they received combined external irradiation and brachytherapy (81.5% locoregional control) or external radiotherapy alone (38.5% locoregional control). Similar differences were observed in survival (68% vs. 33%; $P < 0.001$). This emphasises the importance of the brachytherapy boost which allows the delivery of a higher total dose to the target volume. Since these two groups were comparable regarding stage distribution and tumour volume (greater than 3 cm in 46% vs. 44%), this observation implies that better results are obtained when brachytherapy is part of the treatment strategy.

Treatment complications

Late morbidity to treatment was analysed according to the French–Italian glossary for complications from the treatment of gynaecology malignancies [17]. This is the only international system based upon an accurate description of symptoms and signs of complications allowing a comprehensive scoring and reporting of complications following multidisciplinary treatments.

The incidence and severity of complications per stage are reported in Table 6. All these results are expressed using crude figures since the mean follow-up is of 10 years. G1 represents mild, reversible complications; G2 complications are of moder-

Table 6. Complications per stage and per grade

Total number of complications (n = 139)	Stage 0 (n = 1)	Stage I (n = 34)	Stage II (n = 60)	Stage III (n = 44)
G1	0	20 (59%)	24 (40%)	14 (32%)
G2	0	6 (17.5%)	26 (43%)	24 (54.5%)
G3	0	7 (20.5%)	8 (13.5%)	6 (13.5%)
G4	1 (100%)	1 (3%)	2 (3.5%)	0

Table 7. Complications per organ and per grade (all treatment strategies)

Organ	% of patients with complications of all grades	No. of patients* G1	G2	G3	G4
Rectum	18.5	12	7	5	2
Sigmoid	10	—	10	4	—
Small bowel	3.5	—	3	—	2
Bladder	13	9	8	2	—
Ureter	0.5	—	—	1	—
Vascular system (venous obstruction)	0.5	1	—	—	—
Skin	0.5	—	—	1	—
Genital tract (uterus, vagina, vulva)	30	20	13	5	—
Pelvic tissues (parametrium fibrosis of haematoma)	23.5	14	15	6	—

*Scores as defined by the Franco-Italian glossary.

ate intensity, consistent with a normal life; G3 complications are severe requiring surgical repair or impairing the quality of life; G4 complications are lethal. Altogether, a 30% complication rate is observed (42% G1; 40% G2; 15% G3 and 3% G4). Table 7 shows the distribution and scores of complications according to the tissue or critical organ involved. The most frequent complication is represented by minor or moderate signs and/or symptoms of vaginal stenosis and/or of proctitis, sigmoiditis and cystitis.

Treatment strategy did not appear to influence the site of complication. However, a major finding arose from the analysis of the distribution and score of complication according to the treatment strategy, when radiotherapy alone was compared with radiotherapy and surgery (Table 8). This showed a considerable increase in the incidence of severe and lethal complications for patients treated with the combined modality: 41 vs. 12% for G3; 11 vs. 1% for G4 complications. The three lethal G4 gastrointestinal complications can be summarised as follows: the first was a small bowel fistula occurring after surgery alone. In the second patient treated by brachytherapy and hysterectomy, a recto-vaginal fistula developed in the perioperative period. The third patient treated by radical radiotherapy died from massive rectal bleeding. The reference rectal dose was 80 Gy.

A correlation was found between the G3 complications and the volume of 60 Gy combined isodose of external irradiation and brachytherapy and with the cumulated dose to critical organs [8, 10]. A previous history of abdominal or pelvic surgery was found in all patients with G3 gastrointestinal complications.

DISCUSSION

In the literature, there are few series of more than 200 cases of carcinoma of the cervical stump treated with a homogeneous strategy [4, 9, 21, 26, 30]. Compared to them, our own series brings rather similar information about the estimated incidence, with the delay between subtotal hysterectomy and diagnosis of cancer, and with the distribution by age and stage. However, very few reports give accurate descriptions and scoring of complications. In our own study, all patients were treated according to similar technical recommendations for treatment strategy and had the same modalities for work-up and follow-up. Lastly, as far as we are aware, this is the first time the French–Italian glossary has been used in the analysis of complications for this type of clinical presentation.

Table 8. Complications per treatment strategy and per grade

Treatment strategy	G1	G2	G3	G4
Radiotherapy alone	42.5%	44%	12.5%	1%
Radiotherapy + surgery	26%	22%	41%	11%

Although the relative risk of appearance of malignancies on the cervical stump is difficult to establish, it seems that the range is somewhere between 3 and 10%. Although the age distribution is not different from that of the intact uterus, there are more stages I and II in carcinoma of the cervical stump as compared to carcinoma arising on an intact uterus: in our own data, stages I and IIa represent 59% of patients with stump carcinoma compared with 39% of the same stages in our population of carcinoma with an intact uterus. Vaginal bleeding is an alarming symptom in women without menstruation, thus shortening significantly the delay between vaginal bleeding and first consultation compared to premenopausal women.

Table 9 compares our own data of 5-year local control at equal stages for carcinoma on the intact uterus and carcinoma of the cervical stump. Locoregional control figures are exactly the same in all stages except for stage IV where there are a few 5-year survivors vs. none in carcinoma of the cervical stump. Non-significant differences are observed regarding specific survival figures. Actuarial survival figures are not as good in carcinoma of the cervical stump due to a higher death rate from intercurrent disease.

In our series, the analysis of late complications shows a rather similar figure of complications when cervical stump is compared to the intact uterus (15 vs. 13% for G3; 3 vs. 1.8% for G4). The most surprising finding is the very low percentage of small bowel complications observed in our series of carcinoma of the cervical stump (only 2 vs. 8% for the intact uterus): no grade 3 and 4 small bowel complications were observed in patients with cervical stump treated by radiotherapy alone classically considered to represent a high risk for this type of injury. This may reflect a particular need to monitor dose distribution and to reduce the amount of small bowel in the irradiated volume by using diagnostic radiology methods and customised treatment planning. This implies that the same preventive measures for the treatment of the intact uterus should result in a drastic reduction of the rate of severe small bowel complication.

Another unexpected finding is the very high severe complication rate encountered when treating carcinoma of the cervical stump with a combination of brachytherapy and surgery. Despite the skill of the surgeons, the use of the two methods carries increased risks of perioperative and late complications as compared to radiotherapy alone. Even surgery alone is not free of severe complications, since one perioperative death was observed in the treatment on carcinoma *in situ*. This suggests that, despite equally good results for locoregional control, the treatment strategy of radiotherapy alone (external irradiation plus brachytherapy) should be preferred to the combination of surgery and radiotherapy.

Is it possible to further improve the techniques of radical radiotherapy? The importance of brachytherapy is well documented in our series and brachytherapy should be performed in nearly all cases. This technique is easily carried out in cases with

Table 9. Local control and survival: comparison of the results in cervical stump and intact uterus

UICC-FIGO stage	5-year local control		5-year survival	
	Cervical stump (n = 237)	Intact uterus (n = 1532)	Cervical stump (n = 237)	Intact uterus (n = 1532)
Ib	85%	85%	82%	80%
IIa	80%	80%	80%	78%
IIb	75%	75%	76%	72%
IIIa	70%	70%	51%	55%
IIIb	55%	55%	38%	45%
IV	0	10%	0	0

normal vaginal anatomy and even made easier in cases with a long cervical canal (sometimes up to 4 cm) in the carcinoma of cervical stump. The absence of a cervical canal does not constitute a problem in cases of superficial disease since vaginal ovoids can give a good dose distribution to and around the vaginal vault. Technical difficulties arise in cases of more advanced stage with infiltration of the vaginal vault especially in cases with a narrow vagina. Progress achieved with techniques of interstitial brachytherapy [2, 3] offer good possibilities of extending the contribution of brachytherapy after external irradiation, especially when there is only lateral and posterior residual disease in utero-sacral ligaments. Residual disease located higher or more anteriorly may remain difficult to manage. Although it may be improved by using ultrasonography at the time of implantation, there is probably some room in this particular situation to perform a transperineal or transvaginal implantation simultaneously with a laparotomy to check the position of needle tips.

Finally, this series of cases was collected over a 20-year period during which much progress has been made in the prevention of complications by better use of computer dosimetry [5, 6, 8, 10]. It is, therefore, very likely that the radiation-induced complications observed in this series can easily be lowered with the present tools and experiences of radiotherapy treatment planning in gynaecological malignancies.

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