Has adherence to treatment guidelines for mid/low rectal cancer affected the management of patients? A monocentric study of 604 consecutive patients

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L'application des recommandations pour la pratique clinique a-t-elle eu un impact sur la prise en charge des cancers du rectum sous-péritonéal ? A propos d'une expérience mono-centrique chez 604 patients

Has adherence to treatment guidelines for middle and low rectal cancer affected the management of patients? A monocentric study of 604 consecutive patients

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INTRODUCTION

Over the last three decades, management of subperitoneal rectal cancer has been revolutionized medically [advances in imagery such as endorectal ultra-sonography, magnetic resonance imagery (IRM); arrival of radiation therapy followed by neo-adjuvant chemoradiotherapy)] (1–3) and surgically [validation of total mesorectal excision, extension of sphincter-sparing surgery with a distal margin lower than 2cm, development of intersphincteric resection)], (4–7), thereby substantially improving 5-year cancer survival rates (overall survival > 50% and local recurrence < 10%)(8).

One sign of these deep-seated changes was the 2006 publication, under the aegis of the French national health authority (HAS), of a series of recommendations for clinical practice (RCP) on choices for rectal cancer treatment (9). These guidelines provide indications of the respective roles of the different preoperative explorations necessary for locoregional staging and neoadjuvant treatments (10-11). In addition, quality indicators for surgical removal have been defined, and recording of anatomopathological examination of resection specimens (quality of mesorectum, lateral circumferential margin and distal margin) has been standardized. Assessment of functional sequelae and quality of life has likewise been recommended (12,13). Publication and distribution of these documents was aimed at achieving nationwide standardized management of superficial and invasive rectal cancer. Ten years later, the RCPs were updated under the auspices of the *Groupe de Recherche Chirurgicale sur le Cancer du Rectum* (GRECCAR) and the *Société Nationale Française de coloproctologie* (SNCP), and the their level of evidence was substantially improved (14). Due to its complexity, treatment of subperitoneal rectal cancer calls for multidisciplinary tumor boards, the purpose of which is to propose recommendations in line with the situation of each individual patient. While the impact of existing benchmarks on harmonization of clinical practices and patient prognosis is no longer a matter of controversy (15,16), evaluation of the literature shows inconsistently complete adherence to the guidelines, including those pertaining to rectal cancer (17–19).

The primary objective of this study was to assess the impact of adherence to the RCP guidelines in our center on the management and overall and disease-free survival of patients having undergone curative surgical excision of subperitoneal rectal tumors. The secondary objective was to assess the impact of RCP application on postoperative and oncological outcomes.

PATIENTS AND METHODS

Patients

All consecutive patients suffering from subperitoneal rectal cancer and having undergone surgery between 1 January 1995 and 31 December 2017 were included in our study. Initial data were derived from preparation of a thesis involving retrospective collection of items from January 1995 through December 2005 and prospective collection from January 2006. The data base was declared to the local ethics committee (CNIL declaration number: 2204611 v 0) authorizing analysis of the different data. Given the date of RCP publication (2006), patients were divided into two groups: Gr 1 (≤ 2006) et Gr 2 (>2006). Were included in the study: all patients having undergone curative surgical excision of a subperitoneal (≤10 cm from the anal margin) rectal adenocarcinoma. Were not included: patients with high rectal cancer (treated as colon cancer) and those having undergone narrow local excision of superficial rectal cancer (10) (Figure 1). Were also excluded: patients having undergone palliative treatment for rectal cancer (i.e. unresectable rectal cancer and/or patients with unresectable hepatic metastases or peritoneal carcinoma), patients with chronic inflammatory bowel disease or familial adenomatous polyposis, as well as those with non-adenocarcinomic rectal cancer.

Data collection

Patient data corresponded to the RCP methodology document entitled "*Choix des thérapeutiques du cancer du rectum*"(9). Following presentation of the thesis by Dr J. Chautard and publication of the RCPs in 2006, implementation of the guidelines was multidisciplinary and took place in conjunction with the François Baclesse center (indications for neo-adjuvant treatment) (MPG) and with the radiology (AF), gastroenterology (BD) surgical (GL followed by AA) and anatomopathological (CB) units. Were compiled:

the characteristics of each patient (i.e., age, gender, body mass index, American Society of Anesthesiologists (AS) score, medical comorbidities) and of each rectal tumor (localization, distance lower pole-anal margin); modalities of the locoregional and distant staging (thoracic-abdominal-pelvic scan, endorectal ultrasound and/or pelvic magnetic resonance imagery) determining the pre-therapeutic stage; presentation or non-presentation in a multidisciplinary tumor board and neo-adjuvant treatment modalities (radiotherapy alone or chemoradiotherapy for tumors classified as T3-T4 and/or N+) (9). Perioperative data included surgical approach (laparotomy, laparoscopy, laparoscopic conversion), type de resection (partial mesorectal excision up to 5 cm below the lower pole tumor or total mesorectal excision), the operation performed (abdomino-perineal amputation, low Hartmann's procedure, sphincter-sparing anterior resection), the type of anastomosis (low colorectal, colo-supra-anal, colo-anal with or without mechanical or manual sphincter resection), production or non-production of an ileo-anal pouch or a terminal-lateral anastomosis, production or non-production of a temporary stoma, operation duration and possible need for blood transfusion. Rectal cancer management was "seniorized" in late 2008 with the arrival of a new colorectal surgeon (AA), leading to the creation in 2010 of a unit dedicated to colorectal surgery. As of late 2008, colorectal and, more particularly, carcinological surgical interventions were consequently supervised by two senior surgeons (GL and AA). In addition, perioperative treatment of rectal cancer has benefited not only from development as early as 2008 of the laparoscopic approach, but also from the application of common SFCD-SFAR RCPs on early rehabilitation. One of the surgeons in the unit (AA) was a member of the relevant task forces (20).

In cases of mid-rectal cancer in an elderly subject and/or in the event of poor sphincter tone, it was up to the surgeon to decide on performing either Hartmann's procedure or abdominoperineal amputation. Analysis of the anatomopathological report permitted evaluation and/or measurement of its overall exhaustiveness and, more specifically, of resection completeness (R0), the circumferential and distal margins, the number of ganglions found on the piece, and the presence of vascular boluses and/or perineural sheath. As regards tumor staging, we applied the 4-stage UICC 2009 classification (7th edition) on the basis of the preoperative assessment (cTNM or usTNM), and data from preoperative local and

distant staging as well as operative data and the results of anatomopathological examination of the resected specimen (pTNM) (21)

Mortality and postoperative complications were listed up until D+90 and categorized according to the Dindo-Clavien classification (22). They comprised prevalence of medical and surgical complications, "redo" operations and length of hospital stay. Surgical site infections (SSI) included peritonitis, anastomotic fistulas, pelvic abscesses and perineal disunions.

In order to update follow-up, patients were contacted by telephone or seen in consultation by 1 August 2018 (end of study) and their status was determined: alive or not, alive with or without recurrence. Survival was defined as the time difference between date of the event of interest (death or recurrence) and date of the cancer diagnosis. These items enabled us to calculate overall survival, disease-free survival and prevalence of local and/or distant recurrence..

Evaluation criteria

For each group, the primary endpoints of the study were: analysis of the different pretherapeutic explorations (scanner, endorectal ultrasound and magnetic resonance imagery), frequency of presentation in multidisciplinary tumor board, prevalence of neoadjuvant treatment in accordance with the pretherapeutic stage, assessment of the quality of surgical resection (extrafascial excision of the mesorectum, sphincter conservation, completeness of surgical removal as viewed during the anatomopathological examination, and measurement of the different margins). For each group, the secondary endpoints of the study were: morbi-mortality prevalence at 90 days, long-term oncological outcomes, and survival analysis.

Statistical analysis

Qualitative and quantitative variables were compared using the Chi^2 or Student's tests respectively (Mann-Whitney and Fisher's exact test when the conditions for validity of the Student's and Chi^2 tests were not verified). Identification of risk factors for severe complications (>Dindo 2) was carried out using a model of univariate and multivariate logistic regression. The variables associated with the

variable to be explained in univariate analysis or those with clinical relevance were introduced in the multivariate model. In order to evaluate the effect of each parameter on survival, univariate and multivariate Cox analysis was carried out. Survival was analyzed using the Kaplan-Meier curve. Statistical difference was considered significant at $p<0.05$. All statistical analyses were performed on SAS 9.4 software (SAS Institute, Cary, NC, USA).

RESULTS

Patients

From 1995 to 2017, 604 consecutive patients (Gr1, n=266 and Gr2, n=338) underwent curative surgical excision for subperitoneal rectal cancer (Figure 1). The groups were comparable in terms of age, comorbidities and ASA score (Table 1). On the other hand, women were significantly more numerous in Gr 2 (42% vs 33%, p=0.03), and BMI was significantly more elevated (26 +/- 5 vs 25 +/- 4 kg/m², p<0.0001). While distribution between middle and low rectum was comparable between the “before” and “after” groups, RCP adherence significantly increased frequency of practice: (i) of exhaustive staging, whether general (abdominal and pelvic CT: 95% vs 59%, p<0.0001) or locoregional (MRI 59.8% vs 2.2%, p<0.0001); (ii) of pretherapeutic presentation in a multidisciplinary tumor board (94.4% vs 41%, p<0.0001) and (iii) when necessary, prescription of a neoadjuvant treatment as indicated during the pretherapeutic phase (72.2% vs 48.1%, p<0.0001). While exhaustive staging reduced by nearly 50% the percentage of unknown stage, the difference was not significant (5.3% vs 9.4%, p=0.06).

Operative results and outcomes

RCP adherence was associated with significant quality improvement in terms of (i) extrafascial excision of the mesorectum (94.4% vs 78.6%, p<0.0001); (ii) sphincter conservation (82.8% versus 71.8%, p=0.0005); (iii) development of a pouch in case of low anastomosis (45.2% versus 28.6%, p<0.0001) and (iv) a protective stoma (80.7% vs 44.7%, p<0.0001). While operating time in the two groups was comparable, perioperative blood transfusion was reduced threefold (Table 2). As regards 90-day mortality, the two groups of patients were comparable. On the other hand, following RCP application

overall mortality increased significantly (Table 2). In terms of the Dindo-Clavien classification (22), no significant difference was found between the two study periods (Table 2).

While medical complications were comparable, there were significantly more surgical complications in G2 (44.7% vs 33.8%, p=0.01), even though the prevalence of surgical site infections and "redo" operations was not statistically different. In multivariate analysis, male gender and non-conservation of the sphincter were two independent risk factors for major morbidity (Table 4). Lastly, RCP adherence was associated with significant reduction in length of hospital stay [14.0 (+/- 9.6) vs 17.4 (+/- 12.2) days p<0.0001].

Oncological outcomes

RCP adherence doubled the exhaustiveness of the anatomopathological report (58.6% vs 25.6%, p=0.02) and was associated with significant improvement in surgical resection quality in terms of complete macroscopic exeresis (R0) (93.8% vs 80%, p<0.0001), invaded circumferential margin (5.6% vs 12.8%, p<0.0001) and number of ganglions analyzed (Table 3).

Survival

On the final date covered by the study (1 August 2018), 272 patients (45.1%) were still alive, 292 (48.3%) had died and 40 (6.6%) were lost to follow-up. Even though median follow-up was significantly longer in Gr 1 (75.9 vs 43.1 months, p<0.0001), RCP adherence was significantly associated with increased median survival, whether overall (117.8 vs 82.1 months, p=0.0005) or disease-free (107.6 vs 50.7 months, p=0.0016) (Figures 2 and 3).

In Gr 2, significant reduction in the prevalence of local recurrence (7.4% vs 12.8%, p=0.03) and/or distant recurrence was observed (21% vs 33%, p=0.0008).

The factors associated with improved overall survival in multivariate analysis were: tumor stage lower than 3 (HR =0.69; CI95% : 0.54-0.89; p=0.004), age lower than 70 years (HR=0.56; CI 95%: 0.44-0.72; p<0.0001), ASA score lower than 3 (HR=0.52; CI95%: 0.40-0.68 ; p<0.0001) and postoperative complications classified as Dindo-Clavien 1-2 (HR=0.72; CI95%: 0.56-0.93 ; p=0.01) (Table 5). A period effect with reduced overall

survival in Gr1 was found not only in univariate analysis (HR=1.57; CI95%: 1.22-2.03; p=0.0005) but also after adjustment in multivariate analysis (HR=1.35; CI95%: 1.02-1.78; p=0.035) (Table 5). As regards disease-free survival, in multivariate analysis (Table 6) favorable prognostic factors were age lower than 70 years (HR = 0.60; CI95%: 0.48-0.77; p<0.0001), ASA score lower than 3 (HR = 0.61; CI95% : 0.47-0.79; p=0.03), postoperative complications classified as Dindo-Clavien 1-2 (HR =0.76; CI95% : 0.56-0.93 ; p= 0.03) and complete exeresis R0 (HR = 0.44; CI95%: 0.33-0.59: p<0 .0001). No period effect for disease-free survival was observed in multivariate analysis (HR = 1.21; CI95% : 0.95-1.55; p=0.12).

DISCUSSION

The results of this study suggest that RCP adherence has significantly improved multidisciplinary management of patients with subperitoneal cancer; this has been the case for (1) exhaustive preoperative staging, (2) pretherapeutic discussion in multidisciplinary tumor boards and (3) prescription of neoadjuvant treatment consistent with the pretherapeutic assessment. From a surgical and anatomopathological standpoint, RCP application has been characterized by significant improvement in quality of surgical resection and long-term outcomes.

According to the recent recommendations of GRECCAR and SNCFP (14), one of today's fundamental issues consists is precisely determining locoregional staging in rectal cancer. While nodal status is determined with equivalent accuracy by endoscopic ultrasound and MRI, locoregional staging of invasive cancer is determined by MRI only (23) The emergence of MRI and its increasing availability explain why, as was previously observed in a Danish study (24), its prescription in our center has been multiplied by 30. That much said, MRI is still insufficiently widespread; in four out of ten patients in our center, it does not take place. That said, pre-therapeutic measurement of the circumferential margin in the pT3N0 stages has facilitated selection of patients who would undergo neoadjuvant treatment (25,26). In this respect as well, our practices have undergone considerable modification; the medical records presented in multidisciplinary tumor boards have doubled, and the number of records with "unknown" stage has been halved. Indeed, multidisciplinarity has helped to optimize therapeutic choices and to significantly increase

indications for neoadjuvant treatment (according to pre-therapeutic stage) and for adjuvant chemotherapy. Our observations corroborate the results reported in two recent series in the literature (27,28), which show that in 26 to 29% of cases, medical record rereading has modified treatment and management strategies, especially preoperatively. Changed practices have also proven conducive to more precise definitions of indications and to progress in determination, in accordance with the official recommendations, of the role of local treatment in cases of superficial cancer (14,28).

RCP adherence has also been reflected in significant strides toward fulfilling the quality requirements for surgical resection, particularly instrumentalized extrafascial excision of the middle rectum, now carried out in nearly 95% of patients, as well as sphincter-sparing surgery, which occurs in 4 cases out of 5. Subsequent to the RCPs published in 2006, multidisciplinary management at the Caen CHU of sub-peritoneal rectal cancer has progressed considerably, with close cooperation not only within the establishment but also in conjunction with the François Baclesse center (*Centre Anti Cancer*). In the digestive surgery unit, (1) supervision of cancer surgery activities by two senior physicians, (2) laparoscopy development and (3) RCP implementation in early rehabilitation have improved perioperative outcomes. And in compliance with the recent recommendations of the GRECCAR and SNFCP societies (14), the prevalence of pouches, intersphincteric resection and protective stomas has been significantly correlated with the extended scope of sphincter conservation, as was previously reported in Swedish and Norwegian population studies (29,30). Moreover, extrafascial excision of the mesorectum, supervised since 2010 by two senior physicians, has significantly increased the prevalence of macroscopic total resection (R0) and led to a three-fold decrease in the frequency of tumor spillage, as was highlighted in two recent series (31,32). RCP adherence has also increased the exhaustiveness of anatomopathological reports, of which, subsequent to circulation of a simplified report form, the number has all but doubled, (12). That much said, and notwithstanding the prognostic value of this type of analysis, for close to one out of four patients, this report was incomplete(33,34).

As concerns our secondary endpoints, RCP adherence has not yielded reduced morbi-mortality. Our clinical outcomes in terms of 90-day mortality (close to 3%) are similar to those reported in a French study that

included more than 45500 patients having undergone operations for rectal cancer (35). In addition, we observed significantly more elevated prevalence of surgical complications, and overall morbidity was significantly higher in G2. Several factors help to explain the significant increase in morbidity: prospective collection since 2006 has rendered complication records more exhaustive; neoadjuvant treatments are significantly more prevalent, as is sphincter conservation; surgical schemes (colonic pouch, intersphincteric resection) have grown more and more complex. Taken together and as reported in a recent review of the literature, these factors have led to increased postoperative morbidity (36). In addition, two risk factors independent of major morbidity were found in our study: male gender and absence of sphincter conservation. As examples of the complexity of surgery complicated by pelvic narrowness or tumor volume, the importance of the above-mentioned factors was recently underlined in a study including close to 9000 patients having undergone surgery for rectal cancer (37). On another score, the ongoing development of laparoscopy and instrumentalization of extrafascial mesorectal excision supervised by two senior surgeons probably explains the significant diminution of perioperative transfusion. And to a greater extent than application of RCPs *per se*, enhanced perioperative patient care (improved anesthetist-surgeon coordination, implementation of the SFCD-SFAR RCPs and the development of multimodal SFCD-SFAR rehabilitation programs) have significantly reduced length of hospital stay.

In the long term, RPC adherence helps to explain a significant decrease in local and distant recurrence (Table 3), which generates a significant increase in overall and disease-free survival, as was observed by Palmer et al in their population study (32). That much said, these results should be viewed with caution due to the fact that the patients on group 1 were monitored over a significantly longer time period than those in group 2.

The limits of our study stem from its being monocentric, from its heterogeneous data collection methods (retrospective until 2005, and then prospective from 2006), from its lengthy inclusion period and from the number of patients per year and per period (22 prior to 2006 and more than 30 after 2006). In point of fact, recent works have reported the influence of operative volume not only on RCP implementation, but also on operative results (35,38).

That much said, to our knowledge this is one of the first studies in France aimed at assessing our professional practices, specifically by attempting to measure the impact of RCP implementation on treatment and management of sub-peritoneal rectal cancer. Analysis of our data suggests that RCP adherence in the framework of multidisciplinary management has shown effectiveness at three levels : (i) improved exhaustiveness of locoregional and distant staging; (ii) improved matching of neoadjuvant treatment with the pretherapeutic stage in multidisciplinary tumor boards and (iii) improved observance of quality standards in surgical excision and anatomopathological examination. What we do not know is whether these changes will have an impact on digestive and genitourinary sequels, which often remain little known and poorly assessed (39,40)

Conclusions. RCP adherence substantially enhanced the quality of multidisciplinary management of patients undergoing curative surgery for subperitoneal rectal cancer. However, further progress is still needed to enhance the comprehensiveness of accession to recommendations. And as regards patients' cancer prognosis, other intervening factors such as the volume of patients operated in each center, the individual expertise of surgeons and the cumulative expertise of centers underline the complexity of relevant and effective management.

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Declaration of ties of interest

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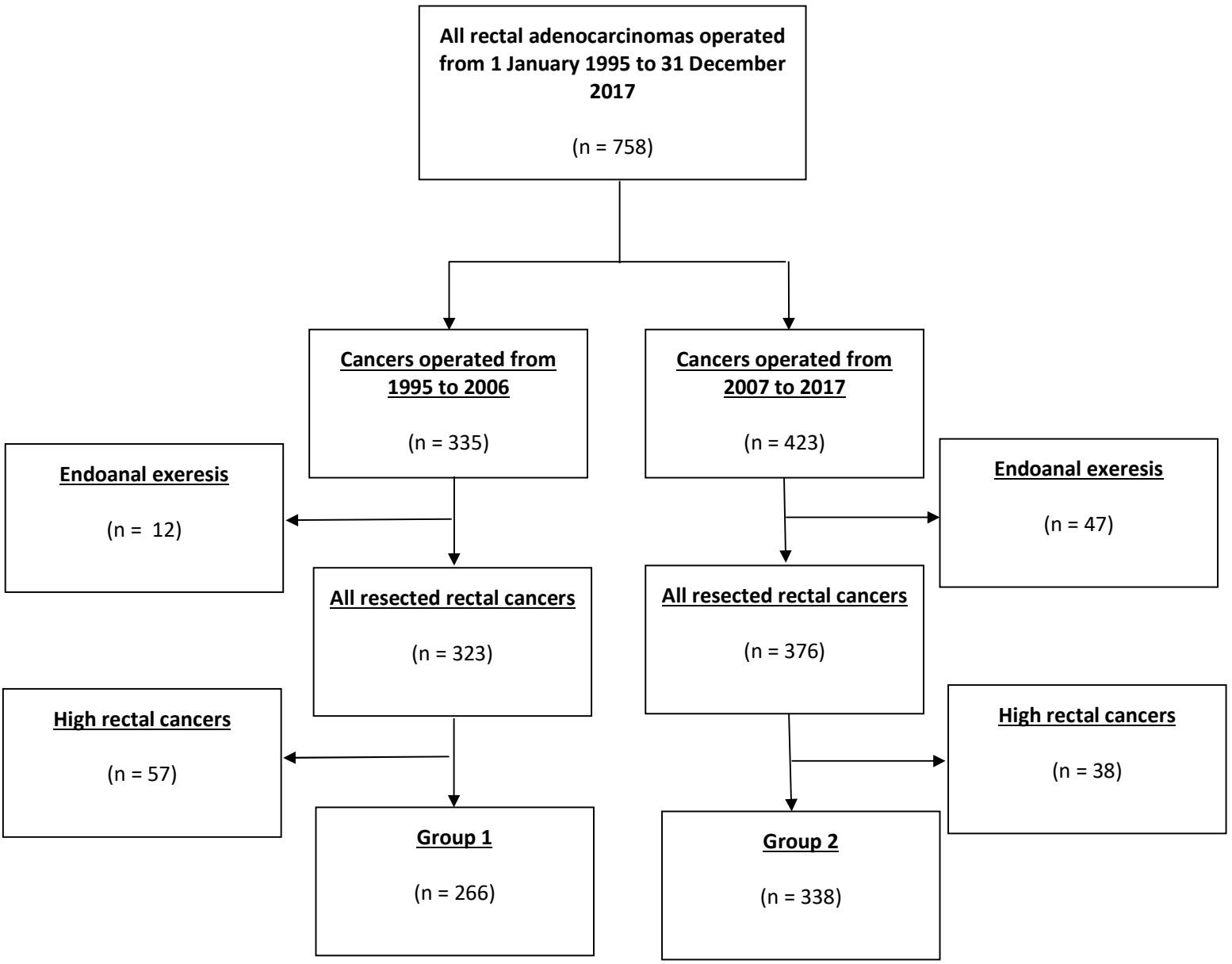
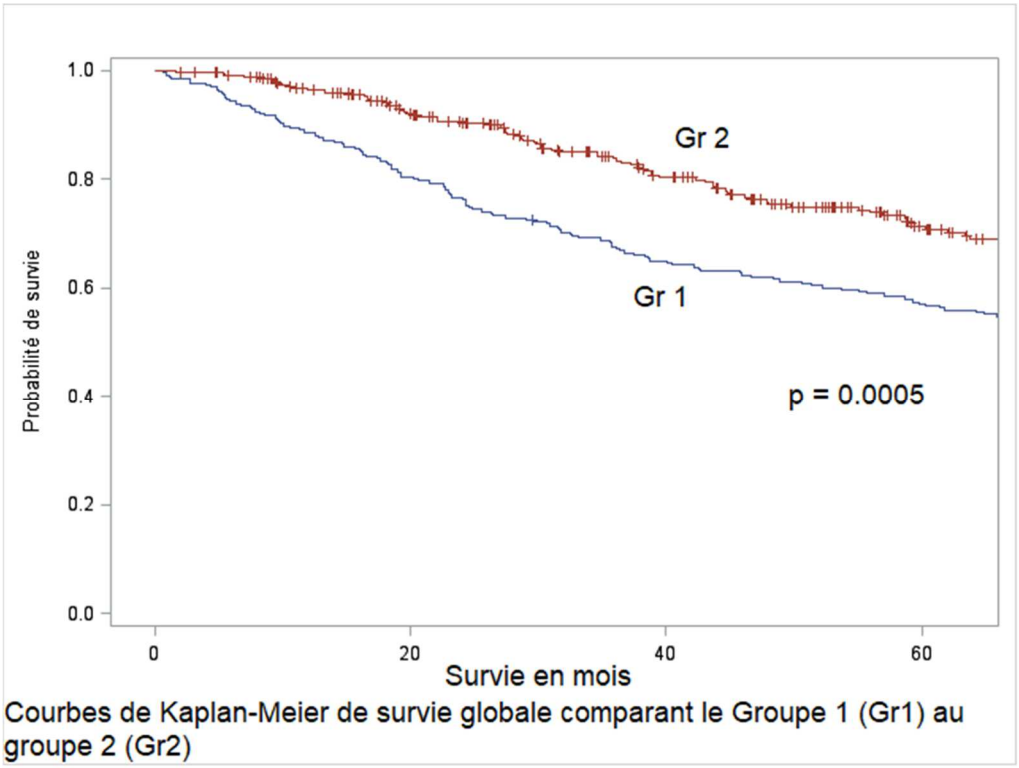


Figure 1 – Flow diagram for the study

Figure 2 – Overall survival according to group (Log-Rank test).

Probabilité de survie = survival probability

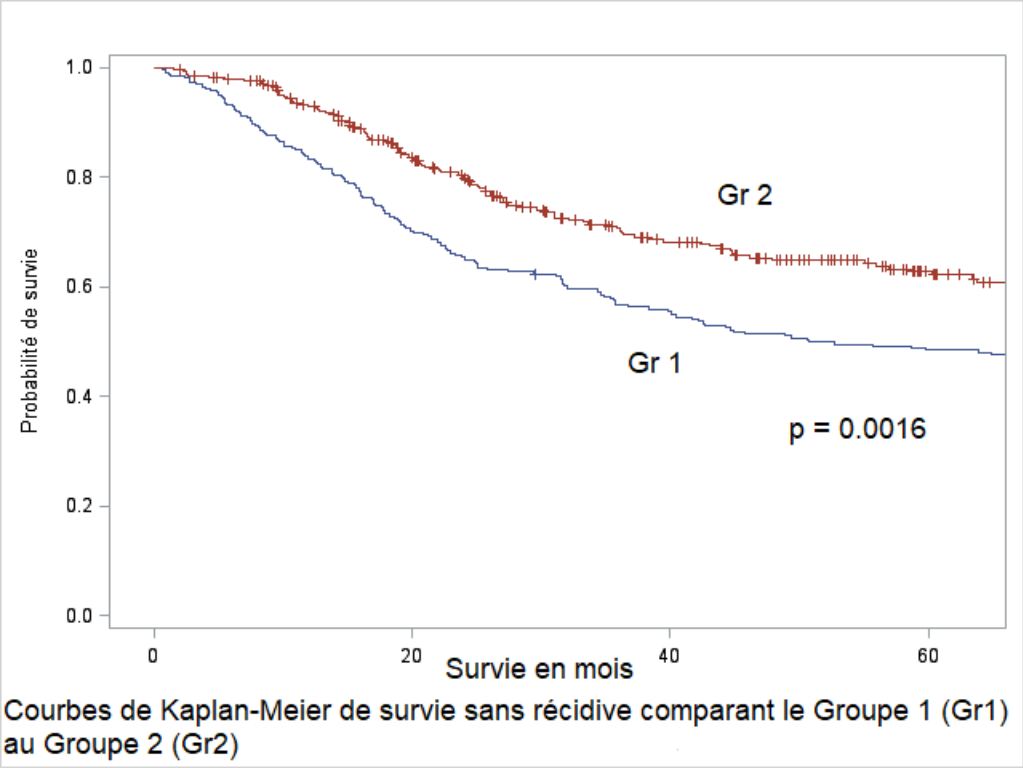


Courbes de Kaplan-Meier de survie globale comparant le Groupe 1 (Gr1) au groupe 2 (Gr2)

Survival (months)

Kaplan-Meier overall survival curves comparing Group 1 (Gr1) and Group 2 (Gr2)

Figure 3 – Disease-free survival according to group (Log-Rank test).



Courbes de Kaplan-Meier de survie sans récidive comparant le Groupe 1 (Gr1) au Groupe 2 (Gr2)

Kaplan-Meier disease-free survival curves comparing Group 1 (Gr1) and Group 2 (Gr2)

Probability of survival

Survival (months)

Table 1 Population characteristics.

Characteristics	Gr 1 n=266 (%)	Gr 2 N=338 (%)	p value
Gender Male/Female	178/88	196/142	**0.03**
Average age in years [+/- standard deviation]	67.5 [+/- 12.0]	65.7 [+/- 11.0]	**0.05**
ASA score ⩽ 2 >2	 206 (77.4%) 60 (22.6%)	 271 (80.2%) 67 (19.8%)	 0.42
Presence of comorbidities	104 (39.1%)	162 (47.9%)	0.15
Body mass index in kg/m² [+/- standard deviation]	25.1 [+/- 4.0]	26.1 [+/- 5.3]	**<0.0001**
Localization *Mid rectum* *Low rectum*	 153 (57.5%) 113 (42.5%)	 195 (57.7%) 143 (42.3%)	 1
Disease staging Endo-rectal ultrasound Pelvic MRI Thoracic-abdominal-pelvic TDM	 108 (40.6%) 6 (2.2%) 157 (59.0%)	 108 (40.6%) 202 (59.8%) 321 (95.0%)	 0.36 **<0.0001** **<0.0001**
Presentation in MCU	109 (41.0%)	319 (94.4%)	**<0.0001**
Pre-therapeutic stage *I/II/III/IV* *Unknown* *T3/T4 and/or N+*	 63/83/60/35 25 (9.4%) 178 (66.9%)	 78/95/128/37 18 (5.3%) 260 (76.9%)	 **<0.0001** 0.06 **0.006**
Neoadjuvant therapy *Short-course radiotherapy* *Neoadjuvant radio chemotherapy* *Chemotherapy*	 50 82 0	 16 217 7	 **<0.0001**

ASA: American Society of Anesthesiologists ; MRI: Magnetic resonance imagery; TDM: Tomodensitometry; MCU: Multidisciplinary Consultation Unit

Table 2 Perioperative outcomes.

Data	Gr 1 n=266 (%)	Gr 2 N=338 (%)	p value
Type of operation			
Hartmann	29 (10.9%)	9 (2.7%)	**<0.0001**
APA	48 (18.0%)	49 (14.5%)	0.26
Sphincter-sparing	189 (71.8%)	280 (82.8%)	**0.0005**
Pouch	76 (28.6%)	153 (45.2%)	**<0.0001**
Intersphincteric excision	26 (9.8%)	92 (27.2%)	**<0.0001**
Total mesorectal excision	209 (78.6%)	319 (94.4%)	**<0.0001**
Temporary stoma	119 (44.7%)	273 (80.7%)	**<0.0001**
Surgical approach			
Laparotomy	250 (94.0%)	141 (41.7%)	**<0.0001**
Laparoscopy	9 (3.4%)	146 (43.2%)	**<0.0001**
Laparoscopic conversion	6 (2.3%)	51 (15.1%)	**<0.0001**
Mean operating time in min [+/- standard deviation]	210 [+/- 70.5]	217 [+/- 72.1]	0.25
Perioperative transfusion	38 (14.3%)	15 (4.4%)	**<0.0001**
90-day mortality	10 (3.8%)	11 (3.3%)	0.82
Overall 90-day postoperative morbidity	92 (34.6%)	192 (56.8%)	**<0.0001**
Dindo-Clavien			
≤ 2	204 (76.7%)	252 (74.6%)	0.54
>2	62 (23.3%)	86 (25.4%)	
Medical complications	66 (24.8%)	92 (27.2%)	0.45
Surgical complications	90 (33.8%)	151 (44.7%)	**0.01**
Reoperation	25 (9.4%)	28 (8.3%)	0.63
Surgical site infection	47 (17.7%)	60 (17.8%)	0.98
Mean length of hospital stay in days [+/- standard deviation]	17.4 [+/-12.2]	14.1 [+/- 9.6]	**<0.0001**

APA: Abdomino-Perineal Amputation; SSI: surgical site infection

Table 3 Anatomopathological and oncological outcomes.

Data	Gr 1 n=266 (%)	Gr 2 N=338 (%)	p value
Anatomo-pathology (%)			
Incomplete record	198 (74.4%)	140 (41.4%)	**0.02**
Tumor spillage	25 (9.4%)	12 (3.6%)	**0.003**
R0	213 (80.0%)	317 (93.8%)	**<0.0001**
Positive CRM	34 (12.8%)	19 (5.6%)	**0.02**
Positive distal margin	19 (7.1%)	2 (0.6%)	**<0.0001**
Number of ganglions [+/- standard deviation]	11.4 [+/- 6.7]	12.7 [+/- 8.2]	**0.04**
Adjuvant chemotherapy	76 (28,6%)	122 (36,1%)	**0.05**
Median follow-up (months)	75.9	43.1	**<0.0001**
Median overall survival (months)	82.1	117.8	**0.0005***
Median disease-free survival (months)	50.7	107.6	**0.0016***
Local recurrence only	34 (12.8%)	25 (7.4%)	**0.03**
Local and distant recurrence	88 (33.1%)	71 (21.0%)	**0.0008**
Overall sites of recurrence			
Liver	29	33	0.12
Lung	21	17	
Peritoneum (carcinosis)	3	3	
Bone	3	0	
Brain	1	4	
Multi-site	6	3	
Unknown	25	11	

CRM: Circumferential resection margin

*Log-Rank test

Table 4 Univariate and multivariate analysis of risk factors for severe postoperative complications (Dindo-Clavien 3-5).

	OR	CI 95%	p	ORa	CI 95%	p
	Univariate model			Multivariate model*		
Male	1.93	[1.28-1.90]	**0.002**	2.22	[1.40-3.53]	**0.0007**
Age (>70 years/<70years)	1.30	[0.90-1.90]	0.16	1.20	[0.76-1.88]	0.43
Period (Gr2/Gr1)	0.89	[0.61-1.30]	0.54	0.66	[0.39-1.10]	0.11
ASA score (>2/<2)	1.36	[0.88-2.10]	0.17	1.18	[0.71-1.96]	0.52
Preoperative radiotherapy	1.35	[0.92-1.99]	0.13	1.47	[0.89-2.43]	0.14
Surgical approach: laparotomy	1.38	[0.92-2.06]	0.12	1.60	[0.94-2.72]	0.085
Non-conserved sphincter	2.41	[1.55-3.75]	**<0.0001**	2.68	[1.66-4.33]	**<0.0001**
Tumor stage (>2/<2)	1.25	[0.84-1.84]	0.27	1.02	[0.65-1.59]	0.94

OR: Odds Ratio; ORa : Adjusted Odds Ratio; Gr1: Group 1; Gr2: Group 2; ASA: American Society of Anesthesiologists, CI : Confidence interval

*All of the variables in the univariate model were retained in the final multivariate model.

Table 5 Univariate and multivariate analysis of the risk factors for overall survival.

	HR	CI 95%	P	HRa	CI 95%	p
	Univariate model			Multivariate model*		
Tumor stage < 3	0.67	[0.52-0.85]	**0.001**	0.69	[0.54-0.89]	**0.004**
Age < 70 years	0.44	[0.35-0.56]	**<0.0001**	0.56	[0.44-0.72]	**<0.0001**
Period (Gr 1)	1.57	[1.22-2.03]	**0.0005**	1.35	[1.02-1.78]	**0.035**
ASA score < 3	0.39	[0.30-0.50]	**<0.0001**	0.52	[0.40-0.68]	**<0.0001**
Dindo-Clavien < 3	0.66	[0.51-0.85]	**0.001**	0.72	[0.56-0.93]	**0.01**
Male gender	1.13	[0.89-1.44]	0.32	0.99	[0.76-1.30]	0.97
Preoperative radiotherapy	1.19	[0.94-1.50]	0.15	-	-	-
Complete exeresis (R0)	1.04	[0.74-1.46]	0.82	-	-	-

HR: Hazard Ratio; HRa: Adjusted Hazard Ratio; Gr1: Group 1; ASA : American Society of Anesthesiologists ; CI: Confidence interval

*Only the significant variables in the univariate model were retained in the final multivariate model (except for the Gender variable, which was forced)

Table 6 Univariate and multivariate analysis of the risk factors for disease-free survival.

	HR	CI 95%	P	HRa	CI 95%	p
	Univariate model			Multivariate model*		
Tumor stage < 3	0.67	[0.53-0.85]	**0.0009**	0.84	[0.67-1.05]	0.12
Age < 70 years	0.55	[0.44-0.68]	**<0.0001**	0.60	[0.48-0.77]	**<0.0001**
Period (Gr 1)	1.35	[1.07-1.72]	**0.01**	1.21	[0.95-1.55]	0.12
ASA score < 3	0.50	[0.39-0.64]	**<0.0001**	0.61	[0.47-0.79]	**0.03**
Dindo-Clavien < 3	0.65	[0.51-0.83]	**0.0005**	0.76	[0.56-0.93]	**0.03**
Complete exeresis (R0)	0.40	[0.30-0.54]	**<0.0001**	0.44	[0.33-0.59]	**<0.0001**
Male gender	1.18	[0.93-1.49]	0.17	1.12	[0.88-1.42]	0.35
Preoperative radiotherapy	1.09	[0.87-1.36]	0.44	-	-	-

HR : Hazard Ratio ; HRa : Adjusted Hazard Ratio; Gr1 : Group 1; ASA : American Society of Anesthesiologists ; CI : Confidence interval

*Only the significant variables in the univariate model were retained in the final multivariate model (except for the Gender variable, which was forced)