Surgical Oncology 30 (2019) 40–46

Contents lists available at ScienceDirect

Surgical Oncology

journal homepage: www.elsevier.com/locate/suronc

Cervical cancer recurrence: Proposal for a classification based on anatomical dissemination pathways and prognosis

Sofiane Bendifallah[a,b], Tiphaine de Foucher[a,*], Alexandre Bricou[c], Lobna Ouldamer[d], Vincent Lavoue[e], Justine Varinot[f], Geoffroy Canlorbe[a], Xavier Carcopino[g], Emilie Raimond[h], Florence Huguet[i], Olivier Graesslin[h], Cyril Touboul[j], Pierre Collinet[k], Cyrille Huchon[l], Emile Daraï[a,b], Marcos Ballester[a,b], For the Groupe de Recherche FRANCOGYN, FRANCE

[a] Department of Gynaecology and Obstetrics, Tenon University Hospital, Assistance Publique des Hôpitaux de Paris (AP-HP), University Pierre and Marie Curie, Paris 6, 4 rue de la Chine, 75020, Paris, France
[b] INSERM UMR_S 938, University Pierre et Marie Curie, Paris 6, 27 rue de Chaligny, 75012, Paris, France
[c] Department of Obstetrics, Gynecology and Reproductive Medicine, CH Jean Verdier, Assistance Publique-Hôpitaux de Paris (AP-HP), av du 14 juillet, 93140, Bondy, France
[d] Department of Obstetrics and Gynaecology, Centre Hospitalier Régional Universitaire de Tours, Hôpital Bretonneau, 2 Boulevard Tonnellé, 37000, Tours, France
[e] CRLCC Eugène-Marquis, service de gynécologie, CHU de Rennes, université de Rennes 1, 2 Rue Henri le Guilloux, 35033, Rennes, France
[f] Department of Pathology, Tenon University Hospital, Assistance Publique des Hôpitaux de Paris (AP-HP), University Pierre and Marie Curie, Paris 6, 4 rue de la Chine, 75020, Paris, France
[g] Department of Obstetrics and Gynaecology, Hôpital Nord, APHM, Aix-Marseille University (AMU), CNRS, IRD, Chemin des Bourrely, 13015, Marseille, France
[h] Department of Obstetrics and Gynaecology, Institute Alix de Champagne University Hospital, 45 Rue Cognacq-Jay, 51100, Reims, France
[i] Department of Radiation oncology, Tenon University Hospital, University Pierre and Marie Curie, 4 rue de la Chine, 75020, Paris, France
[j] Department of Obstetrics and Gynecology, Centre Hospitalier Intercommunal, 40 av de Verdun, 94000, Créteil, France
[k] Department of Gynecologic Surgery, Jeanne de Flandre Hospital, CHU de Lille, Avenue Eugène Avinée, 59120, Loos, France
[l] Department of Obstetrics and Gynecology, Poissy-St Germain Hospital, 10 Rue du Champ Gaillard, 78300, Poissy, France

ARTICLE INFO

Keywords:
Cervical cancer recurrence classification
Prognosis

ABSTRACT

Introduction: Precise definitions of recurrences and optimal treatment strategy are yet to be clearly defined among patients with cervical cancer (CC). The purpose of this study was to develop a reproducible classification of CC recurrence.

Materiel and methods: Data of women with FIGO stages I-IV CC treated between January 2000 and January 2015 were retrospectively abstracted from nine French institutions. We proposed a rTNM classification for recurrence: locoregional (rT), nodal (rN), or distant organ (rM). According to rTNM prognosis, we then defined a rSTAGE classification (I, II, IIIA, IIIB, IVA, IVB).

Results: Among the 1028 women treated for FIGO stages I-IV CC during the study period, 216 recurrences were observed (21%). The 3-year survival after recurrence was 38.8%, with a median time to recurrence of 9 months (95% CI, 30.9–48.7). A trend for a lower 3-year survival after recurrence was observed in women with multiple-site vs single-site recurrence ($p = 0.1$). Among the women in the rT group, a difference in 3-year survival after recurrence was found between rT_1 single site, rT_2 single site and rT_3 single site ($p = 0.02$). The 3-year survival after recurrence was 69.1%, 49.2%, 37.5%, 34.2%, 23.1% and 24.4% for rStage I, II, IIIA, IIIB, IVA and IVB, respectively ($p = 0.007$).

Conclusion: rTNM classifications and rSTAGE are discriminatory and allow all recurrence modalities to be classified.

* Corresponding author. Service de Gynécologie-Obstétrique, Hôpital Tenon, 4 rue de la Chine, 75020, Paris, France.
E-mail addresses: sofiane.bendifallah@yahoo.fr (S. Bendifallah), tiphaine.defoucherdecareil@aphp.fr (T. de Foucher), alex.bricou@gmail.com (A. Bricou), louldamer@yahoo.fr (L. Ouldamer), vincent.lavoue@chu-rennes.fr (V. Lavoue), justine.varinot@aphp.fr (J. Varinot), geoffroy.canlorbe@aphp.fr (G. Canlorbe), xcarco@free.fr (X. Carcopino), emilie_raimond@hotmail.com (E. Raimond), florence.huguet@aphp.fr (F. Huguet), olivier.graesslin@gmail.com (O. Graesslin), cyril.touboul@chicreteil.fr (C. Touboul), pierre.collinet@chru-lille.f (P. Collinet), cyrillehuchon@yahoo.fr (C. Huchon), emile.darai@aphp.fr (E. Daraï), marcos.ballester@aphp.fr (M. Ballester).

https://doi.org/10.1016/j.suronc.2019.05.004
Received 4 January 2019; Received in revised form 5 April 2019; Accepted 10 May 2019

Abbreviations

CC	cervical cancer
FIGO	International Federation of Gynecology and Obstetrics
INCa	French National Institute of Cancer
LN	lymph node
LVSI	lymphovascular space involvement status
MRI	Magnetic Resonance Imaging
OS	Overall survival
PET-CT	Positron Emission Tomography – Computed Tomography
rM	Distant organ recurrence
rN	Nodal recurrence
rT	Locoregional recurrence

1. Introduction

Cervical cancer (CC) is the second most commonly diagnosed cancer in women overall and the third cause of cancer-related death among women in developing countries. Worldwide, there were around 527 600 new cases of CC and 265 700 deaths in 2012 [1–3]. Although most CC-related deaths (90%) occur in underdeveloped countries, CC remains a major public health issue in developed countries with over 58 000 new cases diagnosed annually and causing around 24 000 deaths in Europe every year [2,3]. The 5-year relative survival rate for European women diagnosed with CC in 2000–2007 was 62%, ranging from 57% in Eastern Europe to 67% in Northern Europe [2,3].

The pattern of recurrence after primary treatment of CC has been extensively investigated by several authors who concur that most recurrences occur within 2 years of diagnosis and most deaths are a result of uncontrolled disease [4–7]. Nevertheless, the recurrence rate is widely variable, ranging from 10% to 20% after primary treatment in women with International Federation of Gynecology and Obstetrics (FIGO) stages IB-IIA CC without lymph node involvement, and reaching up to 70% for women with nodal metastases or more locally advanced CC [4,7–9]. The pattern of dissemination can be either locoregional (vaginal or pelvic recurrence), distant or a combination of both [3–5,7]. However, the optimal treatment strategy for women with recurrent disease remains somewhat blurred as most published studies are retrospective with a relatively low number of included patient [2–7].

Several parameters – such as the type of recurrence, type of primary treatment and associated comorbidities – should be taken into account to define the best therapeutic approach. It would also appear to be of major interest to identify which women with recurrent CC might have a better prognosis and for whom the objective of care could be curative. However, many definitions of anatomical CC recurrence have been used in the various published studies rendering the interpretation and comparison of clinical outcomes somewhat difficult [2–7]. Hence, a homogeneous classification of CC recurrence is necessary to better define prognosis and optimal patient management [10,11].

Therefore, the purpose of this study was to develop a reproducible classification of CC recurrence based on prognosis and dissemination pathways (locoregional, lymphatic and hematogenous).

2. Materiel and methods

2.1. Study population

The data of women with histologically proven FIGO stages I-IV CC treated between January 2000 and January 2015 were retrospectively abstracted from nine institutions from the FRANCOGYN study Group with maintained CC databases in France (Tenon University Hospital, Tours University Hospital, Creteil University Hospital, Reims University Hospital, Rennes University Hospital, Jeanne de Flandre University Hospital, Poissy University Hospital, Jean Verdier University Hospital and Marseille North University Hospital). All included patients gave their consent for their information to be used for research purposes. The study was approved by the Ethics Committee of the National College of French Gynaecologists and Obstetricians (CEROG 2016-GYN-0502).

All enrolled women underwent preoperative workup including history, physical examination, cervical biopsy, Magnetic Resonance Imaging (MRI) and Positron Emission Tomography – Computed Tomography (PET-CT) if indicated, according to the FIGO stage and the period of treatment. Cystoscopy and/or proctoscopy were performed if there was a suspicion of bladder or rectal involvement after clinical examination or on MRI. Clinical, surgical, pathological and treatment data were collected: the woman's age, body mass index (BMI; calculated as weight in kilograms divided by the square of height in metres), lymph node status, clinical FIGO stage, final pathological analysis (histological type, tumor grade, lymphovascular space involvement status (LVSI) and tumor size) and treatment modalities. All women were classified according to the FIGO 2009 classification [12] after final pathological analysis.

2.2. Therapeutic management

Therapeutic management was decided on by a multidisciplinary committee on an individual basis, according to the current French National Institute of Cancer (INCa) guidelines [13], depending on FIGO stage and results of PET-CT, when available.

Clinical follow-up consisted of physical examination and the use of imaging techniques according to the findings. Follow-up visits were conducted every 3 months for the first 2 years, every 6 months for the following 3 years, and once a year thereafter.

2.3. Statistical analysis

2.3.1. Recurrence events and classification

Recurrent disease was assessed by physical examination and imaging techniques (ultrasonography, CT, MRI, PET-CT), and histological findings when feasible. We proposed a rTNM classification for recurrence based on the pattern of cancer dissemination [1]: locoregional recurrence (rT), nodal recurrence (rN), or distant organ recurrence (rM) (Table 1). Locoregional recurrences were divided into five stages as follows: rT_x: a recurrence that cannot be assessed; rT_0: no evidence of the recurrent tumor site; rT_1: recurrence in the vaginal vault only; rT_2: centropelvic recurrence with or without vaginal involvement; rT_3: peritoneal carcinomatosis and or ascites. Nodal recurrences were divided into four stages: rN_x: a nodal recurrence that cannot be assessed; rN_0: no evidence of nodal recurrence; rN_1: infradiaphragmatic nodal

Table 1
rTNM classification for cervical cancer recurrence.

r Tumor	
rT_x	A recurrence tumor that cannot be assessed
rT_0	No evidence of recurrent tumor site
rT_1	Recurrence tumor on the vaginal vault only
rT_2	Centropelvic recurrence with or without vaginal involvement.
rT_3	Abdominal and/or pelvic peritoneal carcinomatosis, ascites
r Node	
rN_x	The nodal status cannot be assessed
rN_0	No lymph node recurrence
rN_1	Infradiaphragmatic nodal recurrence
rN_2	Supradiaphragmatic nodal recurrence
r Metastasis	
rM_x	Distant recurrence cannot be assessed
rM_0	No distant recurrence
rM_1	Distant recurrence in one or more organs

recurrence; rN_2: supradiaphragmatic nodal recurrence. Finally, distant recurrences were divided into three groups: rM_x: a distant recurrence that cannot be assessed; rM_0: no evidence of distant recurrence; rM_1: distant organ recurrence. Single site recurrence was defined as a recurrence with only one pathway of dissemination (e.g., a woman with centropelvic recurrence was considered $rT_2N_0M_0$). Multiple site recurrence was defined as recurrence with more than one pathway of dissemination (e.g., a woman with vaginal vault recurrence and bone metastasis was considered $rT_1N_0M_1$).

2.3.2. Statistical analysis

Overall survival (OS) was defined as the time from primary surgery to death from any cause. Kaplan-Meier estimates were used to estimate the event-time distributions, and log-rank test was used to compare the differences in OS between the three groups (rT/rN/rM), between the subgroups within the same group ($rT_1/rT_{2/}$ rT_3; rN_1/rN_2; rM_1), between women with single site recurrence and those with multiple site recurrence. Values of $p < 0.05$ were considered to denote significant differences. Data were managed with an Excel database (Microsoft, Redmond, WA, USA) and analyzed using the R 2.15 software, available online.

3. Results

3.1. Characteristics of the population

Of the 1028 women treated for FIGO stages I-IV CC in the nine participating centers during the study period, 216 women (21%) experienced a recurrence and were included for analysis. The distribution per center was as follows: Tenon University Hospital (59/216; 27%), Tours University Hospital (55/216; 25%), Creteil University Hospital (40/216; 19%), Rennes University Hospital (31/216; 14%), Poissy Hospital (12/216; 6%), Jeanne de Flandre University Hospital (6/216; 3%), Marseille North University Hospital (6/216; 3%), Jean Verdier University Hospital (4/216; 2%), and Reims University Hospital (3/216; 1%).

The median age and BMI of the women with recurrence were respectively 54 years (23–91) and 24.14 kg/m^2 (range 15–46.4). The characteristics of the women are reported in Table 2.

3.2. Patterns of recurrence and time to recurrence according to the rTNM classification

Among the 216 women who experienced a recurrence, 156 (72.2%) experienced a single site recurrence and 60 (27.8%) multiple site recurrences. Overall, a trend for a lower 3-year survival after recurrence was observed in women with multiple-site recurrence ($p = 0.1$) (Fig. 1).

The women with single-site recurrence were classified as follows: $rT_1N_0M_0$ in 25 cases (16.1%); $rT_2N_0M_0$ in 48 cases (30.7%); $rT_3N_0M_0$ in 18 cases (11.5%); $rT_0N_1M_0$ in 23 cases (14.7%); $rT_0N_2M_0$ in 12 cases (7.7%); and $rT_0N_0M_1$ in 30 cases (19.3%) (10 lung, 7 bone, 8 liver, 3 brain, 2 other anatomical locations). The time to recurrence according to rTNM classification and rSTAGE are reported in Table 3.

3.3. Three-year OS after recurrence according to the rTNM classification

The median follow-up after initial diagnosis was 35.6 months (1.1–146.5 months). The median follow-up after recurrence was 13 months (range: 1–93). In the whole population, the 3-year survival after recurrence was 38.8% (95% CI, 30.9–48.7), with a median time to recurrence of 9 months (range:1–93). Ninety-seven women died (44.9%) during the study period.

Among the women with single site recurrence, the 3-year survival after recurrence was 69.1% (95% CI, 48.9–97.7), 35.6% (95% CI, 20.7–61.4), 24.8% (95% CI, 8.1–76.2), 49.2% (95% CI, 26.7–90.7), 22.5% (95% CI, 4.2–100), 35.2% (95% CI, 19.7–62.7), and 24.8% (95% CI, 8.1–76.2) for $rT_1N_0M_0$, $rT_2N_0M_0$, $rT_3N_0M_0$, $rT_0N_1M_0$, $rT_0N_2M_0$, and $rT_0N_0M_1$.

Among the women in the rT group, a difference in 3-year survival after recurrence was found between rT_1 single site, rT_2 single site and rT_3 single site ($p = 0.02$) (Fig. 2A). No difference was found between single site $rT_{1\text{-}3}$ and multiple site recurrence including rT ($p = 0.2$) (Fig. 2B).

Among the women in the rN and rM groups, no difference in 3-year survival after recurrence was observed between single and multiple site recurrence (Fig. 2C, D and 2E).

3.4. Three-year OS after recurrence according to the rSTAGE

According to rTNM prognosis, we defined a rSTAGE classification (I, II, IIIA, IIIB, IVA, IVB) (Table 3). In the whole population, the 3-year survival after recurrence was 69.1% (95% CI, 48.9–97.7), 49.2% (95% CI, 26.7–90.7), 37.5% (95% CI, 22.1–63.6), 34.2% (95% CI, 12.6–92.7), 23.1% (95% CI, 74.6–71.5), 24.4% (95% CI, 14.3–41.7), for rStage I, II, IIIA, IIIB, IVA, IVB, respectively ($p = 0.007$) (Fig. 3).

4. Discussion

We describe for the first time a standardized and reproducible classification of single and multiple site CC recurrence based on a retrospective analysis of prognosis and anatomical distribution from a large multicenter database. Our results show that the rTNM

Table 2
Epidemiological and histological characteristics of the whole population.

Characteristics	Population (n = 216)
Age-median (range)	54 (23–91)
BMI kg/m2-median (range)	24.14 (15–46.4)
Post-menopausal patients (%)	122 (57%)
Tumor size on MRI, mm – median (range)	45 (2–95)
Tumor histology	
- Squamous cell carcinoma (%)	180 (83%)
- Adenocarcinoma (%)	36 (17%)
Histological grade of the tumor	
- Well differentiated (%)	59 (27%)
- Moderately differentiated (%)	66 (31%)
- Poorly differentiated (%)	40 (19%)
- Unclassified (%)	51 (23%)
FIGO classification	
- I (%)	38 (18%)
- II (%)	119 (55%)
- III (%)	25 (12%)
- IV	34 (16%)
LVSI status	
- Positive (%)	32 (15%)
- Negative (%)	66 (31%)
- Unknown (%)	118 (54%)
Treatments	
- CCRT ± VBT	93 (43%)
- CCRT ± VBT followed by radical HT	105 (49%)
- First radical HT ± CCRT ± VBT	18 (8%)
Surgical LN staging at initial diagnosis	
- Node negative women	66 (31%)
- Node positive women	88 (41%)
- Women with unknown LN status	62 (28%)
Recurrence sites	
- Vaginal vault	25 (12%)
- Central pelvic	48 (22%)
- Peritoneal carcinomatosis	18 (8%)
- Infra-diaphragmatic nodes	23 (11%)
- Supra-diaphragmatic nodes	12 (6%)
- One or multiple metastasis	36 (16%)
- Multiple sites recurrence	54 (25%)

Abbreviations: BMI: body mass index; MRI: magnetic resonance imaging, FIGO: International Federation of Gynecology and Obstetrics; LVSI: Lymphovascular Space Involvement; CCRT: concomitant chemoradiotherapy; VBT: vaginal brachytherapy; HT: hysterectomy; LN: lymph node.

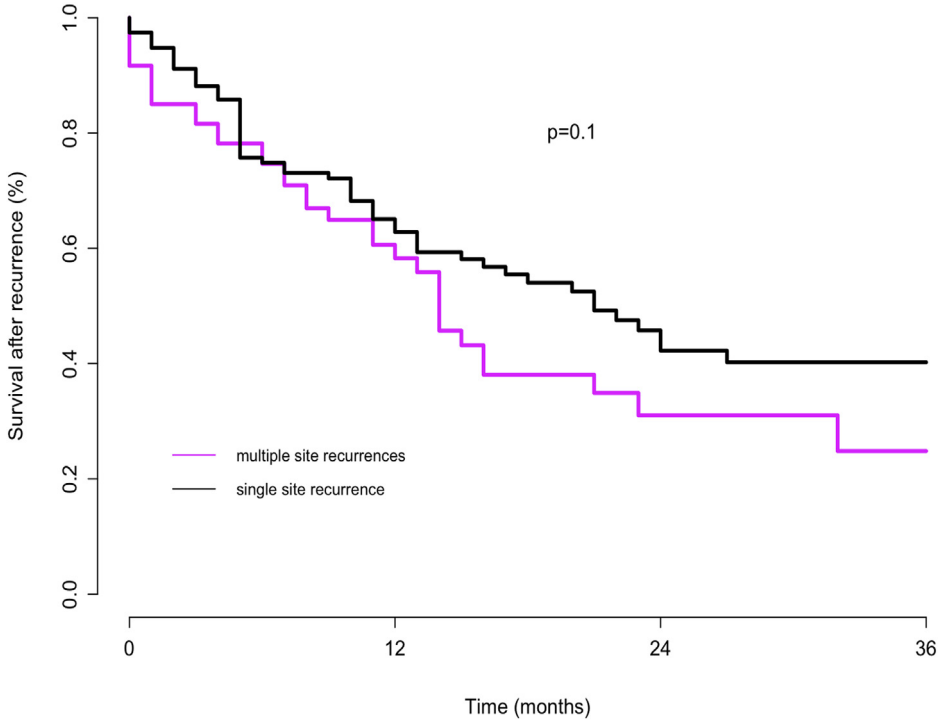

Fig. 1. Survival according to number of site recurrence. A trend for a lower 3-year survival after recurrence was observed in women with multiple-site recurrence.

Table 3
Classification of recurrence pattern, prognosis and time.

rTNM			rSTAGE	Time to recurrence (months) Median (range)	N = 216
T_1	N_0	M_0	I	15 (2–93)	25
$T_{0\text{-}1}$	N_1	M_0	II	10 (1–66)	23
T_2	$N_{0\text{-}1}$	M_0	IIIA	10 (1–66)	51
$T_{0\text{-}2}$	N_2	M_0	IIIB	11 (1–66)	19
T_3	$N_{0\text{-}2}$	M_0	IVA	5 (2–33)	19
$T_{0\text{-}3}$	$N_{0\text{-}2}$	M_1	IVB	7 (2–36)	79

classifications and rSTAGE are discriminatory and allow all recurrence modalities to be classified. We suggest that such a classification may help design specific randomized controlled trials with homogeneous populations to compare clinical outcomes according to treatment strategies and eventually improve the management of CC recurrence.

Management of women with recurrent CC remains a major issue in gynecologic oncology. However, as underlined by the ESMO Clinical Practice Guidelines for CC, there is a major knowledge gap on this topic due to the lack of well-designed studies [2,5,7]. This can partly be explained by the absence of standardized terms or confusion of the nomenclature which is currently used to define CC recurrence in the various studies [2,4,5,7]. As a result, reported recurrence rates vary significantly ranging from 22% to 55% for locoregional recurrence, from 22% to 75% for distant recurrence and from 2% to 50% for combined recurrence [2,4,5,7]. For example, Park et al. [4] defined loco-regional recurrence as tumors "limited to the vagina, bladder, rectum, and/or parametrium, with involvement of the pelvic sidewall, muscles, and/or vasculature of the lateral pelvic wall". In contrast, Choi et al., defined loco-regional recurrence as the "combination of local vaginal relapse and regional lymph nodal recurrence" [14]. This inconsistency clearly limits comparison between studies, which is why believed that an important first step towards overcoming such discrepancies would be to define a standardized classification.

In our study, around 72% of the women experienced single site recurrence and 28% multiple site recurrence. Around half (105/216) of the recurrences occurred within the first year and about 80% (175/216) within 3 years of diagnosis. The median time to recurrence in women with multiple site recurrence was shorter than for single site recurrence, except for peritoneal carcinomatosis ($rT_3N_0M_0$). Moreover, a trend for a lower 3-year survival after recurrence was found for women with multiple site recurrence. These results are in total accordance with the review by Park et al. [4]. However, the recurrence modalities are numerous because of the large number of combinations of anatomical locations. The interest of the rTNM classification we describe here is that it distinguishes between different modalities of multiple site recurrence to identify women who may benefit from surgical treatment or combined chemotherapy and surgery from those for whom medical treatment is the only option.

The most common recurrence modality in our study was locoregional (rT), affecting 46% of the women. We opted to divide this group into three subgroups (rT_1, rT_2, rT_3) based on anatomical progression of the disease and prognosis. Women with vaginal vault recurrence had a better 3-year survival after recurrence than those with centropelvic recurrence with a greater time to occurrence after treatment (16 versus 12 months). This distribution also guides the therapeutic option: in the case of preserved performance status, women classified as $rT_{1\text{-}2}N_0M_0$ can be treated with curative intent. However, it should be noted that this subgroup was heterogeneous as some of the women received pelvic radiotherapy as primary treatment and others did not, directly impacting therapeutic options. In this setting, several prognostic factors have been identified including the disease-free interval, the size of the recurrent tumor, and the preoperative lateral side wall fixation [2–6,15–17] with a better prognosis for women with a disease-free interval greater than 6 months, recurrence < 3 cm in diameter and no side wall fixation [2,3,5]. Women with vaginal (rT1) or resectable central recurrences that involve the bladder and/or rectum, without evidence of intraperitoneal or extrapelvic spread (rT2) had a 5-year OS in the order of 30%–60% after pelvic exenteration. The major subject of debate was whether peritoneal dissemination should be put into the rM or rT subgroup. We decided to include it in the rT subgroup, even if such recurrences can involve abdominal or pelvic organs (essentially because of its anatomical distribution) due to the poor prognosis,

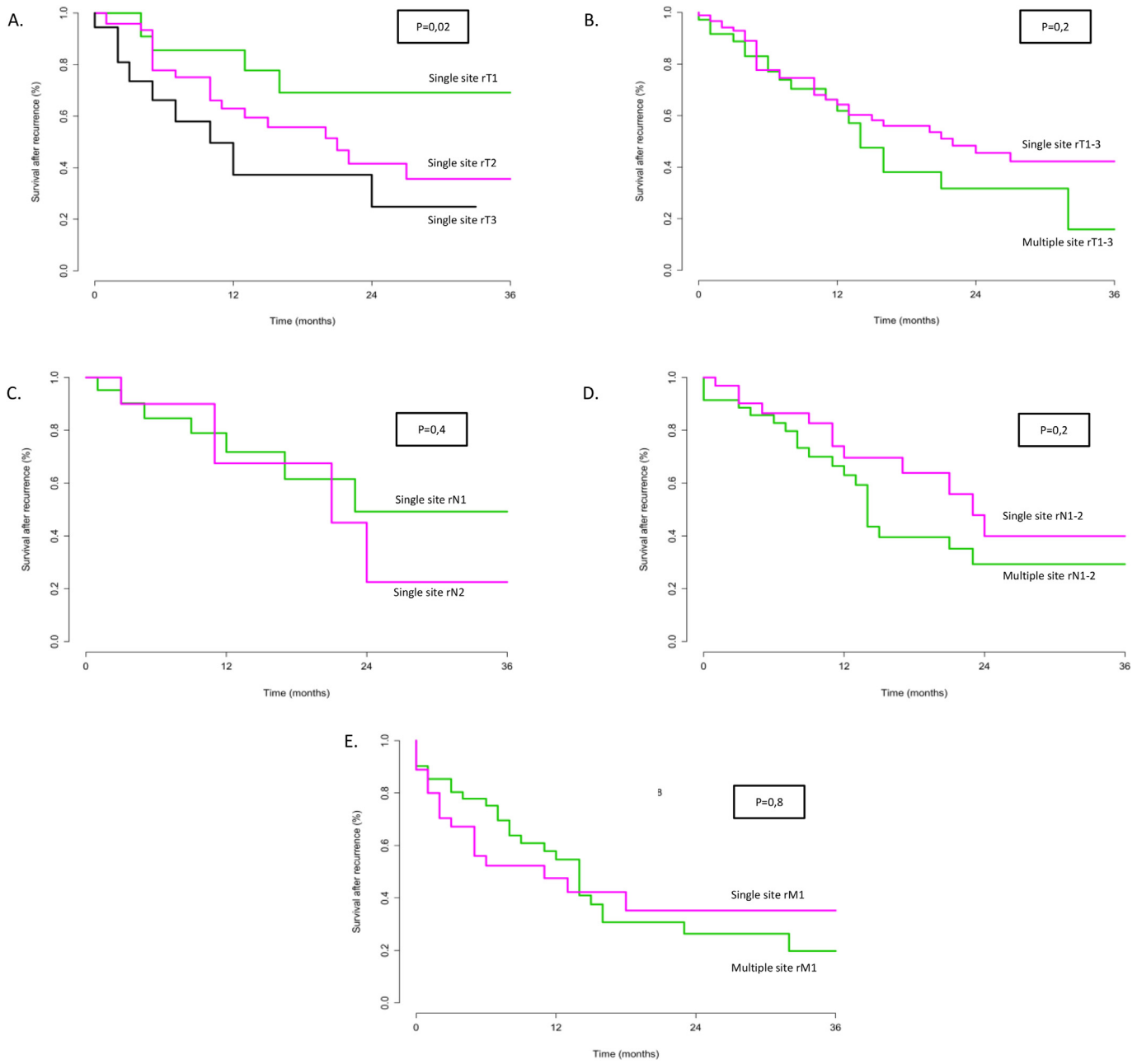

Fig. 2. A: Survival according to localisation of locoregional recurrence. **2B:** Survival according to number of locoregional recurrence. **2C:** Survival according to localisation of nodal recurrence. **2D:** Survival according to number of nodal recurrence. **2E:** Survival according to number of distant organ recurrence.
rT: locoregional recurrence.
Among the women in the rT group, a significant difference in 3-year survival after recurrence was found between rT_1 single site, rT_2 single site and rT_3 single site. No significant difference was found between single site $rT_{1\text{-}3}$ and multiple site recurrence including rT.
rN: nodal recurrence.
Among the women in the rN groups, no difference in 3-year survival after recurrence was observed between single and multiple site recurrence.
rM: distant organ recurrence.
Among the women in the rM groups, no difference in 3-year survival after recurrence was observed between single and multiple site recurrence.

shorter time to recurrence and therapeutic management (medical in most cases). In this context, a large number of agents (e.g., paclitaxel, irinotecan, and gemcitabine) have been combined with cisplatin in phase II studies for women with distant recurrent CC or locally advanced tumors [5,7,18,19]. However, the treatment strategy remains complex and should discussed on an individual basis with the aim of relieving symptoms and improving quality of life.

Concerning the lymphatic dissemination, nodal recurrences represented 16.2% of the total recurrence sites. We distinguished two recurrence groups: rN_1 for infra diaphragmatic nodes and rN_2 for supra-diaphragmatic nodes. The median time (range) to recurrence was 13 [2–54] and 13.5 [1–88] months for rN_1 and rN_2, respectively. Apart from the purely anatomical aspect, we opted for such a subdivision based on potential therapeutic options; for isolated infra-diaphragmatic recurrences, a surgical treatment can be evoked in some cases (i.e. isolated pelvic or para-aortic LNs). Unfortunately, in our retrospective database, we were not able to distinguish pelvic LNs involvement from infra-diaphragmatic para-aortic LNs involvement. Moreover, we did not

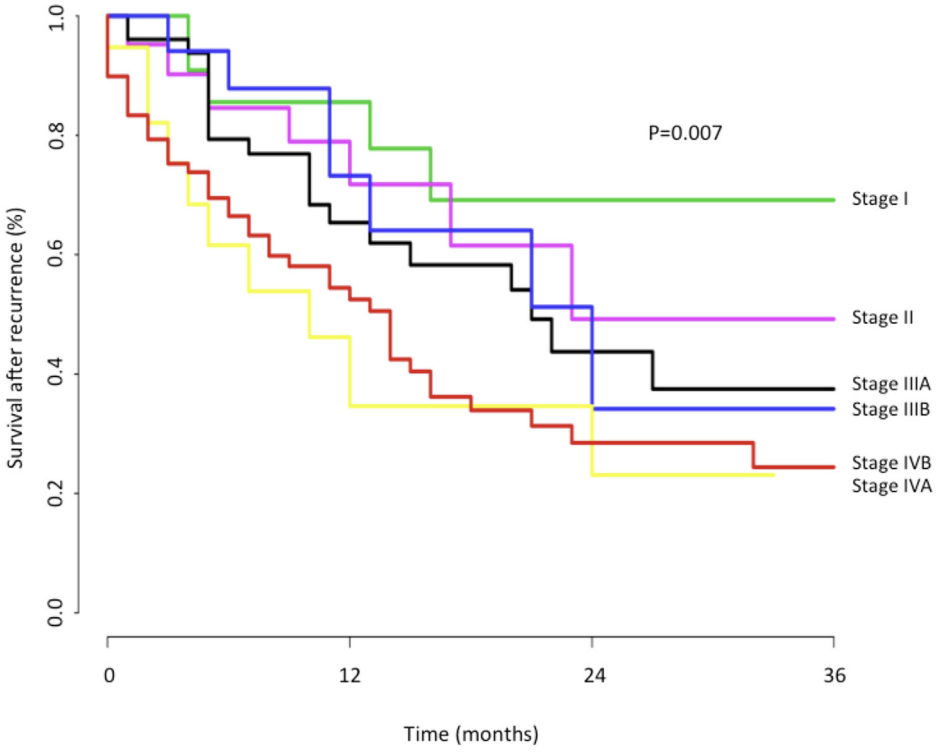

Fig. 3. Survival according to the rSTAGE.
rSTAGE: stage of recurrence.
Our results show that the rTNM classifications and rSTAGE are discriminatory and allow all recurrence modalities to be classified.

found any difference in 3-year survival after recurrence between the rN_1 and the rN_2 groups, when isolated ($p = 0.4$). This could be partly explained by the fact that isolated rN_2 recurrences are rare ($n = 12$) and that nodal recurrences are often associated to other recurrence sites. Indeed, among women who experienced a nodal recurrence, 35 experienced a single site and 35 a multiple site recurrence.

The strengths of our study lie in its multicenter nature and the large number of recurrences analyzed with informative data about incidence and prognosis. However, some limits deserve to be mentioned. We cannot exclude an inherent bias linked its retrospective nature. Furthermore, therapeutic guidelines changed during the period of data collection and this modified the management strategy over the years which may have impacted the recurrence rate as well as patterns of recurrence. However, all included women were treated in regional referral centres applying the current French/European guidelines after systematic multidisciplinary committee approval.

5. Conclusion

Although several authors have shown that the patterns of recurrence in women with CC differ widely in terms of time to recurrence and anatomical sites, our rTNM classification homogenizes the definition of CC recurrence modalities. This first attempt to classify CC recurrence could evolve in the near future: different recurrence modalities such as rT_2 and rN could be further divided with specific subanalysis. Neverthelesss, studies with a larger number of women with recurrent CC are required to validate its accuracy and usefulness in the management of recurrent disease.

Ethics approval and consent to participate

All included patients gave their consent for their information to be used for research purposes. The study was approved by the Ethics Committee of the National College of French Gynaecologists and Obstetricians (CEROG 2016-GYN-0502). The study was performed in accordance with the Declaration of Helsinki.

Consent for publication

Our manuscript contains no individual person's data in any form.

Availability of data and material

Corresponding author can send data supporting the results reported in the article on request.

Conflicts of interest

The authors declare no conflict of interest.

Funding

The authors declare no external source of funding

Authors' contributions

Conceived and designed the experiments: de FOUCHER/ BENDIFALLAH/ BALLESTER.
Analyzed the data: de FOUCHER/ BENDIFALLAH/ BALLESTER.
Contributed reagents/materials/analysis tools: de FOUCHER/ OULDAMER/ BRICOU/ LAVOUE/ VARINOT/ CARCOPINO/ RAIMOND/ HUGUET/ GRAESSLIN/ TOUBOUL/ COLLINET/ HUCHON/ DARAÏ.
Manuscript preparation: ALL THE AUTHORS.
Manuscript editing: ALL THE AUTHORS.
Manuscript review: ALL THE AUTHORS.

References

[1] L.A. Torre, F. Bray, R.L. Siegel, J. Ferlay, J. Lortet-Tieulent, A. Jemal, Global cancer statistics, 2012, CA Cancer J Clin 65 (2) (2015 Mar) 87–108.

[2] C. Marth, F. Landoni, S. Mahner, M. McCormack, A. Gonzalez-Martin, N. Colombo, et al., Cervical cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up, Ann Oncol Off J Eur Soc Med Oncol 28 (suppl_4) (2017 Jul 1) iv72–iv83.

[3] W.-J. Koh, B.E. Greer, N.R. Abu-Rustum, S.M. Apte, S.M. Campos, K.R. Cho, et al., Cervical cancer, version 2.2015, J Natl Compr Cancer Netw JNCCN 13 (4) (2015 Apr) 395–404 quiz 404.

[4] K.J. Park, M. Braschi-Amirfarzan, P.J. DiPiro, A.A. Giardino, J.P. Jagannathan, S.A. Howard, et al., Multimodality imaging of locally recurrent and metastatic cervical cancer: emphasis on histology, prognosis, and management, Abdom Radiol N Y 41 (12) (2016 Dec) 2496–2508.

[5] M. Friedlander, M. GroganU.S. Preventative Services Task Force, Guidelines for the treatment of recurrent and metastatic cervical cancer, Oncol. 7 (4) (2002) 342–347.

[6] G. Dreyer, L.C. Snyman, A. Mouton, B.G. Lindeque, Management of recurrent cervical cancer, Best Pract. Res. Clin. Obstet. Gynaecol. 19 (4) (2005 Aug) 631–644.

[7] R. Salani, N. Khanna, M. Frimer, R.E. Bristow, L.-M. Chen, An update on post-treatment surveillance and diagnosis of recurrence in women with gynecologic malignancies: society of Gynecologic Oncology (SGO) recommendations, Gynecol. Oncol. 146 (1) (2017 Jul) 3–10.

[8] G. Delgado, B. Bundy, R. Zaino, B.U. Sevin, W.T. Creasman, F. Major, Prospective surgical-pathological study of disease-free interval in patients with stage IB squamous cell carcinoma of the cervix: a Gynecologic Oncology Group study, Gynecol. Oncol. 38 (3) (1990 Sep) 352–357.

[9] E. Burghardt, J. Baltzer, A.H. Tulusan, J. Haas, Results of surgical treatment of 1028 cervical cancers studied with volumetry, Cancer 70 (3) (1992 Aug 1) 648–655.

[10] H. Kato, M. Fukuchi, T. Miyazaki, M. Nakajima, H. Kimura, A. Faried, et al., Classification of recurrent esophageal cancer after radical esophagectomy with two- or three-field lymphadenectomy, Anticancer Res. 25 (5) (2005 Oct) 3461–3467.

[11] M. Moossdorff, L.M. van Roozendaal, L.J.A. Strobbe, S. Aebi, D.A. Cameron, J.M. Dixon, et al., Maastricht Delphi consensus on event definitions for classification of recurrence in breast cancer research, J. Natl. Cancer Inst. 106 (12) (2014 Dec).

[12] M.A. Quinn, J.L. Benedet, F. Odicino, P. Maisonneuve, U. Beller, W.T. Creasman, et al., Carcinoma of the cervix uteri. FIGO 26th annual report on the results of treatment in gynecological cancer, Int J Gynaecol Obstet Off Organ Int Fed Gynaecol Obstet 95 (Suppl 1) (2006 Nov) S43–S103.

[13] L'Institut National du Cancer, Le cancer du col de l'utérus en France : état des lieux 2010, Boulogne-Billancourt, juillet, (2010) [Internet]. Available from: www.e-cancer.fr.

[14] Y. Choi, K.J. Ahn, S.K. Park, H. Cho, J.Y. Lee, et al., Adverse effect of excess body weight on survival in cervical cancer patients after surgery and radiotherapy, Radiat. Oncol. J 35 (1) (2017 Mar) 48–54.

[15] H.M. Shingleton, S.J. Soong, M.S. Gelder, K.D. Hatch, V.V. Baker, J.M. Austin, Clinical and histopathologic factors predicting recurrence and survival after pelvic exenteration for cancer of the cervix, Obstet. Gynecol. 73 (6) (1989 Jun) 1027–1034.

[16] F.N. Rutledge, J.P. Smith, J.T. Wharton, A.G. O'Quinn, Pelvic exenteration: analysis of 296 patients, Am. J. Obstet. Gynecol. 129 (8) (1977 Dec 15) 881–892.

[17] R.E. Symmonds, J.H. Pratt, M.J. Webb, Exenterative operations: experience with 198 patients, Am. J. Obstet. Gynecol. 121 (7) (1975 Apr 1) 907–918.

[18] S. Pignata, G. Silvestro, E. Ferrari, L. Selvaggi, F. Perrone, A. Maffeo, et al., Phase II study of cisplatin and vinorelbine as first-line chemotherapy in patients with carcinoma of the uterine cervix, J Clin Oncol Off J Am Soc Clin Oncol 17 (3) (1999 Mar) 756–760.

[19] P.G. Rose, J.A. Blessing, D.M. Gershenson, R. McGehee, Paclitaxel and cisplatin as first-line therapy in recurrent or advanced squamous cell carcinoma of the cervix: a gynecologic oncology group study, J Clin Oncol Off J Am Soc Clin Oncol 17 (9) (1999 Sep) 2676–2680.