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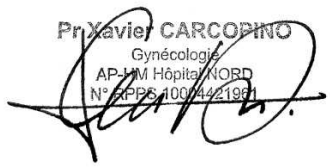
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PROGNOSIS IMPACT OF POSTTREATMENT PELVIC MRI IN PATIENTS TREATED FOR STAGE IB2-IIB CERVICAL CANCER WITH CHEMORADIATION THERAPY

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ABSTRACT

Objectives: To evaluate the performances of systematic posttreatment pelvic magnetic resonance imaging (PPMRI) in predicting prognosis of patients treated with chemoradiation therapy (CRT) for locally advanced cervical cancer (LACC).

Materials and methods: Multi-institutional data from 216 patients presenting FIGO IB2-IIB cervical cancer for which PPMRI was performed following CRT were retrospectively reviewed. Incomplete response was defined as the identification of persistent lesion on PPMRI. Primary endpoints were patients' 5-year recurrence free (RFS) and overall (OS) survivals. Secondary endpoint was the identification of residual histologic disease on hysterectomy specimens when completion surgery was performed.

Results: PPMRI identified an incomplete response in 102 (47.2%) cases. A 70% or more reduction in tumor size on PPMRI was identified as the best predictive cut-off for recurrence (37.7% sensitivity and 78.7% specificity) and death (50% sensitivity and 77.9% specificity) with significant impact on those risks (HRa: 0.42; 95%CI: 0.23-0.77 and HRa: 0.18; 95%CI: 0.06-0.50, respectively). Completion hysterectomy was performed in 117 (54.4%) cases, with histologic residual disease in 55 (47.4%). PPMRI demonstrated 74.5% sensitivity and 50.8% specificity in predicting residual disease. Although survival of patients with complete response at PPMRI was not impacted by completion hysterectomy, it significantly increased 5-year RFS and OS of those with incomplete response: 38.7% vs. 65.3% ($p<0.001$) and 63% vs. 82.9% ($p=0.038$), respectively.

Conclusion: A 70% or more reduction of in tumor size on PPMRI following CRT in patients with LACC is predictive of RFS and OS. PPMRI could help triaging patients who could benefit from completion hysterectomy.

248 words

Keywords: Pelvic MRI; cervical cancer; prognosis; survival; recurrence; chemoradiation

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INTRODUCTION

With 569 847 new cases and 311 365 deaths reported in 2018, cervical cancer represents a genuine worldwide health challenge and the fourth cancer among women [1]. It remains a dramatic disease since it affects young women with high mortality. Although surgery is commonly performed for the management of microinvasive cervical cancer and early FIGO stages, combined chemoradiation therapy (CRT) has been demonstrated as the treatment of choice for patients diagnosed with locally advanced disease [2]. Such combined therapy is now considered as a standard as it was proven to improve overall and progression-free survival and to reduce local and distant recurrences [3–5]. However, despite obvious efficacy of CRT, recurrences are unfortunately still common, occurring mostly within the first two years of follow-up [6,7]. Additionally to the FIGO staging, pelvic and para aortic nodal status and tumor dimensions have been identified as major initial prognosis factors [7,8]. Another key prognosis factor is the identification of posttreatment cervical residual disease. However, the proper evaluation of patients' response to CRT remains challenging as solely the histologic analysis of surgical specimen from patients undergoing completion hysterectomy can reliably asses this parameter.

Pelvic magnetic resonance imaging (MRI) has been shown to be the best imaging examination for the initial staging of patients diagnosed with cervical cancer [9,10]. It provides precise characterization of the disease with the ability to determine the exact tumor dimensions and its local spread with possible involvement of nearby organs such as parameter and ureters, vagina, bladder and rectum [11,12]. Pelvic MRI is also commonly performed for the evaluation of tumor's response following CRT. However, its performances in this precise indication remains questionable. Although previous studies have shown its ability to predict patients' outcome and survival, there is a lack of evidence regarding the ability of

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posttreatment pelvic magnetic resonance imaging (PPMRI) to predict histological cervical residual disease. Thus, only few studies have correlated PPMRI results with the histological analysis of hysterectomy specimens in patients who had undergone completion surgery [13–17]. Additionally, these retrospective studies suffer from limited power with little number of patients included, ranging from 41 to 159 only [13–17].

The possibility to identify post-RCT residual disease represents a genuine challenge as it could allow for tailored surgery in selected patients. To date, the benefit of completion surgery following CRT in locally advanced cervical cancer remains widely debated as it has not shown any improvement in patients' survival and is associated with genuine morbidity [18,19]. Previous data however suggest that completion surgery could improve local control in patients with partial pathological response [20–23]. Finally, completion surgery allows for the identification of patients with incomplete histologic response and higher risk of recurrence that should be submitted to adjuvant therapies [24,25].

The aim of this study was to evaluate the performances of systematic PPMRI in predicting prognosis of patients treated with CRT for locally advanced cervical cancer. We also evaluated the ability of PPMRI in predicting cervical histologic residual disease.

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METHODS

Study population

Data from all patients treated for stage IB2 to IIB cervical cancer by chemoradiation therapy (CRT) in 9 French institutions from April 1996 to May 2016, and for which a systematic PPMRI was performed were retrospectively analyzed. Patients' initial characteristics, therapeutic management and follow up were retrieved from medical charts. Primary endpoint was patients' survival. Secondary endpoint was the histologic identification of residual

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disease on hysterectomy specimens when completion surgery was performed. Informed consent was obtained from all participants. The study protocol received ethical approval from the Institutional Review Board of the Collège National des Gynécologues et Obstétriciens Français (CEROG 2016-GYN-0502).

Patients' pretreatment evaluation included physical examination, cervical biopsy and/or diagnostic conization completed with PET/CT and pelvic MRI. The FIGO staging was established based on the results of physical examination combined with pelvic MRI according to the 2009 FIGO classification [26]. The retrospective nature of the study did not allow for the use of the revised 2019 FIGO classification for cervical cancer [9]. The tumor maximal size was determined on pre-therapeutic pelvic MRI and corresponded to the largest dimension of the tumor. When indicated, initial surgical nodal staging including pelvic and/or para-aortic laparoscopic lymphadenectomy was performed. The patients' lymph node status was therefore classified according to three categories depending of the findings of PET/CT and/or surgical nodal staging when performed. Patients were considered as node positive (N+) when nodal involvement was identified on the pre-therapeutic PET/CT and/or by the surgical nodal staging. Patients were considered as node negative (N-) only after negative surgical nodal staging regardless of the results of the imaging. Finally, patients with negative pre-therapeutic PET/CT but who had not undergone surgical nodal staging or who had had neither pre-treatment PET/CT nor surgical nodal staging were considered as unknown (Nx).

Treatment modalities were established by a local multidisciplinary committee according to the French national guidelines. Although all patients did receive CRT, they could either have received additional vaginal brachytherapy (VBT) and/or completion hysterectomy. Thus, the following four treatment strategies were recorded: exclusive CRT; CRT followed by VBT; CRT followed by completion surgery; CRT followed by VBT and completion surgery. The decision whether to perform completion surgery (i.e. hysterectomy) solely depended on the

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practice of each participating institution, as some systematically did perform completion hysterectomy whilst others did not, and some considered completion surgery only in cases with documented residual disease following CRT.

PPMRI was performed within a 3 month delay following the completion of CRT or after additional VBT when performed. An incomplete response at PPMRI was defined as the identification of persistent cervical and/or nodal lesion. Cervical and nodal incomplete response were defined as a persistent cervical lesion and persistent nodal lesion, respectively. Systematic follow-up included visits every 3 months during the first 2 years, every 6 months during the 3 following years and annually after 5 years. Follow-up included physical examination while imaging including PET/CT and/or pelvic MRI was performed in case of suspected recurrence.

Statistical analysis:

5-year recurrence-free (RFS) and overall (OS) survivals were estimated. RFS and OS were defined as the duration from the date of primary treatment to recurrence and death, respectively. In case no event was reported, they were censored at the date of last follow-up. RFS and OS were estimated for the following variables: age, BMI, parity, menopausal status, FIGO stage, histology, tumor size, nodal status, treatment modality and results of PPMRI. Identification of optimal cut-off in the reduction of cervical tumour's dimension as predictive factor for RFS and OS was performed using the receiver operator characteristics (ROC) curve analysis. Multivariate analysis was conducted including variables that were identified as significant RFS and OS prognostic factors in our study and in literature.

Results of PPMRI were compared to the presence or absence of histologic residual disease on hysterectomy specimens when completion surgery had been performed. PPMRI diagnostic performances for histologic residual disease were evaluated using sensitivity and specificity.

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Patient characteristics were reported using counts (%) for categorical variables and mean ± standard deviation for continuous variables. Chi2 statistics were used to compare indicators of diagnostic performances. 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. Hazard Ratios (HR) in univariate analysis and adjusted Hazard ratios (HRa) in multivariate analysis were estimated using Cox model. A p value of <0.05 was considered statistically significant. Statistical analysis was performed using IBM SPSS Statistics version 20.0 (IBM Inc., New York, NY, USA).

RESULTS

Patients

A total of 216 patients with stage IB2 to IIB cervical cancer who received CRT and for which a systematic posttreatment pelvic MRI had been performed were included in the study. Patients' characteristics are reported in Table 1. An incomplete response was identified on PPMRI in 102 (47.2%) cases. Completion surgery was performed in 117 (54.4%) cases, with histologic residual disease identified in 55 (47.4%) cases, mean size of histologic residual disease was 6 mm (±11.0). Median duration of follow-up was 39.2 months (95%CI: 32.4-46). The 5-year RFS and OS were respectively 60% (95%CI: 53-69) and 82% (95%CI: 75-90).

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Age, mean (± SD) (years)	52.3 (± 12.8)
BMI, mean (± SD) (kg/ m²)	25.6 (± 6.0)
Parity, mean (± SD)	2.7 (± 2.3)
Menopaused	101 (47)
FIGO stage	
IB2	36 (16.7)
IIA	27 (12.5)
IIB	153 (70.8)
Histology	
Squamous	182 (84.3)
Other histology ‡	34(15.7)
Tumor size (MRI) (mm)	
Mean (± SD)	46.8 (± 14.2)
≥ 40	147 (73.1)
Nodal status*£	
N-	106 (49.1)
N+	50 (23.1)
Nx	60 (27.8)
Treatment modality	
Exclusive CT/RT	16 (7.4)
CRT + VBT	80 (37)
CRT + Completion hysterectomy	18 (8.3)
CRT + VBT + Completion hysterectomy	102 (47.2)
PPMRI	
Incomplete cervical response	99 (45.8)
Incomplete nodal response	11 (6)
Incomplete cervical and/or nodal response	102 (47.2)
Completion hysterectomy	117 (54.4)
Cervical residual disease	55 (47.4)
Residual tumor size (± SD) (mm)	6.0 (± 11.1)

Table 1. Patients' characteristics (n=216)
Values are expressed as n (%), unless otherwise indicated

‡ Adenocarcinomas (n=27) and other histology type (n=7)
*Defied as follows:
N+ (N+ on PET/CT or N- on PET/CT but N+ after surgical nodal staging or N+ after surgical nodal staging)
N- (negative surgical nodal staging)
Nx (no PET/CT and no surgical nodal staging or negative PET/CT with no surgical nodal staging)
£ Nodal surgical pretherapeutic staging was performed in 145 (67.1%) patients

SD: Standard deviation; BMI: Body Mass Index; CRT: chemoradiation therapy; PPMRI: posttreatment pelvic MRI; VBT: vaginal brachytherapy

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Predictive factors for recurrence

The 5-year RFS for patients with an incomplete response at PPMRI was 58.4% vs 61.9% for patients with complete metabolic response (p=0.55) (Figure 1A). Although the identification of incomplete response on PPMRI was not found to significantly impact the RFS, the identification of histologic cervical residual disease in women who had undergone completion hysterectomy was significantly associated with an increased risk of recurrence (HR: 3.40; 95% CI: 1.6-7.4; p=0.002). Other factor identified to significantly impact the risk of recurrence was nodal status, with an increased risk of recurrence of Nx and N+ patients when compared to N- (HRa: 2.25; 95%CI: 1.19-4.28; p=0.01 and HRa: 2.340; 95%CI: 1.21-4.76; p=0.01, respectively). Compared to patients who were solely treated with CRT, only patients who received additional VBT followed by completion hysterectomy demonstrated a reduction in the risk of recurrence (HRa: 0.33; 95%CI: 0.14-0.81; p=0.02) (Table 2). Considering the reduction in tumor's size observed when comparing pre and PPMRI, best prediction in patients' RFS was found for a threshold of 70% reduction or more (37.7% sensitivity and 78.7% specificity). Thus, compared to others, a reduction ≥70% in tumor's size was found to significantly reduce the risk of recurrence (HRa: 0.42; 95%CI: 0.23-0.77; p=0.005) (Table 2)

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	HR (95 % CI)	p	HRa (95 % CI)	p
Age (for each extra year)	1.00 (0.98-1.20)	0.89	-	-
BMI (for 1 kg/m² extra)	0.98 (0.94-1.20)	0.35	-	-
Parity (for 1 extra birth)	1.06 (0.96-1.16)	0.26	-	-
Menopaused	0.80 (0.50-1.30)	0.45	-	-
FIGO stage*		0.08		0.12
IB2	1 (ref.)	-	1 (ref.)	-
IIA	1.40 (0.50-4.00)	0.52	1.57 (0.45-5.53)	0.48
IIB	2.30 (1.00-5.00)	0.04	2.49 (0.98-6.34)	0.06
Squamous carcinoma **	1.00 (0.50-2.00)	0.93	1.03 (0.50-2.12)	0.95
Tumor size (for each extra mm)	1.02 (1.00-1.04)	0.01	1.02 (1.00-1.04)	0.09
Nodal status †		<0.001		0.02
N-	1 (ref.)	-	1 (ref.)	-
Nx	2.20 (1.20-3.90)	0.01	2.40 (1.21-4.76)	0.01
N+	2.90 (1.60-5.20)	<0.001	2.25 (1.19-4.28)	0.01
Treatment modality ‡		0.03		0.01
CRT	1 (ref)		1 (ref)	-
CRT + VBT	0.60 (0.20-1.30)	0.18	0.83 (0.34-2.05)	0.69
CRT + Completion hysterectomy	0.60 (0.20-1.80)	0.37	0.45 (0.14-1.45)	0.18
CRT + VBT + Completion hysterectomy	0.30 (0.10-0.80)	0.009	0.33 (0.14-0.81)	0.02
Reduction ≥70% in tumor size on PPMRI results	0.46 (0.27-0.78)	0.004	0.42 (0.23-0.77)	0.005
Incomplete response on PPMRI	1.20 (0.70-1.90)	0.55	-	-

Table 2. Identification of prognostic factors of recurrence.

HR: Hazard Ratio; HRa: Adjusted Hazard; BMI: Body Mass Index; CRT: chemoradiation therapy; PPMRI: posttreatment pelvic MRI.

* Compared to IB2 stage (reference)
** Compared to other histology type
† Compared to N- patients (reference)
‡ Compared to patients treated with exclusive CRT (reference)

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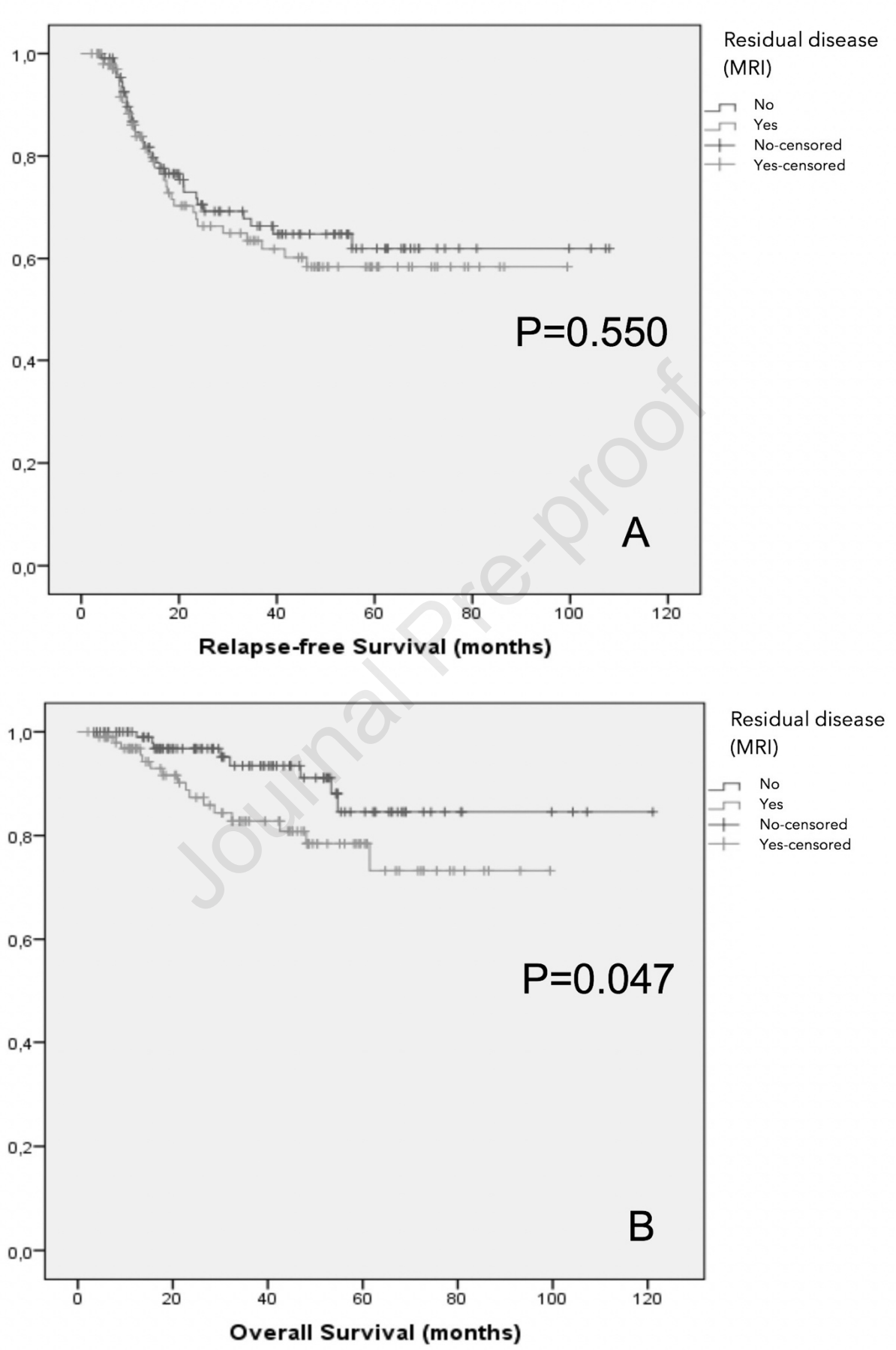


Figure 1. Recurrence-free (A) and overall (B) survivals based on posttreatment PMRI results

Predictive factors for death

The 5-year OS for patients with an incomplete response at PPMRI was 78.4% vs. 84.6% for patients with a complete response (p=0.047) (Figure 1B). An incomplete response at PPMRI was not identified as a significant risk factor of death (Table 3). The best prediction in patients' OS was found for the same threshold of 70% reduction or more in tumor's size with a 50% sensitivity and 77.9% specificity. Thus, a reduction ≥70% in tumor's size was the only factor identified to significantly prevent the risk of death (HRa: 0.18; 95%CI: 0.06-0.50; p=0.001) (Table 3).

	HR (95 % CI)	p	HRa (95 % CI)	p
Age (for each extra year)	0.99 (0.96-1.03)	0.63	-	-
BMI (for 1 kg/m² extra)	0.98 (0.91-1.06)	0.60	-	-
Parity (for 1 extra birth)	1.13 (0.99-1.29)	0.07	-	-
Menopaused	0.70 (0.30-1.50)	0.31	-	-
FIGO stage *		0.24		0.19
IB2	1 (ref.)	-	1 (ref.)	-
IIA	0.40 (0.10-1.70)	0.19	0.30 (0.03-2.58)	0.27
IIB	0.50 (0.20-1.20)	0.14	0.41 (0.15-1.14)	0.09
Squamous carcinoma **	2.30 (0.50-9.60)	0.27	6.37 (0.80-50.8)	0.08
Tumor size (for each extra mm)	1.03 (1.00-1.06)	0.07	1.03 (0.99-1.07)	0.11
Nodal status †		0.11		0.50
N-	1 (ref.)	-	1 (ref.)	-
Nx	1.50 (0.60-4.20)	0.42	1.98 (0.61-6.39)	0.25
N+	2.70 (1.10-7.10)	0.04	1.60 (0.52-4.92)	0.41
Treatment modality ‡		0.03		0.36
CRT	1 (ref.)	-	1 (ref.)	-
CRT + VBT	0.30 (0.10-1.10)	0.08	0.47 (0.11-2.08)	0.32
CRT + Completion hysterectomy	0.90 (0.20-3.90)	0.92	0.46 (0.09-2.41)	0.36
CRT + VBT + Completion hysterectomy	0.20 (0.10-0.90)	0.03	0.27 (0.06-1.16)	0.08
Reduction ≥70% in tumor size on PPMRI results	0.27 (0.12-0.62)	0.002	0.18 (0.06-0.50)	0.001
Incomplete response on PPMRI	2.30 (1.00-5.40)	0.05	-	-

Table 3. Identification of prognostic factors of death.

HR: Hazard Ratio; HRa: Adjusted Hazard; BMI: Body Mass Index; CRT: chemoradiation therapy; PPMRI: posttreatment pelvic MRI.

* Compared to IB2 stage (reference)
** Compared to other histology types
† Compared to N- patients (reference)
‡ Compared to patients treated with exclusive CRT (reference)

Diagnostic performances of PPMRI in predicting cervical residual disease

When only considering the 117 patients who had undergone completion surgery, MRI sensitivity and specificity in predicting histologic cervical residual disease was 75% (95% CI: 63-86) and 51% (95%CI: 38-63), respectively (Table 4). MRI diagnostic performances were not impacted by histology, with comparable results in patients with squamous cervical cancers and others. Only the size of the histologic cervical residue was found to impact the diagnostic performances of PPMRI. Diagnostic performances were better when the size of histologic residual disease was ≥10 mm, with 89.7 % sensitivity vs. 50.0% for smaller residues (p=0.005).

		Cervical residual disease on hysterectomy specimen		
		No	**Yes**	**Total**
Incomplete response on posttreatment pelvic MRI	**No**	31 (50.8)	14 (25.5)	45 (38.8)
	Yes	30 (49.2)	41 (74.5)	71 (61.2)
	Total	61	55	116

Table 4. Diagnostic performances of posttreatment pelvic MRI in predicting documented histologic cervical residual disease in completion hysterectomy specimens after CRT.

All values are expressed as n (%)

Ability of PPMRI to select patients who could benefit from completion surgery

While survival of patients found to have complete response at PPMRI was not impacted by the practice of completion surgery, significant increase in RFS and OS was observed in patients who had undergone completion surgery following the diagnosis of incomplete response at posttreatment PMRI. Thus, among these patients, 5-year RFS was of 65.3% when completion surgery was performed vs 38.7% when not performed (p<0.001); 5-years OS was 82.9% vs 63% (p=0.038), respectively (Figure 2).

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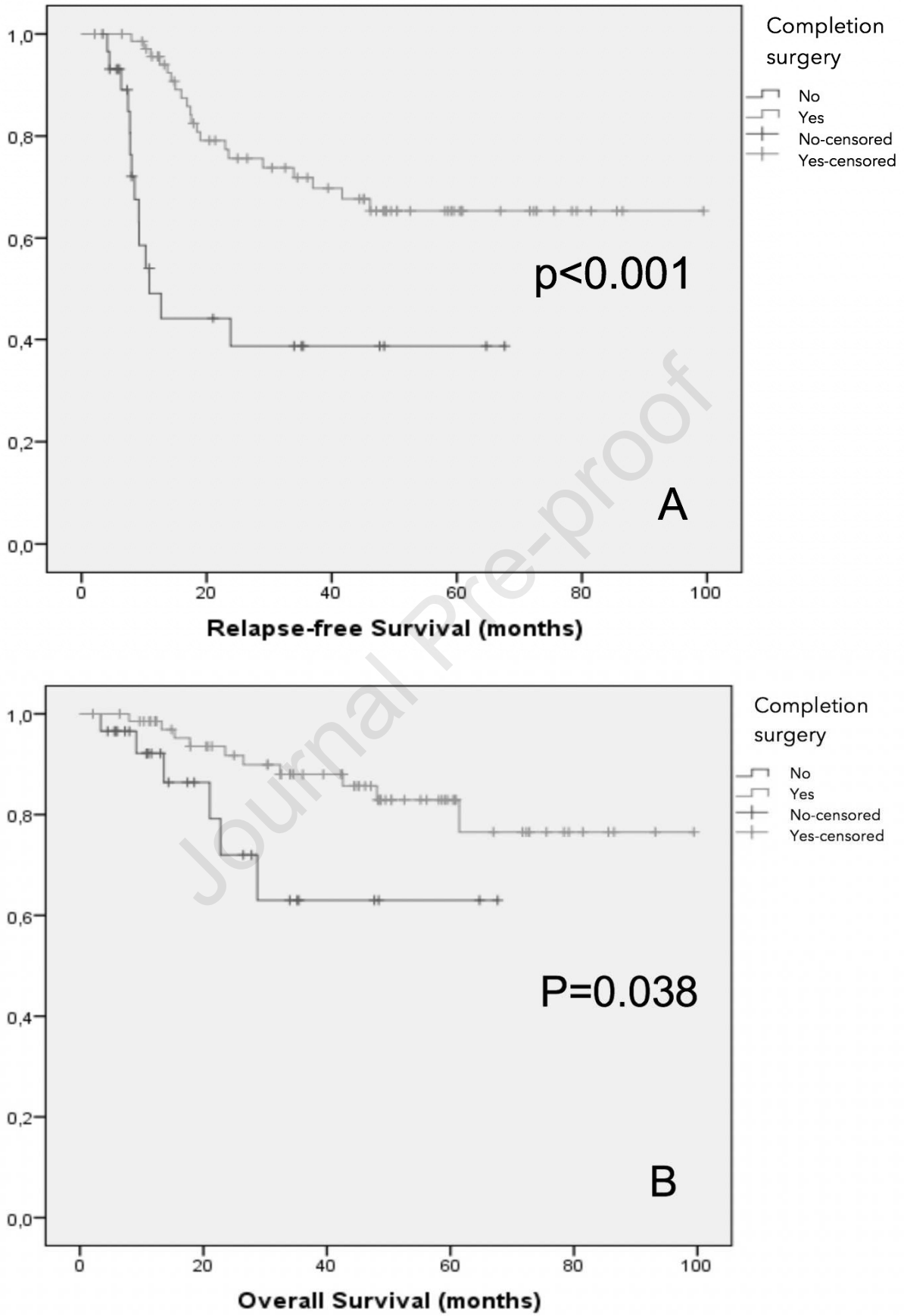


Figure 2. Recurrence-free (A) and overall (B) survivals in cases of incomplete response on posttreatment PMRI depending on whether completion surgery was performed or not.

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DISCUSSION

This study shows systematic PPMRI to be predictive of the prognosis of patients treated with CRT for locally advanced cervical cancer. Best prediction was achieved for patients showing a 70% or more reduction in the dimensions of the lesion. Additionally, PPMRI demonstrated genuine abilities in predicting cervical histologic residual disease, especially when histologic residual disease was10 mm or more.

Our results suggest PPMRI to be a suitable tool for triaging patients that could benefit from completion surgery. Thus, although patients with PPMRI complete response did not show any benefit in undergoing completion surgery, it significantly improved both RFS and OS in patients with incomplete response. The debate about whether or not completion surgery should be performed following CRT has been ongoing for decades. At this stage, available published data reported no obvious benefit of completion surgery but genuine morbidity [18,20,20,23]. Our results are consistent with this statement as the sole practice of completion surgery did not demonstrate any improvement in patients risk of recurrence, nor death (tables 2 and 3). Previous data suggest that completion surgery could be beneficial in selected patients with documented post RCT residual cervical disease and of no therapeutic impact in patients with complete response following CRT [19,27]. Such approach is consistent with our findings. Although our results suggest completion surgery does not improve outcomes of patients that achieved complete response at PPMRI, this option seems genuinely worthwhile in selected cases showing incomplete response and should therefore be considered.

With a 70% threshold in the reduction of the initial dimension of the lesion identified as the best predictor for outcome, our findings raise concerns regarding the possibility of time-related ongoing effects of CRT. Indeed, as PPMRI were performed within a 3 month delay following the completion of CRT, it is possible that patients had achieved complete histologic

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response after PPMRI had been performed. This could at least partially explain why, among 71 patients found with incomplete response on PPMRI, 30 (42.3%) finally showed no histologic residue on hysterectomy specimen (Table 4). This hypothesis is supported by previous published data showing that early MRI evaluation of cervical cancer's response to CRT is less reliable if performed too early, with increased risk of false positive results when performed before a 3 months delay [13,17]. The delay in which imaging exams should be performed following CRT remains widely discussed. To date, there is still no consensus about the optimal time delay when PPMRI should be performed following RCT and practice was shown to vary from 3 weeks to 6 months after completion of CRT across Europe [11]. As morbidity of completion surgery directly depends on the delay following CRT and increases with time, it is however crucial that imaging should be performed early enough to enable surgery to be considered and organized. Unfortunately, the exact date when PPRMI had been performed were not properly documented in a majority of patients' medical charts, therefore not allowing for a precise estimation of the impact of delay following CRT on the prediction of histologic residual disease. We believe this point to be of major importance when interpreting our results and considering exporting those to clinical routine practice as our results cannot be extrapolated to PPMRI performed after the delay of 3 months reported here.

Additionally to the possible time related delay in CRT effect, our results suggest performance of PPMRI to directly depend on the dimensions of cervical residual disease. Thus, only histologic residue of 10 mm or more are likely to be properly identified by PPMRI. This finding provides additional information on the possible reasons and risks of false negative results of PPMRI. Due to the retrospective nature of our analysis, we were not able to provide reliable information regarding MRI types and characteristics, precise MRI sequences used and imaging evaluation. We acknowledge this point to represent a major limitation that should be carefully considered when interpreting our results. It is thus unfortunate that we were not able

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to identify the impact of diffusion-weighted PPMRI on its performance and to assess values of changes in cervical tumour's apparent diffusion coefficient as this data was not systematically recorded. Because it showed high value for the evaluation of tumour viability and prediction of treatment efficacy, this technique is currently routinely used in all our participating centres for PPMRI evaluation [28–32]. With our retrospective analysis running for a 20 year period, only most recent PPMRI examinations from our cohort were likely to have used diffusion-weighted technique. Although we were not able to specifically assess the benefit of this technique, we did not observe any significant change of PPMRI prognosis value over time when assessing the impact of time on patients' outcome.

CONCLUSIONS

Systematic PPMRI is predictive of the prognosis of patients treated with CRT for locally advanced cervical cancer. Best prediction in patients' prognosis was achieved when a reduction of 70% or more in the dimensions of the lesion was observed. Finally, PPMRI demonstrated high sensitivity in predicting cervical histologic residual disease, with optimal prediction achieved for histologic residual disease of at least 10 mm. It therefore could help for the identification of patients with histologic residual disease and therefore for the triage of patients that could benefit from completion surgery. Thus, in patients with IB2-IIB cervical cancer, although the identification of complete response at PPRMI performed within 3 months after CRT does not support the practice of completion surgery, it should be considered in patients with incomplete response.

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