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Resectability rates of previously irradiated recurrent cervical cancer (PIRCC) treated with pelvic exenteration: Is still the clinical involvement of the pelvis wall a real contraindication? A twenty-year experience

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ABSTRACT

Objective. (1) To determine the accuracy of a standard clinical and radiological assessment of resectability in patients with previously irradiated recurrent cervical cancer (PIRCC), and (2) to report the outcome and prognostic factors in this high-risk population treated with an exenterative procedure.

Methods. Forty-eight patients with centrally located ($n=20$, 41.7%) or lateralized ($n=28$, 58.3%) PIRCC treated with exenterative procedures were analyzed. All patients underwent standard assessment of resectability with pelvic exam and radiological studies. Patients with centrally located tumors were considered as resectable and lateralized tumors were deemed unresectable.

Results. Complete surgical resection with negative margins (R0) was achieved in 28.6% of the patients with lateral recurrences and in 65.0% of the patients with central recurrences ($p<0.019$). After a median follow-up of 114.6 months (3.0–244.9 months), the 10-year local control rate for the whole group was 36.3%, 43.1% in the central PIRCC group and 31.5% in the lateral PIRCC group, respectively ($p=0.290$). Multivariate analysis showed that improved local control was significantly associated with the presence of negative margins ($p=0.004$). The 10-year distant failure rate was 69%, 56.6% in the central PIRCC group and 83.2% in the lateral PIRCC group ($p=0.178$), respectively. Multivariate analysis showed that the development of distant metastases was significantly correlated with the absence of local control ($p=0.01$). The 10-year disease-specific survival (DSS) for central and lateral PIRCC was 27.2% and 14.9%, respectively ($p=0.239$). Multivariate analysis showed that negative margins ($p=0.001$), local control ($p=0.001$) and distant control ($p=0.006$) were all significantly associated with improved DSS. Location of PIRCC (central vs. lateral) was irrelevant for DSS in completely resected (R0) patients. Overall morbidity rate was 65.0% and 73.3% for central and lateral PIRCC patients, respectively ($p=0.528$).

Conclusion. About one-third of the patients with lateral PIRCC classified as unresectable with non-surgical means may ultimately undergo complete (R0) resections and about one-third of the patients with centrally located PIRCC and judged as resectable will undergo non-curative (R1) resections. A curative (R0) resection significantly impacts local control rates, distant metastases-free rates and DSS.

Introduction

Locally recurrent tumors grow in tissue scenery that may have been altered through the previous oncologic treatment. This effect can be more pronounced after surgical therapy, which might damage the compartment borders with a loss of their barrier function promoting neoplastic transgression [1]. In addition, surgery and radiation therapy can cause blockage of the normal routes of vascular and lymphatic microcirculation that may explain retrograde tumor embolism or unexpected routes of spread commonly seen in patients with recurrent tumors.

Approximately 10% of all malignant tumors of the lower and middle genital tract progress or relapse in the pelvis without detectable distant metastases at the time of recurrence [2]. Selected patients with central recurrences in a previously irradiated pelvis can be treated with exenteration and long-term survival of up to 50% has been reported [3]. However, patients with post-irradiation recurrences infiltrating the pelvic wall have a much poorer prognosis and no acceptable curative treatment is available so far. Five-year survival rates in this later group of patients are below 10%. Local control is still a goal of therapy in patients with previously irradiated recurrent cervical cancer (PIRCC) because the median life expectancy of the patients whose local relapse is not controlled is still 7 to 9 months [2,4,5].

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While patients with centrally located PIRCC may in some cases be evaluated for exenterative options, patients with lateral recurrences or bulky tumors (>5 cm) [3,6] are usually discarded because the probability of incomplete gross or microscopic resections is high. The presence of positive resection margins after this type of ultraradical surgery has been largely considered a selection failure because the reported 5-year survival rates are close to zero [2]. In addition, patients successfully operated on with negative but close margins (≤5 mm), lymph-vascular space involvement and/or perineural invasion are still at very high risk of isolated local failure [7].

Pelvic exenteration has been combined with intra-operative radiation therapy with electrons (IOERT) or perioperative high dose rate brachytherapy (PHDRB) to deliver a supplemental dose of radiation to a well-defined area that presents high risk of local recurrence. Nevertheless, complete macroscopic tumor resection seems to be mandatory for the potential success of this approach [7–9].

The present report is a retrospective study aimed to determine (1) the accuracy of a standard clinical and radiological assessment of resectability in patients with PIRCC, and (2) to report the outcome and prognostic factors in this high-risk population treated with an exenterative procedure.

Patients and methods

Patients and tumor characteristics

The Institutional Review Board approval was obtained for this retrospective study. From January 1988 to December 2008, 114 patients with gynecological cancer underwent pelvic exenteration at our institution by the same surgical team. A total of 52 patients met the criterion of PIRCC. In four patients (7.7%), the pelvic exenteration was aborted, one with central recurrence and peritoneal carcinomatosis found at surgery (adenocarcinoma), and the other three with lateral recurrence due to an extensive infiltration of the pelvic wall in two, and proximal plus posterior infiltration of the hypogastric system in one. So, in total clinical and surgical records from 48 patients were reviewed. Twenty patients (41.7%) had a central recurrence and 28 (58.3%) had a lateral recurrence according to clinical and radiological exam (CT scan or MRI).

Mean age was 49.3 years, ranging from 25 to 71 years old. Thirty-seven (77%) tumors were SCC and 11 (23%) were adenocarcinoma. Mean time to recurrence was 16 months, ranging from 0 to 156 months. As primary treatment, 16 patients (33.3%) had EBRT (external beam radiotherapy) +/- vaginal brachytherapy and 32 (66.7%) patients had undergone EBRT plus radical hysterectomy. No statistical difference was found for all these variables between the groups, lateral vs. central.

Mean tumor size was significantly larger in lateral recurrences (5.0 cm vs. 3.2 cm) ($p=0.002$) as it was for BMI (28.3 vs. 24.9) ($p=0.054$).

Central recurrence was defined as any disease placed in the center or midline of the pelvis although some anterior, posterior or lateral extension but clearly distant from the pelvic wall was allowed. Lateral recurrence was defined as the presence of tumor with or without central component but extended up to or stuck to the pelvic wall by clinical exam (no free space by palpation between the tumor and pelvic wall) and suspicion of pelvic wall involvement by imaging. This was always confirmed by pelvic examination immediately before the exenterative procedure.

Patients with persistent tumor after primary radiation therapy or chemo-radiation and treated with adjuvant exenteration were not considered as true recurrences and were not included in this study. Patients with multiple nodal pelvic or aortic, or distant metastases by CT or PET scan were also excluded. Patients with isolated metastases were considered for pelvic exenteration.

Table 1 shows the treatment characteristics of the whole series.

Table 1
Treatment characteristics.

	Central (%)	Lateral (%)	P value
Pelvic exenteration			
Anterior	6(30.0)	8(27.6)	0.710
Posterior	0	1(3.3)	
Total	14(70.0)	19(67.7)	
Ileal/colon conduit	18/2	25/3	0.820
Colostomy	9(45.0)	11(39.3)	0.707
CRA	5(25.0)	9(32.1)	0.836
Omental plasty	7(35.0)	18(64.3)	0.078
Neovagina	9(39.0)	14(60.9)	0.728
Pelvic LND	4(21.1)	4(12.9)	0.445
Aortic LND	2(10.5)	2(6.5)	0.606
NACT	4(21.1)	17(63.0)	0.007
IOERT	11(55.0)	11(57.9)	0.756
PHDRB	0	9(32.1)	NA
Surgery length[a] (h)	9.70(2.9)	10.7(3.0)	0.203
BU I.O.	4.8(2.0)	6.9(4.2)	0.069
BU P.O.	1.9(1.3)	2.4(2.0)	0.362
ICU stay	1.1(0.4)	1.8(2.5)	0.268
Hospital stay[a] (days)	23.6(13.5)	22.8(12.5)	0.958

CRA, colorectal anastomosis; LND, lymph node dissection; BU, blood units transfused; I.O., intraoperative; P.O., postoperative; ICU, intensive care unit.
[a] Expressed as mean, standard deviation in parentheses.

Treatment program

Patients diagnosed as having a resectable central recurrence after clinical and imaging evaluation were treated with radical surgery. Patients with unresectable tumors (determined by the presence of tumor fixation to the pelvic wall by clinical exam and/or imaging) were discussed at the Tumor Board to evaluate downsizing neo-adjuvant chemotherapy (NACT) (two to three courses) before proceeding with pelvic exenteration. Chemotherapy usually consisted of a combination of cisplatin, doxorubicin and ifosfamide. Since 1999, this treatment regimen was changed by a combination of a platinum derivative plus paclitaxel. Once NACT was finished, patients were reevaluated with CT or PET scan.

Pelvic exenteration procedure has been described in detail elsewhere [10]. Our customary technique mostly met the new concepts of ultra-radical surgery that means en-block multimeso-visceral excision that includes total mesometrial resection, total mesorectal excision, and removal of the ureterovesical compartment if a total pelvic exenteration is being performed or two of these morfogenetic units when an anterior or posterior pelvic exenteration is the case. The dissection planes are adjusted to the borders of the morphogenetic units. As almost all lateral recurrences were of the paravisceral type, its correspondent paravisceral fat pad structure was included in the resection. No pelvic floor muscle resection or complete hypogastric system approach was performed [1,11,12]. A total vaginectomy together with removal of the distal urethra from the introitus was also performed, with en-block resection of the supralevator part. Removing the entire vagina is helpful because a certain grade of stricture may develop at the level of the anastomosis between the flap and the vagina left behind after supralevator exenteration [13].

As for the pelvic wall dissection for lateral recurrences, a final decision on resectability was made when tumor boundaries surrounded by an apparently normal tissue could be removed from the otherwise normal endopelvic fascia. Any suspicion of involvement of fascial or other endopelvic structures was confirmed by frozen section biopsy. Once resectability was confirmed, the following surgical procedure for the removal followed the previously described surgical principles. IOERT was used in the initial part of this series (1988–1999) in 22 patients [8]. In this group of patients, IOERT was performed at the discretion of the gynecologist and the