Locally advanced cervical cancer: a descriptive analysis of 20 patients with a visceral recurrence

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ABSTRACT

Purpose: To perform a descriptive analysis of patients with locally advanced cervical cancer (LACC) who developed a visceral recurrence, and to identify factors that may favor this atypical aggressive progression.

Patients and methods: The data from twenty patients with LACC and visceral recurrence were retrospectively reviewed.

Results: The majority of the patients (85%) developed a recurrence within 2 years of their primary therapy. All died from their cancer, with a median survival of 28.7 months (range 13.4 - 35.9 months). None of the characteristics related to the patient, the tumor, or the treatment were associated with visceral recurrence (p> 0.05).

The International Federation of Gynaecology and Obstetrics (FIGO) 2009 classification only plays a partial role in predicting the risk of recurrence. On the other hand, the FIGO 2018 version appears to be more discriminating by taking the lymph node status into account.

Conclusion: LACC is a heterogeneous group of diseases with a wide range of outcomes. No clear prognostic factors are associated with visceral progression. Other variables–probably linked to the molecular changes within the tumor itself–may constitute a means to stratify the development risk once identified and standardized, but may also be useful for targeted therapies.

KEYWORDS

Locally advanced cervical cancer, chemoradiotherapy, visceral recurrence, prognostic factors, FIGO, outcome.

Introduction

Cervical cancer (CC) is the fourth most common cancer among women worldwide [1].

Screening and Human Papillomavirus (HPV)-vaccination campaigns have not been capable of eradicating the disease in Western Countries where CC remains a significant health issue.

In Belgium, 622 new cases were diagnosed in 2017 and this number has been largely stable over the last decade, with a 5-year survival rate of 70% [2]. This steady figure has been maintained despite the publication and application of standardized recommendations for treatments. These latter are based on the disease staging published by FIGO 2009 and 2018 [3-5].

Locally advanced cervical cancer (LACC) (stage ≥IB2 according to the FIGO 2009) is treated by concomitant cisplatin-based chemoradiotherapy (CCRT) followed by image-guided adaptive brachytherapy (IGABT). Recurrences can be local, in the pelvic or para-aortic (PAo) lymph nodes (LN) by lymphatic dissemination, or visceral via hematogenous spread. The most frequent sites of distance relapse are pulmonary (36.5%), skeletal (16.3%), hepatic or peritoneal [6].

Authors report a dismal prognosis with a one-year mortality rate of 69.2% with a single metastasis and 82.7% for patients with multifocal metastases [7,8].

In this study, we describe the characteristics of the visceral recurrence (site(s), survival without recurrence, time without treatment after recurrence and overall survival). We try to determine whether some clinical, pathological, or therapeutic elements are associated with this unfavorable evolution, especially in cases of recurrence occurring less than 2 years after treatment.

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Patients and method

Patients

Between January 2010 and August 2017, 134 patients with LACC received CCRT followed by IGABT at the University Hospital of Liège, Liège, Belgium.

From this population, 20 patients developed a visceral recurrence and constituted our present retrospective study population. The follow-up was carried out until March 2019.

All the patients benefited from an initial assessment using clinical exam, pelvic Magnetic Resonance Imaging (MRI) and Positron Emission Tomography/Computed Tomography

(PET/CT) using ^{18}F-2'-deoxy-2'-fluorodeoxyglucose ([^{18}F](FDG-PET/CT), but also a PAo LN dissection-this latter was realized in the absence of contraindications in 17 of cases (85%).

Treatment

The standard treatment consisted of CCRT followed by IGABT. Extended-field radiotherapy (RT) to treat the para-aortic region was based on [^{18}F) FDG-PET/CT and laparoscopic LN staging. Radiation boost up to 60 Gy to pathologic nodes was prescribed on individual basis.

Clinical Data analysis

The following characteristics were collected:

- patient: age, Body Mass Index (BMI), smoking status, percentage of lymphocytes at diagnosis.
- tumor: size from MRI, FIGO 2009 and 2018 stages, histology, LN status.
- treatment: dose, duration and administration methods for RT; administration and dose of IGABT; type, dose and number of concomitant chemotherapy (CT) cycles; intervals between the different treatment phases, and reasons to discontinue treatment.

Patients were followed up every 3 months for the first 2 years, every 6 months for year 3 to 5, and annually thereafter. At 3 months post-treatment [^{18}F]FDG-PET/CT and pelvic MRI were performed to check the treatment response.

We have defined visceral recurrence as the metastatic involvement of an organ outside the pelvis, including peritoneal carcinomatosis, which was confirmed clinically, histologically or by imaging.

Overall survival (OS) was defined as the time between initiation of treatment and death from any cause. Visceral recurrence-free survival (VRFS) was defined as the time between starting treatment and the diagnosis of a visceral recurrence.

Time without treatment (TWT) after the recurrence is defined as the cumulative period without RT, CT or immunotherapy between the diagnosis of the recurrence and death. This last outcome is useful in indirectly assessing the quality of life for these patients.

Descriptive Statistical Analysis

The results are presented as averages and standard deviation (SD), medians and quartiles, and extremes for continuous variables and, lastly, in frequency tables for qualitative variables. Overall survival and survival without recurrence are represented using Kaplan-Meier curves. A student's or a Kruskal-Wallis test was used for continuous variables and the Fisher's exact test was used for qualitative variables, in order to compare patients with recurrence before, or after, 2 years. The results are considered significant at the 5% uncertainty levels ($p<0.05$). Calculations were made using SAS version 9.4 and the graphics using R version 3.6.

Results

The median age at diagnosis was 47 years (range 30-88 years) and the mean BMI was 24.19 kg/m^2 (SD: 5.35). Seventy percent of patients were active smokers and the mean percentage of lymphocytes at diagnosis was 21.15% (range 5-38%).

The characteristics of the tumor are outlined in Table 1. This cohort was initially staged according to the FIGO 2009 classification. By applying the FIGO 2018 version a posteriori, there was a decrease from 18 cases of stages I–II (90%) to 8 cases (40%), and an increase from 2 cases (10%) to 12 cases (60%) in the stages III–IV.

Histologic analysis revealed 13 patients with squamous cell carcinoma (65%), 2 with adenocarcinoma (10%) and 5 with a rare histology (25%) represented by 1 large cell neuroendo-

Table 1 Tumor characteristics.

Variable	Categories	N	Number (Percent)
FIGO 2009		20	
	IB2		6 (30.0)
	IIA1		1 (5.0)
	IIA2		2 (10.0)
	IIB		9 (45.0)
	IIIA		0 (0.0)
	IIIB		2(10.0)
	IVA		0 (0.0)
FIGO 2018		20	
	IB2		2 (10.0)
	IB3		2 (10.0)
	IIA1		0 (0.0)
	IIA2		1 (5.0)
	IIB		3 (15.0)
	IIIA		0 (0.0)
	IIIB		0 (0.0)
	IIIC1		9 (45.0)
	IIIC2		3 (15.0)
	IVA		0 (0.0)
Histology		20	
	Adenocarcinoma		2 (10.0)
	Others		5 (25.0)
	Squamous cell carcinoma		13 (65.0)
Tumor size MRI ≥ 40 mm		20	
	No		3 (15.0)
	Yes		17 (85.0)
Pelvic lymph node		20	
	No		11 (55.0)
	Yes		9 (45.0)
Para-aortic lymph node		20	
	No		17 (85.0)
	Yes		3 (15.0)

crine carcinoma, 1 papillary squamotransitional carcinoma, 1 mesonephric adenocarcinoma and 2 adenosquamous cell carcinomas. In 17 patients (85%), the tumor was ≥ 40 mm with a mean size of 55.75 mm (SD: 26.02) and the median size was 48.50 mm (range 28 - 148 mm). Pelvic or PAo LN involvement was described in 12 patients (60%).

Three patients underwent a hysterectomy based on favorable staging (stages IB2 and IIA), the absence of LN involvement by imaging and their young age [9]. One young patient underwent surgery on the basis of a rare, particularly aggressive histology (large cell neuroendocrine carcinoma). All patients received a conventional external-beam radiotherapy (EBRT) with a mean dose administered of 47.79 Gy (SD: 5.95). For 14 patients (70%), the radiation field was limited to the pelvis; for 6 patients (30%), this was extended to the PAo region.

Concomitant cisplatin CT was performed on 18 patients. Ten patients (50%) received six cycles, three received five and the remaining patients received a fewer number of cycles, primarily due to the occurrence of renal and/or hematological toxicities. Radiation boost was administered to six patients, with a mean dose of 9.37 Gy (SD: 3.78). IGABT was subsequently performed on 17 patients, with a mean dose of 26.68 Gy (SD: 9.06). On average, the interval between diagnosis and the beginning of treatment was 71.75 days (SD: 36.92) and the mean total duration was 57.95 days (SD: 25.71), taking less than 55 days for 15 patients (75%).

The initial post-treatment [^{18}F] FDG-PET/CT showed a complete response in 13 cases (65%), a partial response in 2 cases (10%) and a visceral recurrence in 3 cases (15%). Unfortunately, data are missing for two patients. The remaining 17 cases of visceral recurrences occurred later in their progression. It should be noted that 15% of patients showed no symptoms at the time of their recurrence and so, the diagnosis was based on the clinical and/or imaging follow-up.

The median VRFS was 344 days (range 99-1312 days) i.e. 11.3 months (Figure 1). The characteristics of the visceral recurrence are outlined in Table 2.

Visceral recurrences were distributed as 10 isolated visceral recurrences and 10 with also a local and/or LN recurrence. In 55% of cases, visceral recurrences affected only one organ. In the remaining cases, there was multiple organ involvement.

Sixteen patients (80%) received treatment for their recurrence: nine were treated with CT, four with a combination of

Figure 1 Visceral recurrence-free survival and overall survival.

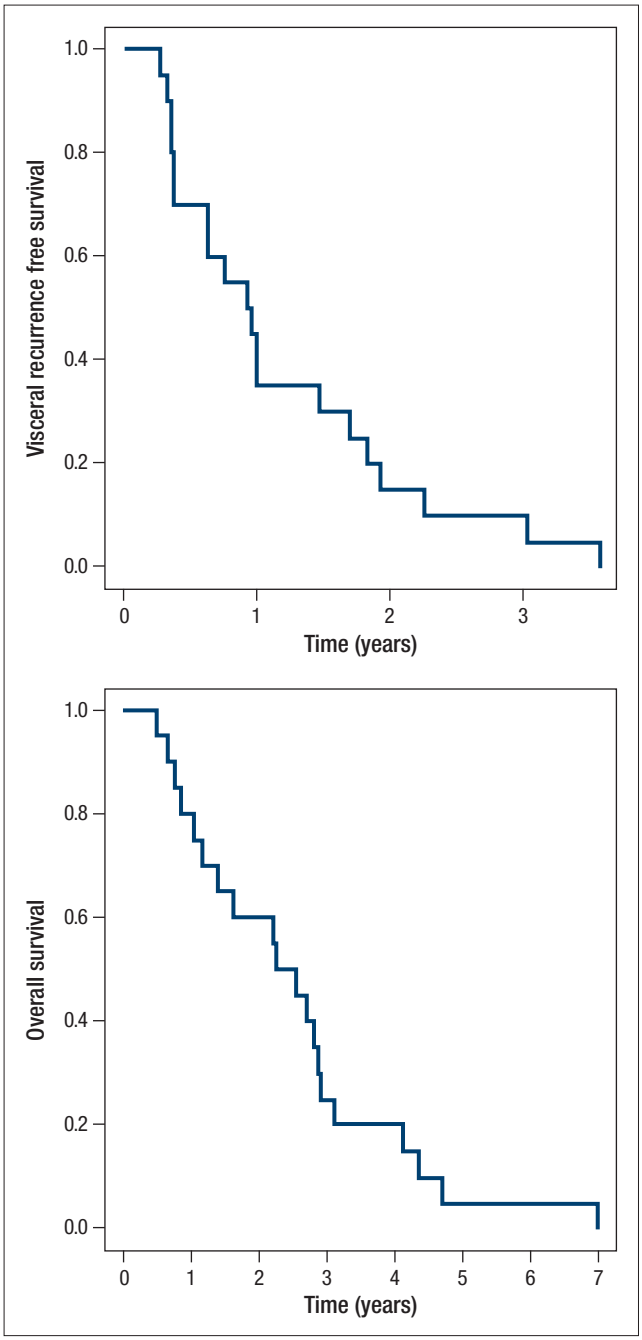

Table 2 Recurrence characteristics.

2A COMBINATION OF RECURRENCE TYPES						
Visceral recurrence	**Local recurrence**	**Pelvic lymph node recurrence**	**Para-aortic lymph node recurrence**	**Distant lymph node recurrence**	**Frequency**	**%**
1	0	0	0	0	10	50.00
1	0	0	0	1	4	20.00
1	0	1	0	0	1	5.00
1	1	0	0	0	2	10.00
1	1	0	1	0	2	10.00
1	1	1	1	1	1	5.00

Table 2 Recurrence characteristics.

2B COMBINATION OF VISCERAL RECURRENCE TYPES						
Bone	**Peritoneal**	**Lung**	**Liver**	**Brain**	**Frequency**	**%**
1	0	0	0	0	5	25.00
0	1	0	0	0	4	20.00
1	0	1	1	0	2	10.00
0	0	1	1	0	2	10.00
0	0	1	0	0	2	10.00
0	1	0	1	0	2	10.00
0	0	1	0	1	1	5.00
1	0	1	0	1	1	5.00
0	1	1	1	0	1	5.00

CT and radiosurgery, two with surgery followed by CT, and one with surgery alone. The three patients who underwent surgical treatment presented digestive occlusion.

All these patients died as a result of their CC. The median OS was 872 days (range 184-2549 days), that means 28.7 months (Figure 1). For completeness of data, the median OS of the remaining 114 patients without visceral recurrence is more than 84 months and is significantly better than that of our group of interest (other article under review). The TWT for the 20 patients described, starting from the diagnosis of the recurrence, was recorded for 15 patients treated. Between the diagnosis of the recurrence and death, 8 patients experienced a period without treatment that exceeded 50% of their survival. The extremes were 14.9% and 89.71%.

For 85% of patients, the recurrence occurred within 2 years of their initial treatment.

We compared the data of patients who experienced a visceral recurrence before, or after, 2 years from the start of their treatment (Table 3).

In this univariate analysis, the majority of the factors related to the patient (age, BMI, smoking status), the tumor (size, FIGO 2009 and 2018 stage, LN involvement), or the treatment (total RT dose, number of CT cycles) have no significant prognostic impact on survival without a visceral recurrence at 2 years ($p > 0.05$).

However, the percentage of lymphocytes at diagnosis is significantly different between the 2 groups ($p < 0.05$).

Discussion

The 5-year OS of patients suffering from LACC reaches 70% when consensual modern therapy is delivered [10]. Treatment of recurrence is usually disappointing with a dismal short term prognosis. Therefore, amongst patients with LACC, identifying those at high risk of recurrence for whom treatment intensification could be considered is of crucial importance [11]. The latter patients deserve a stricter follow-up planning and could be considered for inclusion in international studies testing modern therapies for recurrence. This report presents a review of 20 patients who developed a visceral recurrence and were followed-up until death. The objective is to investigate risk factors that could potentially predict this atypical type of recurrence.

In terms of the risk of distant recurrences, a recent study highlighted the role of glandular histology and LN invasion as factors that negatively impact survival without visceral metastases [12]. In 2012, KANG *et al*. identified four factors associated with a risk of distant recurrence: positivity of the pelvic or PAo LN on [^{18}F]FDG-PET/CT, non-epidermoid histology and a high level of antigens associated with squamous cell carcinoma (SCCA) [13]. A predictive model for distant recurrences developed from this study was validated and proved useful in a clinical setting [14]. In 2014, SCHMIDT *et al*. showed that the FIGO stage, LN status, and the extent of tumor regression during treatment were significant predictors of recurrence [15]. In 2004, HIRAKAWA *et al*. found that only the rate of SCCA was associated with late recurrence [16]. Therefore, different clinical and pathological risk factors seem to be associated with distant recurrences in patients with LACC, but with conflicting results. In our study, no prognostic factors were relevant probably due to the limited number of patients.

Our study demonstrates that 85% of patients develop their visceral recurrence within 2 years of the start of treatment. By comparing the groups of patients who presented their recurrence before or after this two-year period, we observe that the percentage of lymphocytes at diagnosis had a significant prognostic value for survival without visceral recurrence at two years: high lymphocyte percentage at diagnosis is a predictive factor for survival without visceral recurrence at two years. Our study supports the conclusions of the trial published by Jeong *et al*. This latter is the only one reported the prognostic value of the lymphocyte percentage at diagnosis in patients with LACC treated by RT or CCRT. Similar data were also described in other neoplasia [17-20]. Our team recently demonstrated similar results based on the initial cohort of the 134 patients, with lymphocytes percentage at diagnosis having borderline impact on OS (HR 0.952, 95% CI 0.906-1.001, p=0.066) (data not published). Moreover, we also demonstrated that lymphocytes blood count at diagnosis (but not during the treatment) was

Table 3 Visceral recurrence < or > 2 years: characteristics of patients, tumor and treatment.

Variable	N	Mean	SD	SE	Min	Q1	Median	Q3	Max	*p*-value
Age at diagnosis (years)										
< 2 years	15	53.20	15.293	3.949	30.00	44.00	53.00	61.00	88.00	**0.18**
≥ 2 years	5	43.20	7.791	3.484	36.00	38.00	40.00	47.00	55.00	
BMI (kg/m²)										
< 2 years	14	25.26	5.609	1.499	17.72	20.90	24.57	27.73	38.51	**0.15**
≥ 2 years	5	21.21	3.373	1.508	17.06	19.05	21.72	22.32	25.91	
Lymphocyte at diagnosis (%)										
< 2 years	14	17.53	7.409	1.980	5.00	13.70	15.50	23.60	30.00	**0.0095**
≥ 2 years	5	31.28	7.668	3.429	22.10	23.90	35.00	37.40	38.00	
Tumor size by MRI (mm)										
< 2 years	15	59.13	29.108	7.516	28.00	43.00	52.00	72.00	148.00	**0.26**
≥ 2 years	5	45.60	8.820	3.945	37.00	40.00	41.00	53.00	57.00	
Total dose of radiotherapy										
< 2 years	15	71.29	17.133	4.424	41.50	55.00	80.40	85.40	92.40	**0.40**
≥ 2 years	5	79.22	12.379	5.536	60.50	76.00	80.40	85.40	93.80	

Variable	Categories	N	< 2 years Number (%)	N	≥2 years Number (%)	*p*-value
Chemotherapy cycle number		13		5		**0.54**
	1		1 (7.7)		0 (0.0)	
	3		2 (15.4)		0 (0.0)	
	4		2 (15.4)		0 (0.0)	
	5		1 (7.7)		2 (40.0)	
	6		7 (53.8)		3 (60.0)	

a potential survival predictor in patients treated by CCRT in LACC [21]. Indeed, the immune system plays a major role in tumor progression [22]. Currently, it is well established that tumor infiltrative lymphocytes (TILs) play a major role in mediating response to CT or RT and that the presence of TILs correlated with outcomes of patients with different tumor including CC [23-25]. On the other hand, the mechanism by which peripheral blood lymphocytes influences the prognosis is not fully elucidated. In addition to a potential association with decreased functional status and predisposition to infections, lymphocytes can have antitumoral effects through migration and proliferation inhibition, through apoptosis but also through CT or RT response modulation [26]. These results support the hypothesis that cell-mediated immunity plays an important role in controlling or even eliminate cancer cells [27].

The FIGO 2009 classification, which forms the basis for the majority of available clinical studies, distinguishes prognostic groups based on the clinical evaluation and serves as a basis for the standardization of the treatment planning. It seems that LACCs are distinguished by their heterogeneity. Each FIGO 2009 stage is associated with a wide range of types of progressions. An updated FIGO classification was published in 2018 and it takes LN involvement into account; it is expected to bring greater homogeneity in terms of prognostic value. By applying the FIGO 2018 classification to our patients, a redistribution of the stages was observed, with a greater representation of stages III and IV compared to stages I and II. Stages III and IV are found in 60% of cases – compared to 10% before – which appears to be more consistent with the progression observed.

Currently, the standard treatment for LACC involves CCRT followed by IGABT. CCRT is beneficial because it improves local control but additionally exerts a systemic effect decreasing the occurrence of metastases, at cost of increased toxicity [28,29]. Based on these observations, a randomized study considered the role of adjuvant CT for patients with LACC [30]. These results show the importance of identifying high risk patients that could benefit from intensified treatment.

Studies suggest the prognostic role of tumor-specific biological factors such as HPV-16 variants (European vs. non-European) [31] or molecular abnormalities in tumor-associated proteins (cytoplasmic maspin, p53 protein) [32-35].

These markers, once identified, characterized and standardized, could constitute a first step in classifying patients according to their risk of progression. They may also be targets for the

development of new treatments approaches.

These new alternative and/or complementary therapies to CT are of an even greater importance due to the immunosuppression caused directly by CT, or the consequences of CT (such as the need for blood transfusions) which may reduce the patient's response to the treatment and thus favor the progression and spread of the cancer [36].

Currently, in cases of a metastatic recurrence, CT can potentially be combined with an angiogenesis inhibitor such as bevacizumab [37]. Several studies based on immunotherapy are currently underway targeting programmed cell death 1 protein (PD-1) or ligand 1 (PD-L1), using vaccine therapy or autologous T cells [38].

Our study is retrospective and monocentric and the results must therefore be considered cautiously. The limited number of patients in this cohort should also be emphasized. Additionally, the method for collecting patients could result in data loss or errors. Conversely, there is a reasonable level of homogeneity in the diagnosis modalities and the treatment administered. If this treatment was incomplete for some patients, it was due to an adaptation linked to tolerance. Finally, no definition of visceral recurrence in the literature is unambiguous, which could therefore create comparison bias with other studies.

Conclusion

LACC comprises a heterogeneous group of diseases. Tumor-specific biological factors are most likely the major cause of this heterogeneity. To identify them could lead to indication for targeted therapies.

Despite receiving standard and correctly administered treatment, some patients present a visceral recurrence. Their prognosis is poor. The median survival in our group was 28.7 months, while LACC is associated with a median OS of 91.2 months [39].

It is therefore of paramount importance that research is undertaken to identify patients with a high risk to develop this type of recurrence.

In our study, as in the literature, there are few clinical factors that seem to be discriminatory in terms of predicting the risk of visceral recurrence. However, we have highlighted the potential importance of a high lymphocyte count (which reflects the immune system vigilance) as a predictive factor for survival without visceral recurrence at two years.

It is important to note that our series contained a high proportion of tumors with an atypical histology (25%).

It should also be noted that by applying the new FIGO 2018 classification, instead of the 2009 version, the percentage of patients in stages III and IV moved from 10% to 60%. This confirms its greater prognostic relevance.

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