Ann Surg Oncol (2016) 23:2315–2322
DOI 10.1245/s10434-016-5143-1

Annals of
SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

ORIGINAL ARTICLE – GASTROINTESTINAL ONCOLOGY

Cytoreductive Surgery Combined with Hyperthermic Intraperitoneal Chemotherapy with Oxaliplatin Increases the Risk of Postoperative Hemorrhagic Complications: Analysis of Predictive Factors

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ABSTRACT

Background. Treatment of peritoneal carcinomatosis (PC) using cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) is recommended as curative treatment for selected patients. Modalities of HIPEC remain heterogeneous and HIPEC using oxaliplatin (HIPEC-Ox) appears to increase the risk of postoperative hemorrhagic complications (HCs).

Objective. The aim of this study was to assess the risk of HCs after CRS combined with HIPEC-Ox versus other drugs, and to determine predictive factors for HCs after HIPEC-Ox.

Methods. Data from 701 patients included in the National French Registry who were treated with CRS and HIPEC at 24 centers between 1998 and 2007 were used to evaluate the incidence of HCs following HIPEC with or without oxaliplatin. Overall, 771 patients treated with HIPEC-Ox at five French specialty centers were then analyzed to determine factors associated with the occurrence of HCs.

Results. The overall incidence of HCs was 9.8 %. When used with HIPEC, oxaliplatin significantly and independently increased the rate of HCs (15.7 vs. 2.6 % for other drugs; $p = 0.004$, odds ratio 32.4). Among the 771 patients who underwent HIPEC-Ox, HCs occurred in 14.3 % of patients. The only independent risk factor for HCs was an extended PC with a Peritoneal Cancer Index (PCI) >12 ($p = 0.040$).

Conclusion. HIPEC-Ox increases the risk of HCs compared with HIPEC with other drugs. The potential oncologic benefit of oxaliplatin and the risk of HCs should be considered in patients with PC who have a high PCI, as well as in at-risk patients.

The occurrence of peritoneal carcinomatosis (PC) from digestive cancer is a forerunner of advanced stage malignancy associated with poor prognosis and historically treated with palliative chemotherapy or surgery. Many trials have repeatedly reported improved survival with the combination of cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) as treatment for selected patients with PC. Consequently, this therapy is becoming the standard of care for patients with colorectal PC,[1–5] pseudomyxoma peritonei (PMP),[6–8] and malignant peritoneal mesothelioma (MPM).[9,10]

Techniques for CRS and peritonectomy are well described,[11,12] but modalities for HIPEC may vary between centers according to the exposure, open or closed

On behalf of the BIG-RENAPE Group.

First Received: 30 November 2015;
Published Online: 26 February 2016

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techniques, and drugs used. In 2006, the Milan consensus concluded that there was a lack of evidence in the literature to promote any one technique.[13] A major step forward in the treatment of metastatic colorectal cancer was the introduction of oxaliplatin- and irinotecan-based systemic chemotherapy. Elias et al. extended the use of these new drugs to HIPEC with oxaliplatin alone[2,14] or irinotecan.[15,16] The same authors reported improved survival after CRS and HIPEC using oxaliplatin (HIPEC-Ox) for colorectal PC,[2] leading several teams to prefer oxaliplatin during HIPEC for colorectal PC and PMP, and it is now used routinely during HIPEC for these diseases.

Postoperative morbidity following CRS with HIPEC is significant but remains acceptable when considering the oncological benefits of this procedure.[3,8,9,17] In 2010, Pomel et al.[18] reported a high incidence of hemorrhagic complications (HCs) following CRS with HIPEC-Ox in ovarian PC. The study was terminated after results suggested that HIPEC-Ox may increase the incidence of HCs.

Because HIPEC-Ox is widely used in the treatment of non-gynecologic PCs, we hypothesize that HCs may also occur. Our objective was to determine the impact of HIPEC-Ox on HCs, and to identify factors influencing HCs after HIPEC-Ox.

METHODS

A first analysis was performed to compare the incidence of HCs following HIPEC with and without oxaliplatin. We selected consecutive patients from the French BIG RENAPE registry[19] with pathologically-confirmed colorectal PC, PMP, or MPM who were treated with CRS and HIPEC at 24 centers between February 1989 and December 2007. Patients with incomplete data on HIPEC or follow-up on HCs were excluded. A standard data form was created to retrieve the following information: origin of PC, age, sex, extent of PC scored according to the Peritoneal Cancer Index (PCI),[20] the completeness of CRS using the completeness of cancer resection score (CC-score),[20] previous treatment with systemic chemotherapy, the simultaneous resection of liver metastasis, and modality of HIPEC (cytotoxic drugs used, exposure, 'closed' or 'open' wall, temperature, and duration of the procedure). Deep venous thrombosis prophylaxis was performed for all patients with isocoagulation subcutaneous or intravenous heparin. Patients treated with oxaliplatin during HIPEC were compared with those treated with other drugs.

Oxaliplatin or others drugs in HIPEC were chosen into each institution with regard to current ongoing protocol, and not with regard to the patient's conditions. The doses of oxaliplatin were 300, 360, or 460 mg/m^2 with or without systemic 5-fluorouracil. The doses of mitomycin C were 30–50 mg/m^2 and doses of cisplatin were 50–100 mg/m^2. Oxaliplatin was delivered over 30 min at 43 °C, and mitomycin C and cisplatin were delivered over 60–120 min at 41–42.5 °C. Iso-osmotic 5 % dextrose (2 L/m^2) was used as a carrier solution. Bevacizumab in systemic chemotherapy was always stopped at least 6 weeks before the procedure.

A second analysis was performed to evaluate predictive factors for HCs following HIPEC-Ox. Data from five French specialty centers were retrospectively recorded, and consecutive patients with colorectal PC, PMP, and MPM who were treated with CRS and HIPEC-Ox between November 1998 and December 2012 were included. The analyses were divided into three equivalent time periods; before 2003, between 2004 and 2008, and between 2009 and 2012. Major HCs were classified according to the National Cancer Institute's Common Toxicity Criteria (NCI-CTC). We reported grade 3 complications when transfusion, interventional radiology, endoscopic, or surgery were needed; grade 4 complications for life-threatening consequences requiring a major urgent intervention; and grade 5 complications leading to patient death. Among patients with HCs, the following data were gathered: type of hemorrhagic event such as intraperitoneal hemorrhage, hematoma, externalized hemorrhage, asymptomatic bleeding, digestive hemorrhage, and the postoperative day (POD) of occurrence.

Statistical Analyses

Statistical analyses were performed using SAS® software, version 9.2 (SAS Institute, Inc., Cary, NC, USA). Qualitative variables are described using numbers and percentages, and the distributions of continuous variables are described as mean ± standard deviation (SD) or median (interquartile range). Differences in patient characteristics were compared using univariate logistic regression models adjusted by institution. Univariate and multivariate logistic regression models were used to determine predictive factors for postoperative HCs, and were adjusted by institution. Multivariate models were constructed using the stepwise selection process, and the threshold to enter the model was 0.20, and 0.15 to remain in the model. A p-value <0.05 was considered statistically significant.

RESULTS

First Analysis: Comparison of Oxaliplatin with Other Drugs Used in Hyperthermic Intraperitoneal Chemotherapy (HIPEC)

A total of 701 consecutive patients (408 women) from the BIG RENAPE registry, with a mean (SD) age of 52.4 (11.9) years were included in the study (Table 1). The

TABLE 1 Characteristics of the 701 patients treated with cytoreductive surgery plus HIPEC with oxaliplatin versus other drugs (from the BIG RENAPE Registry)

	HIPEC with oxaliplatin [$n = 389$]	HIPEC with other drugs [$n = 312$]	p value
Mean age, years	50.4	54.8	0.27
Sex [n (%)]			0.81
Male	158 (41)	135 (43)	
Female	231 (59)	177 (57)	
Origin of PC [n (%)]			0.015*
Colorectal	193 (50)	184 (59)	
Pseudomyxoma peritonei	162 (42)	92 (29)	
Malignant peritoneal mesothelioma	34 (8)	36 (12)	
Preoperative systemic chemotherapy [n (%)]			0.007*
Yes	223 (57)	161 (52)	
No	166 (43)	151 (48)	
Extent of PC (PCI) [n (%)]			0.17
0–9	121 (31.4)	117 (43)	
10–14	92 (24)	49 (18)	
≥15	172 (45)	106 (39)	
Missing data	4 (–)	40 (–)	
Synchronous liver resection [n (%)]			0.12
Yes	34 (9)	21 (9)	
No	343 (91)	217 (91)	
Missing data	12 (–)	74 (–)	
Cancer resection score [n (%)]			0.35
CC-0	331 (86)	211 (69)	
CC-1	52 (13)	62 (20)	
CC-2	3 (1)	34 (11)	
Missing data	3 (–)	5 (–)	
Hemorrhagic complications [n (%)]			0.009*
Yes	61 (15.7)	8 (2.5)	
No	328 (84.3)	304 (97.5)	

HIPEC hyperthermic intraperitoneal chemotherapy, *PC* peritoneal carcinomatosis, *PCI* Peritoneal Cancer Index, *CC* completeness of cytoreduction

* Indicates statistically significant results

origin of PC was colorectal, PMP, and MPM for 377 (54 %), 254 (36 %), and 70 (10 %) patients, respectively. Overall, 384 patients (55 %) received preoperative chemotherapy. The mean (SD) PCI was 14.2 (9.3), and CC-scores for CC-0, CC-1, and CC-2 were 542 (78 %), 114 (17 %), and 37 (5 %) patients, respectively. The cytotoxic drugs used in HIPEC included oxaliplatin, with or without irinotecan, for 389 patients (55.5 %), and mitomycin C, with or without cisplatin, for 312 patients (44.5 %).

The origin of the PC was significantly different between the two groups, with more PMP in the HIPEC-Ox group (42 vs. 29 % for other drugs; $p = 0.015$). Patients in the HIPEC-Ox group had received significantly more preoperative chemotherapy (57 vs. 52 %; $p = 0.007$).

Postoperative HCs occurred in 69 patients (9.8 %), with a significantly higher rate in the HIPEC-Ox group (15.7 vs. 2.6 %). In the univariate analysis (Table 2), the incidence of HCs was significantly higher after HIPEC-Ox ($p < 0.01$), and in patients with PMP and MPM ($p = 0.003$), extended PC according to the PCI ($p = 0.013$), and those who did not receive preoperative chemotherapy ($p = 0.033$). In the multivariate analysis, two factors significantly influenced the incidence of HCs—HIPEC with oxaliplatin ($p = 0.004$) and origin of the PC ($p < 0.001$).

Second Analysis: Predictive Factors for Hemorrhagic Complications among Patients Treated with HIPEC Using Oxiliplatin

A total of 771 consecutive patients from five institutions who were treated with CRS and HIPEC-Ox were included in this analysis (250 patients were also included in the BIG RENAPE registry). Overall, 121 (16 %) patients were treated before 2003, 262 (34 %) were treated between 2004 and 2008, and 388 (50 %) were treated after 2009. Mean (SD) age was 52.6 (11.5) years and 453 women (59 %) were included. The origin of PC was colorectal, PMP, and MPM for 468 (60.7 %), 240 (31.1 %), and 63 (8.2 %) patients, respectively. Preoperative chemotherapy was received by 529 patients (69 %), and 177 received bevacizumab. The mean (SD) PCI was 13.2 (8.8). Sixty-seven patients (9 %) presented with synchronous liver metastases. After CRS, 658 (85 %), 99 (13 %), and 14 (2 %) patients had CC-0, CC-1, and CC-2, respectively. At all but one center, HIPEC was performed after CRS using the coliseum technique. With this technique, the oxaliplatin dose was 460 mg/m^2 when used alone, or 300 mg/m^2 when used in combination with irinotecan. With the closed technique, the dose of oxaliplatin was 360 mg/m^2.

There were 110 HCs after HIPEC-Ox, with an overall incidence of 14.3 %; 63 patients (8 %) needed a reoperation for hemostasis. The incidence was stable over the three analysis periods; 14.0 % before 2004, 12.6 % between 2004 and 2008, and 15.5 % between 2009 and 2012 ($p = 0.712$). There were 66 (60 %) grade 3 HCs, 42 (38 %) grade 4 HCs, and 2 (2 %) grade 5 HCs. HCs occurred with a mean (SD) delay of 8.9 (9.2) days after CRS and HIPEX-Ox. HCs included intraperitoneal hematoma, intraperitoneal hemorrhage, digestive tract bleeding, externalized bleeding, or other internal asymptomatic bleeding for 13 (12 %), 67 (61 %), 13 (12 %), 7 (6 %), and 10 (9 %) patients, respectively. Therefore, there were 90 intraperitoneal bleeding events. During surgical exploration performed for

TABLE 2 Univariate and multivariate analyses of factors associated with the occurrence of hemorrhagic complications after cytoreductive surgery and HIPEC in 701 patients from the BIG RENAPE Registry

Variable	*N*	Incidence (%)	Univariate analysis *p* value	Multivariate analysis	
				OR (95 % CI)	*p*-Value
HIPEC drug regimens			<0.01*		<0.001*
Oxaliplatin	389	15.7		32.5 (3.0–348.3)	
Other drugs	312	2.6			
Origin of PC			<0.01*		<0.001*
Colorectal	377	6.4			
Pseudomyxoma peritonei	254	14.2		4.1 (2.0–8.3)	
Malignant peritoneal mesothelioma	70	12.9		4.7 (1.7–12.9)	
Sex			0.683		
Female	408	10.0			
Male	293	9.5			
Preoperative systemic chemotherapy			0.033*		
Yes	384	7.8			
No	317	12.3			
PCI			0.013*		
0–9	238	6.7			
10–14	141	9.2			
≥15	278	14.0			
Missing data	44	–			
Synchronous liver resection			0.455		
Yes	55	10.9			
No	560	10.7			
Missing data	86	–			
Cancer resection score			0.096		
CC-0	542	10.0			
CC-1	114	9.6			
CC-2	37	10.8			
Missing data	8	–			

HIPEC hyperthermic intraperitoneal chemotherapy, *PC* peritoneal carcinomatosis, *PCI* Peritoneal Cancer Index, *CC* completeness of cytoreduction, *OR* odds ratio, *CI* confidence interval

* Indicates statistically significant results

hemoperitoneum, the etiology of hemorrhage was found in only 24 % of cases.

In the univariate analysis, CC-score and the extent of PC according to the PCI were significantly associated with a higher risk of HCs (Table 3). In the multivariate analysis, PCI remained the only independent predictive factor ($p = 0.04$). The occurrence of HCs was not influenced by the origin of the PC, sex, receipt of preoperative chemotherapy, use of bevacizumab, time period of surgery, HIPEC modality (open vs. closed abdomen or the addition of irinotecan), and synchronous resection of liver metastases.

DISCUSSION

The results of our study suggest that the risk of bleeding after HIPEC-Ox must be carefully managed during the postoperative course. The rate of HCs was 2.6 % for HIPEC-other drugs and 15.7 % for HIPEC-Ox. The use of oxaliplatin was an independent risk factor for HCs. The most frequently occurring HC was intraperitoneal hemorrhage, which occurred most often at the end of the first postoperative week, with a mean delay of 8.9 days without surgical or biological explanation. The only difference between groups treated with and without oxaliplatin was a higher use of preoperative systemic chemotherapy into the HIPEC-Ox. This may reflect a potential higher toxicity of neoadjuvant systemic chemotherapy and its influence on postoperative complications, as well as initial worse disease. We do not know which mechanism could explain this adverse event as no biological abnormalities such as thrombocytopenia or biologic coagulation disorders were observed. This should be further investigated; however,

TABLE 3 Univariate and multivariate analyses of the factors associated with the occurrence of hemorrhagic complications after cytoreductive surgery and HIPEC with oxaliplatin in 771 patients from five institutions

Variable	*N*	No. of HCs (incidence %)	Univariate analysis *p* value	Multivariate analysis	
				OR (95 % CI)	*p*-Value
Origin of PC			0.059		
Colorectal	468	57 (12.2)			
Pseudomyxoma peritonei	240	41 (17.1)			
Malignant peritoneal mesothelioma	63	12 (19.0)			
Sex			0.703		
Female	453	66 (14.6)			
Male	317	44 (13.9)			
Missing data	1	–			
Preoperative systemic chemotherapy			0.409		
Yes	529	73 (13.8)			
No	235	37 (15.7)			
Missing data	7	–			
Neoadjuvant systemic chemotherapy			0.820		
With bevacizumab	177	25 (14.1)			
Without bevacizumab	578	83 (14.4)			
Missing data	16	–			
PCI			0.008*		0.040*
Limited PC (1–12)	375	44 (11.7)			
Extended PC (13–39)	353	65 (18.4)		1.6 (1.0–2.5)	
Missing data	43	–			
Synchronous liver resection			0.527		
Yes	67	8 (11.9)			
No	690	99 (14.3)			
Missing data	14	–			
Cancer resection score			0.017*		0.07
CC-0	658	86 (13.1)			
CC-1 and CC-2	113	24 (21.2)		1.6 (0.9–2.8)	
Period of procedure			0.712		
≤2003	121	17 (14.0)			
2004–2008	262	33 (12.6)			
≥2009	388	60 (15.5)			
HIPEC modalities					
Addition of irinotecan			0.650		
Yes	370	53 (14.3)			
No	401	57 (14.2)			
Exposure			0.954		
Open wall	672	93 (13.8)			
Closed wall	99	17 (17.2)			

HIPEC hyperthermic intraperitoneal chemotherapy, *HCs* hemorrhagic complications, *PC* peritoneal carcinomatosis, *PCI* Peritoneal Cancer Index, *OR* odds ratio, *CI* confidence interval, *CC* completeness of cytoreduction

* Indicates statistically significant results

platelet adhesion disorders may provide an explanation. In addition, as no explanation for hemorrhage was found during laparotomy in most cases, we hypothesize that oxaliplatin may have a direct local toxicity over operated areas and residual tumor nodules.

The reported frequency of HCs after CRS and HIPEC with drugs other than oxaliplatin varies between 1.9 and 6.8 % (Table 4).[21–26] In 2006, Elias et al.[27] reported a pharmacologic study evaluating oxaliplatin associated with different HIPEC modalities, and found an important rate of

TABLE 4 Postoperative incidence of hemorrhagic complications following cytoreductive surgery and intraperitoneal chemotherapy

Reference	Procedures (*n*)	Drugs used	Modalities of intraperitoneal chemotherapy	Origin of PC	Incidence of HCs (%)
Kusamura et al.[22]	205	CDDP + MMC CDDP + Dx	HIPEC Closed abdomen	50 MPM 49 PMP 41 OC 13 CRC	1.9
Gusani et al.[23]	124	MMC	HIPEC Closed abdomen	47 PMP 28 CRC 16 MPM 16 OC	2.4
Iversen et al.[24]	80	MMC CDDP	HIPEC Open abdomen	34 CRC 29 PMP 13 AC 4 MPM	3.8
Stephens et al.[25]	200	MMC	HIPEC ± EPIC Open abdomen	150 PMP 21 CRC 7 GC	4.5
Verwaal et al.[21]	102	MMC	HIPEC Open abdomen	102 CRC	2.8
Saxena et al.[26]	145	CDDP + MMC CDDP + Dx	HIPEC ± EPIC Open abdomen	145 PMP	6.8

HIPEC hyperthermic intraperitoneal chemotherapy, *EPIC* early postoperative intraperitoneal chemotherapy, *MPM* peritoneal mesothelioma, *PMP* pseudomyxoma peritonei, *OC* ovarian cancer, *CRC* colorectal cancer, *GC* gastric cancer, *CDDP* cisplatin, *MMC* mitomycin C, *Dx* doxorubicin

HCs (5/16 patients) in a group of patients who received HIPEC-Ox with hypo-osmotic solutions. They suggested that the use of hypotonic solutions increases the risk of postoperative HCs. To confirm the association with CRS and HIPEC-Ox, Elias et al. reported two larger clinical studies. The first, in 2007,[28] evaluated the morbidity and mortality of patients after CRS and HIPEC-Ox for PCs of different origins. HIPEC was performed using an open technique, and oxaliplatin 360 mg/m^2 was combined with irinotecan 360 mg/m^2 in 2 L/m^2 of 5 % dextrose administered over 30 min at 43 °C. After analysis of 106 consecutive patients, a mortality rate of 4 % and a morbidity rate of 66 % with no HCs was reported. In the second study evaluating the results of CRS plus HIPEX-Ox for PMP,[29] Elias et al. used oxaliplatin alone at 460 mg/m^2 in 2 L/m^2 of iso-osmotic 5 % dextrose in 27 patients, and oxaliplatin 360 mg/m^2 combined with irinotecan 360 mg/m^2 in 63 patients. Morbidity was high but the incidence of HCs was not specifically mentioned. These two retrospective studies suggest the feasibility and low postoperative risk of HCs at an expert center with extensive experience.

Smaller trials of HIPEX-Ox have been reported with interesting results in terms of prognostic factors, but always with an important incidence of postoperative HCs or unexplained hemoperitoneum.[30,31] In 2010, Pomel et al.[18] reported a prospective multicenter study evaluating HIPEC-Ox in advanced epithelial ovarian carcinoma. Five of eight centers involved in the study had more than 10 years of experience in HIPEC procedures. Oxaliplatin was used at 460 mg/m^2 in 2 L/m^2 of dextrose administered over 30 min at 42–44 °C using an open technique, but the dose was reduced to 350 mg/m^2. Nine of 31 (29 %) patients experienced grade 3 HCs requiring surgery, and the incidence of HCs was not decreased by reducing the oxaliplatin dose from 460 to 350 mg/m^2. As a result of this high incidence of HCs, the trial was closed. More recently, the postoperative results of Prodige 7, a prospective, phase III trial that compared CRS alone with CRS combined with HIPEC-Ox, confirmed that the only intraperitoneal complication that was significantly increased by HIPEC at 30 days was intraperitoneal hemorrhage.[32] More studies are required to determine the impact of oxaliplatin dose reduction on the risk of HCs without reducing patient survival.

The only independent factor that significantly increased the risk of HCs after HIPEC-Ox was a PCI >12. As previously reported,[29,33] an extended PCI was frequently associated with major abdominal surgery (multiple peritonectomy procedures and digestive anastomoses, duration

of surgery) leading to increased morbidity and mortality and an increased risk of HCs. In the first analysis, there was more PMP in the HIPEC-Ox group than in the HIPEC-other drugs group. This pathology often requires more extensive peritonectomy procedures and may partly explain an increased risk of HCs.

Recently, the American Society of Peritoneal Surface Malignancies[34] reported interesting results for colorectal PCs treated using HIPEC with mitomycin C. This group conducted an international retrospective study, including 584 patients treated for colorectal PCs with CRS and HIPEC-Ox or HIPEC-mitomycin C. Patients were stratified by Peritoneal Surface Disease Severity Score (PSDSS). Survival results were better in the oxaliplatin group, but not significantly improved for patients with non-favorable prognostic factors such as high PCI (PSDSS III and IV), whereas survival was significantly better for the mitomycin C group in patients with more favorable prognostic factors such as low PCI (PSDSS I and II). Although mitomycin C may appear to be an alternative to oxaliplatin in patients with a high risk of postoperative bleeding, these results underline the difficult choice between potential oncologic benefit and higher postoperative risk for patients with a high PCI. The choice is difficult because intravenous oxaliplatin and/or irinotecan are the only drugs that have helped patients achieve complete responses, especially in colorectal PCs. Additionally, although the HC risk with HIPEC-Ox is higher, only 2 (2 %) of 110 patients who experienced HCs died of hemorrhage.

Considering the retrospective design of our study, we acknowledge certain limitations. We encountered difficulties in gathering information on the use of anticoagulant treatments at curative doses in the perioperative setting to evaluate its impact on the risk of HCs. However, our results suggest it is important to be very careful with patients with hemostasis disorders and those who require curative anticoagulant treatment, which does not constitute an exceptional condition in patients with PC. Previous studies[9,21] suggested that peri- and postoperative bleeding have an important impact on survival, and particular attention has been given to limiting blood effusion in the perioperative setting.

CONCLUSION

Although HIPEC-Ox may offer oncologic benefit in the management of PC, its use should be discussed in patients at risk of bleeding (curative anticoagulation, hemostasis disorders) and for those with disease that has extensive intraperitoneal lesions but low-grade pathology, such as PMP, for which the use of mitomycin C demonstrated equivalent long-term survival.

ACKNOWLEDGMENT The authors thank Laurent Villeneuve, Emilie Mathiotte, Isabelle Bonnefoy, and Perrine Capolino for collecting the RENAPE and BIG RENAPE data.

DISCLOSURE Thibaut Charrier, Guillaume Passot, Julien Peron, Christelle Maurice, Sashka Gocevska, François Quénet, Clarisse Eveno, Marc Pocard, Diane Goere, Dominique Elias, Pablo Ortega-Deballon, Delphine Vaudoyer, Eddy Cotte, and Olivier Glehen have no conflicts of interest to declare.

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