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Patterns of recurrence and prognosis in locally advanced FIGO stage IB2 to IIB cervical cancer: retrospective multicentre study from the FRANCOGYN Group.

Short version of title: Recurrence and prognosis for locally advanced cervical cancer

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Abbreviations:

BMI: body mass index

CC: cervical cancer

CCRT: concomitant chemo-radiotherapy

CIs: confidence intervals

DR: distant recurrence

FIGO: International Federation of Gynecology and Obstetrics

HT: first radical hysterectomy

INCa: French National Institute of Cancer

LACC: locally advanced cervical cancer

LN: lymph node

LRR: local regional recurrence

LVSI: lympho-vascular space invasion

MRI: Magnetic Resonance Imaging

OS: Overall survival

PAL: para-aortic lymph node dissection

PET-CT: Positron Emission Tomography–Computed Tomography

RFS: recurrence free survival

VBT: vaginal brachytherapy

ABSTRACT

Introduction: Evidence-based data describing patterns of recurrence and prognosis in women with FIGO stage IB2 to IIB locally advanced cervical cancer (LACC) are scarce. The purpose of this study was to analyse patterns of recurrence in LACC and their correlation with prognosis, depending on FIGO stage, lymph node (LN) status and treatment modalities. The endpoints of this study were the type of recurrence (locoregional or distant, and time to recurrence), the recurrence free survival, the overall survival and the cumulative incidence for both locoregional and distant recurrence.

Materials and Methods: Data of women with FIGO stage IB2 to IIB CC treated between April 1996 and May 2016 were retrospectively abstracted from nine French institutions.

Results: The median follow-up for the 501 women included was 35.6 months. Recurrences were observed in 158 (31.5%), with a mean time to recurrence of 20.7 months. Women with IIB CC had poorer prognosis, lower 3-year RFS and higher 3-year cumulative incidence of both locoregional and distant recurrences. Women with positive or unknown LN status had poorer prognosis with higher 3-year cumulative incidence of distant recurrence. Women who underwent concomitant chemo-radiotherapy +/- vaginal brachytherapy had poorer prognosis, with lower 3-year RFS and higher 3-year cumulative incidence of distant recurrence.

Conclusions: Recurrence location and time to recurrence differ widely depending on the FIGO stage, LN status and treatment modalities, with potential impact on follow-up modalities and therapeutic approaches.

Key words: locally advanced cervical cancer, recurrence, pattern, survival

INTRODUCTION

Cervical cancer (CC) is the fourth most common cancer in women, with an estimated worldwide incidence of 527 600 and a death rate of 265 700 reported in 2015 [1]. In women with FIGO (International Federation of Gynecology and Obstetrics) stage IB2 to IIB locally advanced cervical cancer (LACC), recurrences have been reported to occur in 15% to 40%, with a 5-year recurrence-free survival (RFS) averaging from 50% to 70% [2][3][4][5][6].

It is now well established that most events in CC are observed within 2 years following the diagnosis [7]. Recurrences after primary treatment are often located in the true pelvis, but other locations including distant recurrences or peritoneal carcinomatosis can also be observed underlining the prognostic heterogeneity of the disease [8][9][10][11]. To reduce this heterogeneity, several epidemiological, histological and treatment prognostic factors for recurrence and survival have been reported and are currently used to define optimal CC management [12][13]. In this setting, different models have been developed based on the prognostic factors to predict recurrence and survival in LACC [6][14][15][16]. However, to date, few evidence-based data are available about patterns of recurrence (location, timing from initial treatment) and prognosis for FIGO stage IB2 to IIB CC. As a result, LACC management guidelines from various countries are heterogeneous, especially concerning: (i) the prognostic and therapeutic value of surgical nodal staging, (ii) the optimal treatment modalities, and (iii) the rationale of post-operative follow-up [17][18][19][20][21].

The aim of the study was to analyse pattern of recurrence in women with LACC based on a large retrospective French multicentre database. Analyses were stratified according to FIGO stage, lymph node (LN) status and treatment modalities.

MATERIAL AND METHODS

1. Study population

The data of women with histologically proven FIGO stage IB2 to IIB CC treated between April 1996 and May 2016 were retrospectively abstracted from nine institutions with prospectively 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 Hospital and Marseille North University Hospital). All the women had given written consent to participate in the study, and the research protocol was approved by the Institutional Review Board of the Collège National des Gynécologues et Obstétriciens Français (CEROG 2016-GYN-0502).

All enrolled women underwent pre-operative 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 and pathological data as well as details of adjuvant therapies were collected: the woman's age, body mass index (BMI; calculated as weight in kilograms divided by the square of height in meters), surgical procedure (type of hysterectomy and/or LN staging), FIGO stage, final pathological analysis (histological type, tumour grade, tumour size and lympho-vascular space invasion (LVSI) status), treatment modalities and prognosis (recurrence, death). All women were classified according to the 2009 FIGO classification [22].

2. Therapeutic management

Therapeutic management was decided on by a multidisciplinary committee on an individual basis, according to the French National Institute of Cancer (INCa) guidelines [21], depending on FIGO stage and results of PET-CT when available. When indicated, laparoscopic LN staging was performed including para-aortic (PAL) +/- pelvic lymph node dissection. We applied the following definitions to describe the LN status: women were considered as node positive when they had metastatic LNs on PET-CT or after surgical nodal staging; as node negative when they had disease free LN on surgical nodal staging; and as nodal status unknown if neither PET-CT nor surgical staging had been performed or with negative PET-CT but without surgical nodal staging.

Clinical follow-up consisted of physical examinations and the use of imaging

techniques according to the findings. Follow-up sessions were conducted every 3 months for the first 2 years, every 6 months for the following 3 years, and once a year thereafter.

3. Definition and classification of recurrence

Recurrent disease was assessed by physical examination, imaging techniques and biopsy when feasible.

According to a previous report [23], we applied the following definition to describe the patterns of recurrence: local regional recurrence (LRR) was defined recurrences including (i) the cervix, (ii) the vaginal vault, (iii) pelvic LNs, and (iv) the pelvic walls. Distant recurrence (DR) could include (i) metastatic spread to organs whatever the location, (ii) peritoneal carcinomatosis and (iii) extra pelvic LN involvement.

RFS was defined as the time from the date of primary treatment to any CC recurrence and was censored at the date of last follow-up or death without recurrence. Overall survival (OS) was defined as the time from primary treatment to death as a result of any cause.

4. Statistical analysis

The women's characteristics, and tumour and treatment characteristics were analysed using Chi-square statistics or Fisher's exact test for categorical variables and the t-test or analysis of variance (ANOVA) for continuous variables. Kaplan-Meier estimates were used to estimate the event-time distributions, and log-rank test was used to compare the differences among the different groups in terms of RFS and OS. The kernel-smoothed hazard functions of RFS were estimated on the basis of the method described by Cardoso et al. [24]. Time to the first CC recurrence for a specific site was evaluated by cumulative incidence analysis (Gray's test) and competing risk regression analysis to estimate sub-distribution hazard ratios (HRs) and 95% confidence intervals (CIs). Analysis was stratified according to FIGO stage, LN status and treatment modalities. Values of $p < 0.05$ were considered to denote significant differences. Data were managed with an Excel database (Microsoft, Redmond, WA, USA) and analysed using the R 2.15 software, available online.

RESULTS

1. Epidemiological and surgical characteristics of the population.

During the study period, 501 women with FIGO stage IB2 to IIB LACC were documented as having received treatment. Recurrences were observed in 158 (31.5%): 72 were LRR and 86 DR (among which 20 were both LRR and DR). The study flow chart is shown in Figure 1. Epidemiological and histological characteristics of the population are reported in Table 1.

2. OS and RFS according to FIGO stage, LN status and treatment modalities.

The median follow-up was 35.6 months (1.1-146.5 months). In the whole population, the respective 3-year OS and RFS were 83.5% (95% CI, 79.8-87.3) and 67.4% (95% CI, 63.1 – 72.1), $p < 0.05$. The respective 3-year OS according to recurrence location were 66.1% (95% CI, 54.4-80.3) for LRR and 56.1% (95% CI, 45.2-69.6) for DR.

The respective 3-year RFS for women with FIGO stages IB2, IIA and IIB were 79.1% (95% CI, 69.5 – 89.9), 79.1% (95% CI, 70.2 – 89.1) and 62.0% (95% CI, 56.6 – 68.0), respectively, ($p < 0.001$). No difference was found in 3-year OS according to FIGO stage.

The respective 3-year OS were 87.1% (95% CI, 82.4 – 92.0), 78.7% (95% CI, 71.9 – 86.1) and 81.7% (95% CI, 72.4 – 92.3), for node negative women, node positive women and those with unknown LN status, respectively ($p < 0.001$). The respective 3-year RFS were 76.8 % (95% CI, 71.1- 82.9), 58.4% (95% CI, 50.7 – 67.3), and 61.8 % (95% CI, 51.2 – 74.5), for node negative women, node positive women and those with unknown LN status, respectively ($p < 0.0001$).

The respective 3-year OS were 90.7% (95% CI, 82.3 – 99.9), 85.2% (95% CI, 80.1 – 90.7) and 79.1% (95% CI, 73.0 – 85.8), for women who underwent a first radical hysterectomy (HT) +/- concomitant chemo-radiotherapy (CCRT) +/- vaginal brachytherapy (VBT), CCRT +/- VBT followed by radical HT and CCRT +/- VBT, respectively ($p < 0.01$). The respective 3-year RFS were 75.8% (95% CI, 64.9 – 88.5), 74.3 % (95% CI, 68.1- 81.1) and 59.2 % (95% CI, 52.3 – 65.6), for women who underwent a first radical HT +/- CCRT +/- VBT, CCRT +/- VBT followed by radical HT

and CCRT +/- VBT, respectively ($p < 0.0001$).

As reported in Table 2, after multivariate analysis FIGO stage and LN status remain significant independent risk factors for recurrence.

3. Cumulative incidence for LRR and DR according to FIGO stage, LN status and treatment.

Overall, recurrences were observed in 158 of the 501 women (31.5%). The mean time to recurrence was 20.72 months (3-122months). The 3-year cumulative incidences of LRR and DR in the whole population were 16.1% and 18.8%, respectively.

The 3-year cumulative incidence rates and their distribution according to FIGO stage, LN status and treatment modalities are reported in Figure 2 (A, B, C, D, E, F). Women with FIGO stage IIB CC had a higher 3-year cumulative incidence for both LRR and DR than women with FIGO stage IIA or IB2 CC (19.4% and 22.4% vs. 12.5% and 9.6%, and 7.4% and 13.4% respectively, $p < 0.01$). Node positive women and women with unknown LN status had a higher 3-year cumulative incidence of DR than node negative women (29.1% and 25.1% vs. 10.7%, $p < 0.001$). No significant difference in LRR was observed according to LN status. Women treated with CCRT +/- VBT had a higher 3-year cumulative incidence of DR than women treated with CCRT +/- VBT followed by radical HT or first radical HT +/- CCRT +/- VBT (27.8% (95% CI, 20.3 – 34.6), 13.9% (95% CI, 8.4 - 19) and 7.1 % (95% CI, 1 – 13.6), $p < 0.001$). No significant difference in LRR was observed according to treatment modalities.

DISCUSSION

This study reports specific site and time patterns of first recurrence for LACC according to the main prognostic factors (i.e. FIGO stage and LN status) and treatment modalities. Our results confirm that FIGO stage IIB, positive LNs as well as unknown LN status are major prognostic factors which affect the time to first recurrence and site as well as the HR for recurrence. Such results are of interest to adapt long-term clinical follow-up and as a starting point to improve therapeutic management of LACC.

LN status is known to be a major prognostic factor for all stages of CC [5].

However, the prognostic impact of surgical LN staging in the standard management of FIGO stage IB2 to IIB CC remains to be proved, as published results concerning the superiority of surgical over radiological staging are contradictory [25] [26]. For example, Lai et al. found no benefit of surgical staging in a randomized controlled trial comparing surgical to clinical staging. In contrast, Gold et al. found that surgical exclusion of positive para-aortic LNs in patients with LACC who received chemoradiation had a significant prognostic impact compared with radiographic exclusion. In our study, 60% of the women underwent radiological nodal staging and 72% surgical nodal staging, highlighting the considerable heterogeneity in practice within the same country. We found that women without optimal LN staging (i.e. with neither radiological nor surgical LN staging or with negative radiological staging and no surgical staging) had poorer 3-year RFS and OS, close to that of node positive women (61.8% vs. 58.4% and 81.7% vs. 78.7%). We found no significant difference in LRR according to LN status, but a significantly higher rate of DR among node positive women and women without optimal LN staging than among node negative women (29.1% and 25.1% vs. 10.7%)($p < 0.001$). For women with positive nodes, these results are consistent with literature [13]. Our results are of importance for women with unknown LN status, as surgical staging is currently considered a key procedure to plan the extent of radiation therapy (RT) strategy in France. Thus, we can hypothesize that some of the women without optimal LN staging were undertreated, explaining such a poor prognosis. In this setting, several authors have suggested performing systematic CCRT in all women with LACC, with a prophylactic extension of the radiation field to the para-aortic area regardless of the staging [26][27]. This latter option must be questioned in the light of our results, especially for women who did not undergo optimal nodal staging.

Although it is commonly accepted that the treatment of LACC is primarily based on CCRT [21], treatment guidelines are inconsistent [17][18][19][20][21] and the place of radical HT remains to be determined [28][29]. In our study, women treated with exclusive CCRT +/- VBT had poorer prognosis (with a lower 3-year RFS and a higher 3-year cumulative incidence of DR) than women who underwent either first radical HT +/- CCRT +/- VBT or CCRT +/- VBT followed by radical rather than completion HT. Nevertheless, these results should be interpreted in the light of the LN status as

French guidelines recommend exclusive CCRT +/- VBT for node positive women while completion HT is restricted to patients with negative lymph node status. Among the 222 women treated by exclusive CCRT +/- VBT, 97 (43.9%) had positive LNs and 47 (21.2%) had unknown LN status while among the 279 women who underwent other treatment modalities, 59 (21.1%) had positive LNs and 38 (13.6%) had unknown LN status. A meta-analysis studying the impact of adjuvant hysterectomy in patients with LACC treated with CCRT showed no improvement on OS, although hysterectomy seemed to reduce the risk of recurrence. Moreover, the author recommended that routine use of hysterectomy should be avoided due to significant morbidity in these patients [30]. Legge F et al., after analyzing the patterns of recurrence and their association with clinical outcome in LACC patients submitted to primary chemoradiation followed by radical surgery, found most of the recurrences were outside the irradiated field (57.3%). This is consistent with our results, as we observed 56.9% of DR. Among the parameters of recurrence associated with RFS they bring out, only secondary radical surgery retains an independent predictive role in reducing the risk of death ($p=0.037$) [31]. Hence, future randomized trials are needed to clearly define the place of first intention radical HT and of completion HT in the treatment of FIGO stage IB2 to IIB CC.

A better knowledge of stage IB2 to IIB patterns of recurrence is also needed to adapt follow-up modalities as, to date, post-treatment monitoring programmes differ widely from country to country [32]. Current international guidelines recommend physical examination every 3-6 months for 2 years, then every 6 months or annually. Imaging studies are recommended when clinically indicated, testing for serum tumour markers is optional, and the frequency of the pap-smear test is controversial [18][19][20][21]. However, clinical examination alone seems to be insufficient as several authors report the low performance of clinical monitoring to detect asymptomatic recurrences. This suggests a need of prospective cost-effectiveness studies as well as multicentre randomized clinical trials to compare various follow-up policies [8][33][34]. Furthermore, there is limited evidence of a significant impact on survival of systematic regular CT scans or MRI for asymptomatic patients [35][36] [37] [39] [40]. Even though PET-CT has been shown to be useful in the diagnosis of recurrent CC, especially in the case of unexplained elevation of

serum tumour markers without evidence of recurrent disease on conventional workup [41], the exact indications of this exam in the setting of CC recurrence are yet to be defined. However, no study to date has focused on the follow-up modalities for women at increased risk of recurrence. Our results suggest that closer monitoring including systematic imaging procedures would be of benefit to these patients, especially for those with positive or unknown LN status.

The strengths of our study lie in its multicentre nature and the large number of women included, but some limits deserve to be mentioned. First, we cannot exclude an inherent bias linked its retrospective multicenter nature. Indeed, the guidelines changed during the period of data collection and PET-CT was introduced which incurred modification to the management strategy over the years. In the following retrospective long-term study especially concerning the surgical strategy of pelvic lymphadenectomy is not homogeneous. However, all included women were treated in regional referral centres applying French/European guidelines after systematic multidisciplinary committee approval. Second, there are considerable differences in describing the recurrences from study to study which could also bias the comparison of reported rates. Based on previous reports, we opted to combine cervical, vaginal vault, pelvic LN, and pelvic wall recurrences as LRR, and organ metastasis, peritoneal carcinomatosis and extra-pelvic LN recurrences as DR [23]. Third, even if our results allowed us to describe patterns of recurrences in LACC, they should be carefully analysed beyond 3 years before drawing any firm conclusion. Finally, our results are consistent with previous report. Indeed, Rose et al. and Ferrandina et al. also suggested that clinical stage and LN status were significantly associated with clinical outcomes [15] [42].

CONCLUSION

Our results show that the patterns of recurrence in women with LACC differ widely in terms of time to recurrence and site, depending on the FIGO stage, LN status and treatment modalities. We hypothesize that characterizing and understanding the behaviour of these tumours may have profound implications on treatment options and follow-up modalities. Thus our results could give rise to improved monitoring programmes and should be taken into account when designing

future therapeutic approaches.

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TABLES

Table 1: Epidemiological and histological characteristics of the whole population.

Characteristics	Population % n=501
Age -median [range]	54 [23-91]
BMI kg/m ² -median [range]	37 [12 - 49]
Post-menopausal patients [%]	258 [51%]
Tumor size on MRI, mm – median [range]	45 [2-95]
Tumor histology	
-Squamous cell carcinoma [%]	426 [85%]
-Adenocarcinoma [%]	75 [15%]
Histological grade of the tumor	
-Well differentiated [%]	149 [30%]
-Moderately differentiated [%]	129 [26%]
-Poorly differentiated [%]	81 [16%]
-Unclassified [%]	142 [28%]
FIGO classification	
-IB2 [%]	83 [17%]
-IIA [%]	69 [14%]

-IIB [%]	349 [69%]
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LVSI status

-Positive [%]	67 [13%]
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-Negative [%]	163 [33%]
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-Unknown [%]	271 [54%]
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Treatments

-CCRT +/- VBT	222 [44%]
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-CCRT +/- VBT followed by radical HT	211 [42%]
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-First radical HT +/- CCRT +/- VBT	68 [14%]
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Radiological LN staging

- Radiological staging by PET-scan	300 [60%]
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- No radiological staging by PET-scan	201 [40%]
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Surgical LN staging

-PL or PAL or PL+PAL	359 [72%]
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-No surgical staging	142 [28%]
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Lymph node status

-Node positive women	161 [32%]
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-Node negative women	255 [51%]
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-Women with unknown LN status	85 [17%]
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Abbreviations: BMI, Body Mass Index; MRI, Magnetic Resonance Imaging; FIGO, International Federation of Gynaecology and Obstetrics; LVSI, Lymphovascular Space Involvement; CCRT, concomitant ; VBT, vaginal brachytherapy; HT, hysterectomy; LN,

lymph node; PET, Positron Emission Tomography; PL, pelvic lymphadenectomy; PAL, para-aortic lymphadenectomy.

Table 2: multivariate analysis for RFS and OS

	RFS			OS		
	Coefficient	95% IC	p	Coefficient	95% IC	p
FIGO classification						
IB2	= reference			= reference		
IIA	1,4	0,69 – 2,96	0,32	0,7	0,31 – 1,82	0,47
IIB	2,6	1,48- 4,60	<0,001	1,2	0,68 – 2,27	0,52
Lymph Node Status						
Node negative women	= reference			= reference		
Node positive women	1,4	0,90 – 2,20	0,12	1,8	1,00- 3,17	<0,05
Women with unknown LN status	2,2	1,49 – 3,21	<0,001	2,1	1,24- 3,56	<0,01
Treatments						
CCRT +/- VBT	= reference			= reference		
CCRT +/- VBT	0,7	0,47	<0,05	0,8	0,51- 0,35	0,35

followed by radical HT		- 0,97			1,28	
First radical HT +/- CCRT +/- VBT	0,7	0,38 - 1,19	0,18	0,3	0,11- 0,90	<0,05

Abbreviations: FIGO, International Federation of Gynaecology and Obstetrics; CCRT, concomitant ; VBT, vaginal brachytherapy; HT, hysterectomy; RFS, recurrence free survival; OS, overall survival.

FIGURES

Figure 1: Flow Chart of the study

Abbreviations: FIGO, International Federation of Gynaecology and Obstetrics.

Figure 2 A: Three-year cumulative incidence rates of loco regional recurrences according to FIGO stage

Figure 2 B: Three-year cumulative incidence rates of distant recurrences according to FIGO stage

Figure 2 C: Three-year cumulative incidence rates of loco regional recurrences according to LN status

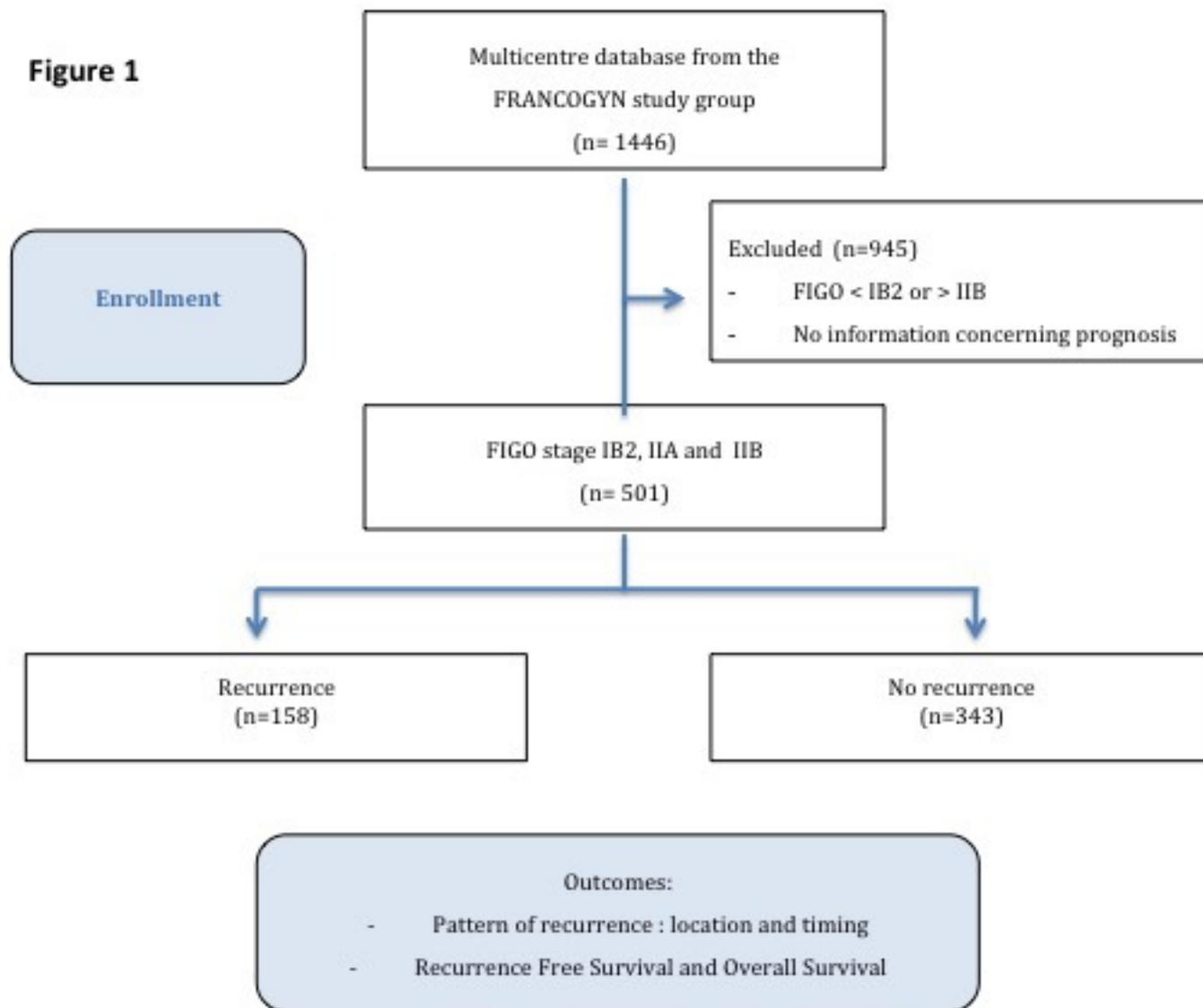
Figure 2 D: Three-year cumulative incidence rates of distant recurrences according to LN status

Figure 2 E: Three-year cumulative incidence rates of loco regional recurrences according to treatment modalities

Figure 2 F: Three-year cumulative incidence rates of distant recurrences according to treatment modalities

Abbreviations: FIGO, International Federation of Gynaecology and Obstetrics; LN, lymph node; N+, Node positive women; N-, Node negative women; CCRT, concomitant ; VBT, vaginal brachytherapy; HT, hysterectomy

Figure 1



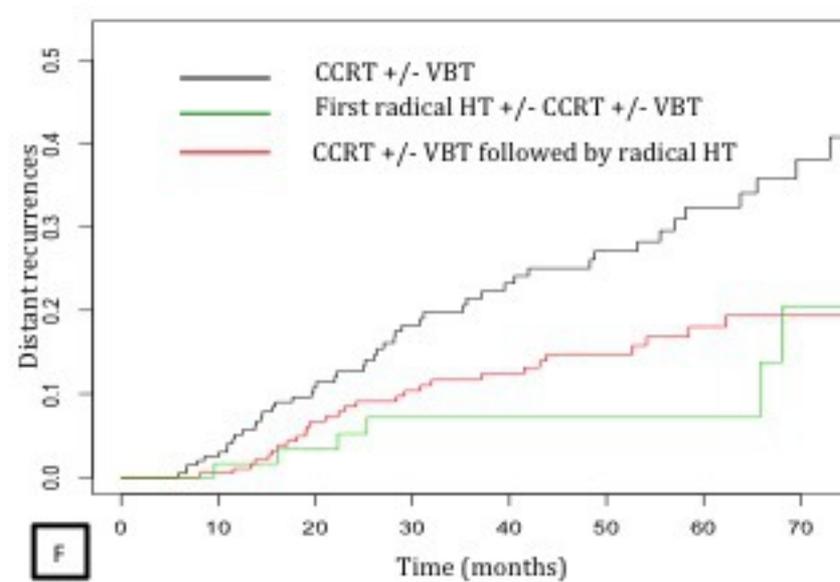
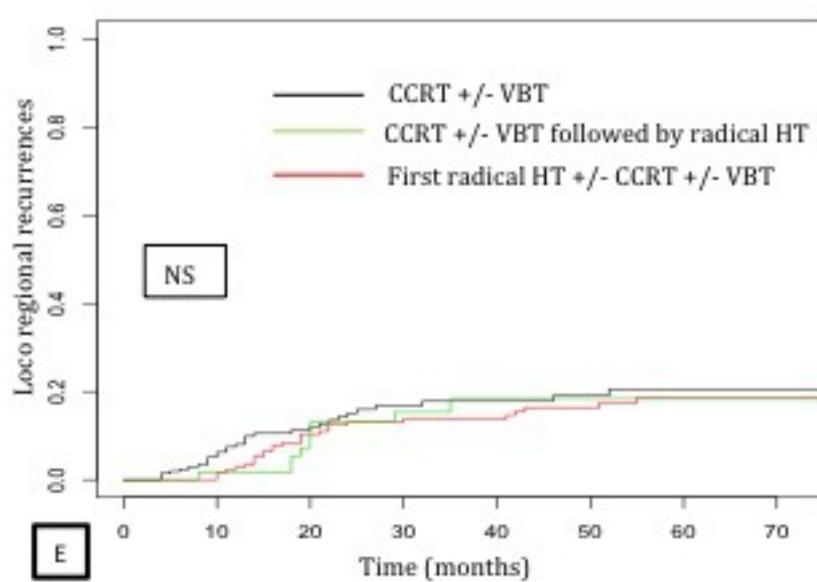
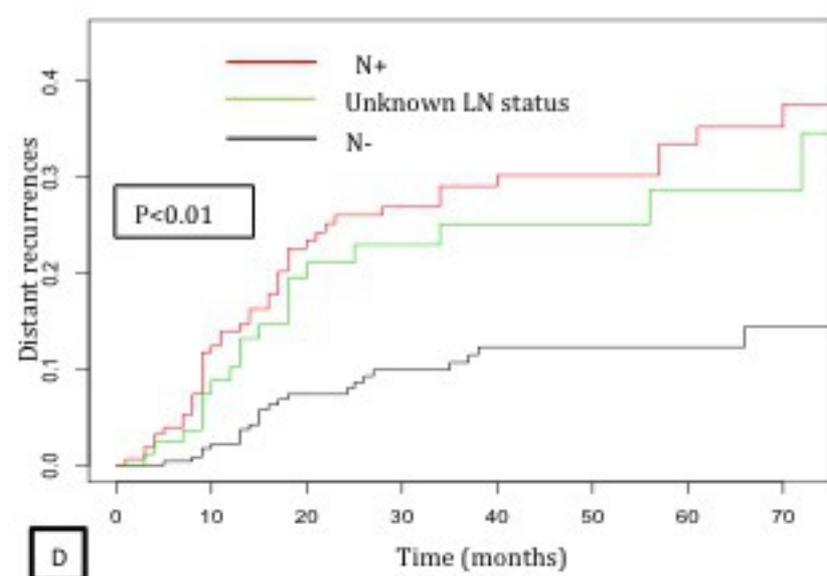
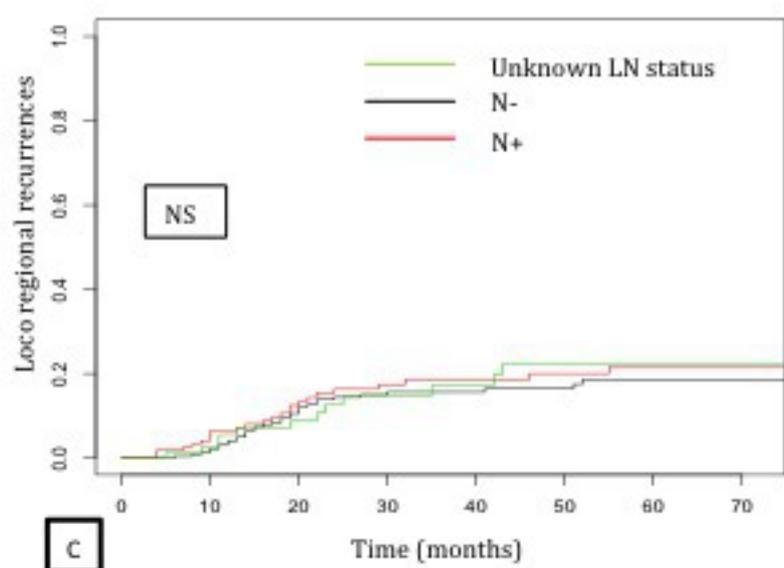
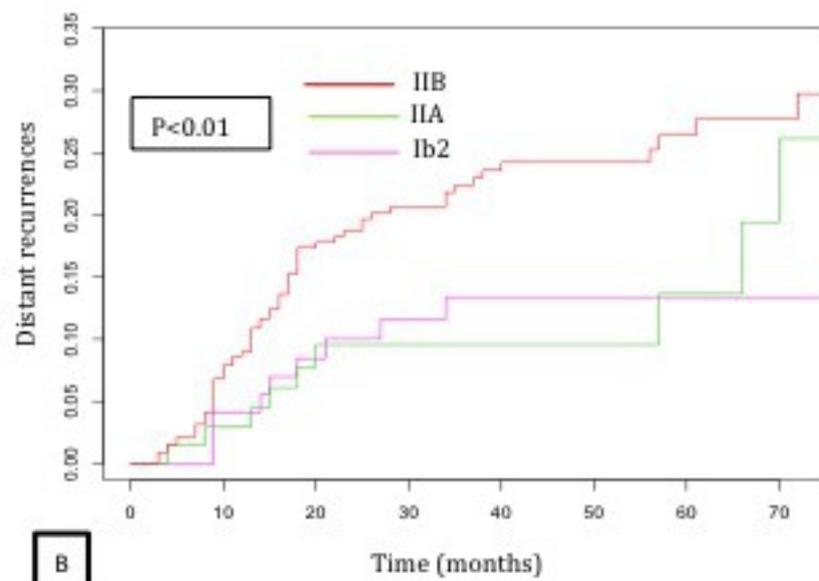
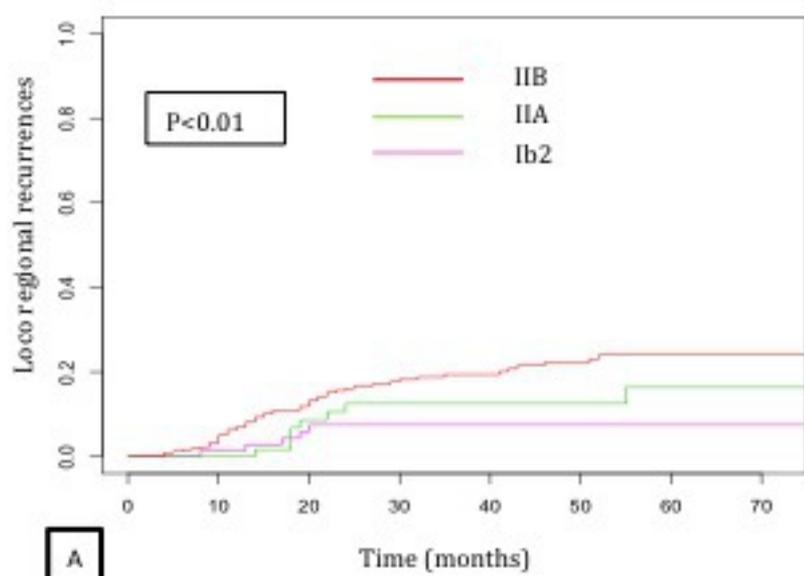


Figure 2