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Original Research

Portal vein embolization does not affect the long-term survival and risk of cancer recurrence among colorectal liver metastases patients: A prospective cohort study

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ABSTRACT

Background: Previous studies comparing the survival outcomes of liver resections with and without preoperative portal vein embolization (PVE) for colorectal liver metastases (CLM) have linked PVE to higher rate of tumor progression, lower overall survival (OS) and lower disease-free survival (DFS). The lack of adjusted models to compare these outcomes is a limitation of these studies since patients requiring PVE may differ significantly from the ones receiving upfront surgery.

Materials and methods: Prospective cohort study of 128 patients undergoing CLM resection. The OS analysis followed an intent-to-treat (ITT) approach. The adjusted impact of PVE on OS and DFS was evaluated using multivariate Cox regression models.

Results: Seventy-one patients underwent PVE before attempting a liver resection while 57 received upfront surgery (NoPVE). All NoPVE patients were resected while 14 PVE participants (19.7%) were not operated (tumor progression = 9/14). PVE patients had a significantly higher preoperative lesions count (3 [1.75–4] vs 1 [1–2.5]; $p < 0.001$), a higher prevalence of bilateral metastases (23.5% vs 8.8, $p = 0.028$) and a higher count of neo-adjuvant chemotherapy cycles compared to NoPVE patients. The OS of PVE patients was similar to NoPVE participants (44.7 months [26.9–69.5] vs 49.0 [24.9–64.8], $p = 0.761$). The DFS of resected PVE patients was higher than NoPVE patients (33.2 months [10.7–54.6] vs 23.4 months [14.1–58.1], $p = 0.991$). In the adjusted models, preoperative lesions count was the only significant predictor of overall mortality ($HR + IC_{95} = 1.06$ (1.02–1.11) $p = 0.005$) and cancer recurrence ($HR + IC_{95} = 1.14$ (1.03–1.27) $p = 0.012$).

Conclusion: In the context of CLM, patients requiring PVE differ significantly from patients receiving upfront surgery. This confirms the need for adjusted models when comparing the clinical outcomes of both groups. Our adjusted analysis suggests that PVE is not a significant predictor of a lower OS or DFS. PVE allowed the resection of 80% of participants with initially unresectable CLM.

Institutional protocol number: 12.106

Study registration number: NCT03168230.

1. Introduction

For patients with colorectal liver metastasis (CLM), the prospect of long-term survival relies on liver resection. Unfortunately, 75% of patients with CLM are initially unresectable, due to an insufficient future liver remnant (FLR) volume [1,2]. In order to increase the FLR, most patients will first receive chemotherapy to reduce the tumor load (downsizing) [3]. When chemotherapy is insufficient to provide an adequate postoperative FLR, portal vein embolization (PVE) can be performed. This intervention has a high rate of success since 60–100%

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of patients undergoing PVE will receive a subsequent liver resection [4–6].

While PVE is recognized for its efficacy to induce liver hypertrophy, several studies have expressed concerns regarding the potential adverse effect of this intervention on pre-resection tumor progression [7–11], increased risk of cancer recurrence following resection [4,8,11] and reduced overall survival following resection [1,4,11].

In a 2017 systematic review [6], the data of 13 distinct studies were combined to compare the survival outcomes of 539 patients requiring PVE before attempting liver resection for CLM to 806 patients receiving upfront surgery (NoPVE). The results suggested that 30% of PVE patients could not proceed to liver resection, mainly due to post-PVE tumor progression (84% of not resected patients). In comparison, tumor progression was the cause of non-resection for only 1 NoPVE patient (0.12%). The median OS after liver resection for NoPVE patients was 45.6 months, compared to 38.9 months for PVE patients. The median DFS of NoPVE patients was 21.7 months, compared to 15.2 months for PVE patients [6]. The authors highlighted that the poorer DFS of PVE patients could be attributed to the high rate of post-PVE tumor growth. As mentioned in the review, some methodological limitations have to be considered when interpreting the results. The included studies had limited sample sizes (median = 28 PVE patients) and, most importantly, presented their survival outcomes analysis without adjusting for patients and disease characteristics. Since PVE is performed when the burden of the disease is extensive to the point where an upfront surgery is not possible, adjusting for those characteristics is an essential part of the comparison of the survival outcomes between NoPVE patients and PVE patients.

It is also worth noting that other studies [5,10,12], including a 2016 meta-analysis [2], found no significant association between PVE and negative oncological outcomes.

As mentioned in almost every study cited above, adjusted multivariate models are required to evaluate the independent impact of PVE on survival outcomes following liver resection for CLM. Intent-to-treat (ITT) analysis would also be relevant since many studies have evaluated the impact of PVE on overall survival exclusively among resected patients. Unresected patients have to be included in the OS analysis.

The aim of this study is to evaluate the impact of PVE on ITT overall survival and DFS using multivariate-adjusted regression models. Our hypothesis is that PVE patients could have a lower OS and DSF compared to NoPVE patients. However, after adjusting for patients/disease characteristics, we think PVE is not going to be an independent predictor of OS or DFS.

2. Materials & methods

2.1. Study design

A single center prospective cohort study was conducted between February 27th, 2004 and May 21st, 2016 in (Name of the hospital). The study was registered (NCT03168230) and approved by the (Acronym of the hospital) human research ethics board (Approval ID Number) There were no changes to methods after study initiation. The research has been reported in line with the STROCSS criteria [13].

2.2. Participants

Adult patients (≥18 years old) affected by colorectal liver metastasis (CLM) and scheduled for a one-stage right/extended right hepatectomy between February 27th, 2004 and March 5th, 2012 were approached to seek consent. Individuals requiring a two-stage hepatectomy or that had a previous hepatectomy were excluded. Participants requiring PVE before attempting liver resection were allocated to the PVE group while patients able to receive upfront surgery were allocated to the NoPVE group.

2.3. Study conduct

Prior to surgery, all participants had a volumetric assessment of their future liver remnant (FLR) using CT-Scan. The FLR was calculated using the following formula: FLR = (total liver volume (TVL) – resected liver volume)/(TLV – tumor volume) x 100. The decision to perform PVE prior to the attempt of liver resection was left to the surgeon's discretion. While the literature is not uniform regarding the exact FLR requiring PVE should be performed, this intervention is generally recommended when the FLR represents less than 25% of the TLV or less than 40% of TLV for patients with other liver dysfunctions (fibrosis, cirrhosis, etc.) [14]. Neoadjuvant chemotherapy was administered in both groups (following individual tumor board discussions). The regimens consisted of FOLFIRI or FOLFOX with or without bevacizumab. Every PVE (ipsilateral or contralateral access) was performed at our institution by experimented interventional radiology team. Lipiodol and hystoacryl were used for occlusion with a 6:1 ratio. Segment IV supra-selective embolization was performed in cases of extended right hepatectomy. Depending on the operating surgeon's preference, an energy device or a staples technique was used. Intermittent hilar clamping was also used according to surgeon's preference. No case required the use of concomitant ablative therapy such as radiofrequency ablation. Since many factors (including tumor progression, FLR growth, detection of new lesions, cancer dissemination, etc.) have to be considered before attempting post-PVE liver resection, this decision was also left to the surgeon's discretion.

2.4. Outcome measurement

Demographic characteristics (sex, age, body mass index, smoking habits and prevalence of several comorbidities) and oncologic characteristics (bilateral lesions, metastases count, tumoral volume and neoadjuvant chemotherapy) were extracted from every patient medical record. Blood losses, operative time, hospital stay duration and postoperative complications were also compiled from the medical record. International Study Group on Liver Surgery (ISGLS) definitions were considered to define each complication [15]. Survival outcomes (OS + DFS) were also extracted from the participant's medical record.

2.5. Statistical analysis

OS analyses were performed with an intention-to-treat (ITT) approach. For PVE patients who could not proceed to liver resection, overall survival was calculated from the day PVE was attempted. Alpha significance was set at 0.05. All *P* values were derived from two-tailed tests. Univariate Cox proportional hazards models were first performed to assess the impact of every covariate on OS and DFS. The covariates with a *p*-value ≤ 0.20 (in univariate models) were subsequently included in the multivariate Cox models. PVE was forced into both multivariate models since the objective of realizing those analyses was to evaluate the adjusted impact of PVE on the survival outcomes. SPSS, Version 23.0. Armonk, NY: IBM Corp.

2.6. Unresected patients

As intended in an ITT approach, participants who were not resected following PVE (tumor progression/insufficient hypertrophy/liver condition) were integrated into the PVE group for the OS analysis. These patients received palliative chemotherapy and comfort care.

2.7. Withdrawal

All patients approached to participate in the study did consent and no patient was withdrawn/excluded following consent.

Table 1
Comparison of demographic and disease characteristics from NoPVE and portal vein embolization (PVE) groups.

	NoPVE (n = 57)	PVE (n = 71)	*p-value*
Demographic characteristics			
Sex ratio (Male: Female)	34:23	49:22	0.270
Age (years ± SD)	61.3 ± 9.0	60.0 ± 10.6	0.470
BMI (kg/m^2 ± SD)	25.6 [21.5–28.9]	26.3 [23.7–29.9]	0.647
Smoker	25.5%	26.2%	0.931
Comorbidities			
Diabetes	14.9%	19.2%	0.568
Cardiovascular diseases [a]	52.4%	54.2%	0.791
Hematologic diseases ¤	13.8%	7.1%	0.433
Cirrhosis	0%	0%	N.A
Disease characteristics			
Bilateral lesions	8.8%	23.5%	**0.028**
Extrahepatic metastasis	3.5%	5.8%	0.689
Right lesions count (median + IQR)	1 [1–2]	2 [1–4]	< **0.001**
Left lesions count (median + IQR)	0 [0-0]	0 [0–1]	0.088
Total lesions count (median + IQR)	1 [1–2.5]	3 [1.75–4]	< **0.001**
Pre-PVE tumoral volume % (% of total liver volume)	Not applicable	1.17 [0.39–4.64]	
Post-PVE tumoral volume % (% of total liver volume)	Non-available	2.15 [0.55–8.26]	

[a] Includes stroke, hypertension, arrhythmia and/or angina ¤ Includes deep vein thrombosis/anemia.

3. Results

3.1. Demographic and disease characteristics

Among the 128 participants, 71 required PVE while 57 received upfront surgery (NoPVE). The comparisons of the demographic and oncologic characteristics of NoPVE (n = 57) vs PVE (n = 71) patients are presented in Table 1. PVE patients had a significantly higher prevalence of bilateral lesions (23.5% vs 8.8%, $p = 0.028$) compared to NoPVE patients and a significantly higher median lesion count (3 [1.75–4] vs 1 [1–2.5], $p < 0.001$).

3.2. Preoperative chemotherapy, PVE impact and surgical characteristics

The comparisons of the preoperative chemotherapy regimens and surgical characteristics of NoPVE vs PVE patients are presented in Table 2. The impact of PVE on FLR (descriptive only) is also presented in Table 2. PVE patients had significantly more neoadjuvant chemotherapy cycles than NoPVE patients (6 [2.5–7] vs 4 [0–6], $p = 0.038$). Every patient in the NoPVE group was resected compared to 80.3% of PVE patients ($p < 0.001$). The causes of non-resection among PVE patients were: tumor progression (9/14), insufficient hypertrophy (3/14), hepatic steatosis (1/14) and patient's refusal of surgery (1/14). PVE-resected patients had significantly higher blood losses during their liver resection (700 cc [500–1000] vs 500 cc [300–800], $p = 0.016$) and significantly higher operative times (220 min [185–265] vs 190 min [150–229], $p = 0.002$) compared to NoPVE patients. The median FLR of the PVE group improved from 31.12% [27.65–34.71] to 43.94% [27.65–34.71] after the intervention.

3.3. Complications

The comparisons of the rates of perioperative and postoperative complications between NoPVE and PVE patients are presented in Table 3. Post-PVE complications (descriptive only) are also presented in Table 3. There was no statistically significant difference between PVE-resected and NoPVE-resected groups regarding the rates of all post-hepatectomy complications. No patient died perioperatively in either group. PVE was well tolerated with no mortality and few complications.

Table 2
Comparison of preoperative chemotherapy regimen, portal vein embolization (PVE) impact on future liver remnant (FLR) and surgical characteristics from NoPVE and PVE groups.

	NoPVE (n = 57)	PVE (n = 71)	*p-value*
Neo-adjuvant chemotherapy characteristics			
Neo-adjuvant chemotherapy	63.2%	77.5%	0.076
Chemotherapy nature			
FOLFIRI	16.7%	31.5%	0.104
FOLFIRI + BEVACIZUMAB	11.1%	5.6%	
FOLFOX	25.0%	37%	
FOLFOX + BEVACIZUMAB	41.7%	25.9%	
OTHER (Xeloda/5-FU Leucovorin)	5.6%	0%	
Total neo-adjuvant chemotherapy cycles (median + IQR)	4 [0–6]	6 [2.5–7]	**0.038**
PVE impact on FLR			
Pre-PVE FLR (median % + IQR)		31.12 [27.65–34.71]	
Post-PVE FLR (median % + IQR)		43.94 [39.21–46.97]	
Hepatectomy characteristics			
Performed hepatectomy	100%	80.3%	< **0.001**
Type of hepatectomy[a]			
Right[a]	73.7%	61.4%	0.161
Extended-right[a]	26.3%	38.6%	
Operative time (minutes)[a]	190 [150–229]	220 [185–265]	**0.002**
Blood losses (ml) (median + IQR)[a]	500 [300–800]	700 [500–1000]	**0.016**

Text in bold indicates a significant association ($p < 0.05$).
(PVE-resected n = 57) (NoPVE-resected n = 57).
[a] Analyses performed on patients for which the hepatectomy was performed.

Table 3
Comparison of perioperative and postoperative complications following portal vein embolization (PVE) and hepatectomy for the NoPVE and PVE groups.

	NoPVE (n = 57)	PVE (n = 71)	*p-value*
Post-PVE complications			
Fever		5.6%	
Hematoma		1.4%	
Leukocytosis		11.27%	
Contralateral thrombosis		1.4%	
Post-hepatectomy complications[a]			
Wound infection[a]	12.3%	12.7%	1.000
Catheter sepsis[a]	1.8%	0.0%	0.445
Prolonged ileus[a]	8.8%	7.0%	0.717
Anemia[a]	1.8%	1.4%	1.000
Fever[a]	0.0%	2.8%	0.502
Diarrhea[a]	1.8%	2.8%	1.000
Wound dehiscence[a]	3.5%	1.4%	0.585
Atrial fibrillation/bradycardia[a]	5.3%	1.4%	0.323
Pleural effusion[a]	1.8%	9.9%	0.075
Atelectasis[a]	7.0%	2.8%	0.406
Acute kidney failure[a]	3.5%	2.8%	1.000
Urinary tract infection[a]	1.8%	2.8%	1.000
Liver complication (all types)[a]	22.8%	16.9%	0.402
Ascites[a]	1.8%	2.8%	1.000
Bile leakage[a]	10.5%	7.0%	0.538
Liver abscess[a]	1.8%	4.2%	0.628
Liver Failure[a]	3.5%	2.8%	1.000
Other liver-related complications[a,b]	8.8%	2.8%	0.241

(PVE-resected n = 57) (NoPVE-resected n = 57).
[a] Analyses performed on patients for which the hepatectomy was performed.
[b] Includes perihepatic fluid collection, biliary fistula, seroma & hematoma.

Table 4
Predictors of ITT overall mortality following portal vein embolization (PVE) and/or liver resection[a] for colorectal liver metastasis (univariate and multivariate cox regression model).

	Crude hazard ratio (95% CI)	*p*	Adjusted hazard ratio (95% CI)	*p*
Sex (Female)	1.061 (0.653–1.725)	0.811	- -	
Age (↗)	1.020 (0.995–1.045)	0.121	1.008 (0.976–1.042)	0.620
Body mass index (km/m^2)	0.993 (0.973–1.013)	0.496	- -	
Smoker	0.755 (0.429–1.329)	0.330	- -	
Portal vein embolization (PVE)	1.039 (0.648–1.666)	0.873	0.845 (0.481–1.483)	0.557
Diabetes	1.417 (0.749–2.679)	0.284	- -	
Prevalence of at least one cardiovascular disease [b]	1.402 (0.873–2.250)	0.162	1.304 (0.706–2.407)	0.396
Prevalence of at least one hematologic diseases [c]	1.240 (0.488–3.153)	0.651	- -	
Bilateral lesions	1.376 (0.764–2.481)	0.288	- -	
Extrahepatic metastasis	0.688 (0.168–2.815)	0.603	- -	
Total lesions count (↗)	1.050 (1.011–1.091)	0.012	**1.063 (1.018–1.110)**	**0.005**
Number of neo-adjuvant chemotherapy cycles (↗)	1.019 (0.962–1.080)	0.519	- -	
Extended right hepatectomy	1.163 (0.669–2.020)	0.593	- -	
Operative time (↗)	0.997 (0.993–1.001)	0.125	0.997 (0.993–1.001)	0.169
Blood losses (↗)	1.000 (1.000–1.001)	0.404	- -	
Incidence of at least one post-operative liver complication [d]	0.737 (0.362–1.503)	0.402	- -	
Pre-PVE tumoral volume % (↗)[e] (% of total liver volume)	1.032 (0.982–1.079)	0.174	- -	

Text in bold indicates a significant association in the multivariate model ($p < 0.05$).
[a] Due to the intent-to-treat nature of our survival outcomes analysis, patients who were not resected following PVE are included in the PVE group. For unresected patients, the "overall survival" (OS) time began after PVE was performed. For all other patients, the OS time began after liver resection.
[b] Includes stroke, hypertension, arrhythmia and angina.
[c] Includes deep vein thrombosis and anemia.
[d] Includes ascites, bile leakage, liver absess, liver failure, perihepatic fluid collection, biliary fistula, seroma and hematoma.
[e] The tumoral volumes (%) were only available among the medical records of PVE patients. Therefore, this variable was not included in the adjusted model.

3.4. Survival outcomes

The ITT median OS of PVE participants was similar to NoPVE patients (44.7 months [26.9–69.5] vs 49.0 months [24.9–64.8], $p = 0.761$). The DFS of resected PVE patients was higher than NoPVE patients (33.2 months [10.7–54.6] vs 23.4 months [14.1–58.1], $p = 0.991$) but the difference was not statistically significant.

3.5. Multivariate COX regression models

The univariate and multivariate COX regression models used to evaluate the adjusted impact of PVE are presented in Table 4 and Table 5. The preoperative lesions count was the only significant predictor of overall mortality ($HR + IC_{95} = 1.06$ (1.02–1.11) $p = 0.005$) and cancer recurrence ($HR + IC_{95} = 1.14$ (1.03–1.27) $p = 0.012$). PVE was not an independent predictor of OS or DFS.

4. Discussion

4.1. Post PVE resectability and intergroup variation

In respect to our initial hypotheses/assumptions, patients requiring PVE before attempting liver resection for CLM expressed several oncologic/surgical characteristics (prevalence of bilateral lesions, lesion

Table 5
Predictors of cancer recurrence following liver resection for colorectal liver metastasis (univariate and multivariate cox regression model).[a]

	Crude hazard ratio (95% CI)	*p*	Adjusted hazard ratio (95% CI)	*p*
Sex (Female)	1.097 (0.650–1.850)	0.729	- -	
Age (↗)	1.008 (0.982–1.034)	0.549	- -	
Body mass index (km/m^2)	0.993 (0.975–1.011)	0.439	- -	
Smoker	0.793 (0.428–1.469)	0.460	- -	
Portal vein embolization (PVE)	1.261 (0.760–2.090)	0.369	0.917 (0.494–1.705)	0.785
Diabetes	1.815 (0.916–3.594)	0.088	1.818 (0.747–4.423)	0.187
Prevalence of at least one cardiovascular disease [b]	1.477 (0.889–2.455)	0.133	1.141 (0.538–2.418)	0.731
Prevalence of at least one hematologic diseases [c]	1.588 (0.557–4.525)	0.387	- -	
Bilateral lesions	1.934 (1.044–3.582)	**0.036**	1.124 (0.504–2.507)	0.776
Extrahepatic metastasis	0.775 (0.189–3.179)	0.724	- -	
Total lesions count (↗)	1.205 (1.088–1.335)	**< 0.001**	1.142 (1.030–1.267)	**0.012**
Number of neo-adjuvant chemotherapy cycles (↗)	1.078 (1.009–1.153)	**0.027**	1.046 (0.969–1.129)	0.251
Extended right hepatectomy	1.054 (0.617–1.800)	0.847	- -	
Operative time (↗)	1.002 (0.998–1.006)	0.423	- -	
Blood losses (↗)	1.000 (1.000–1.001)	0.634	- -	
Incidence of at least one post-operative liver complication [d]	0.980 (0.521–1.843)	0.950	- -	
Pre-PVE tumoral volume % (↗)[e] (% of total liver volume)	1.001 (0.998–1.004)	0.685	- -	

Text in bold indicates a significant association in the multivariate model ($p < 0.05$).
[a] Unresected PVE patients were excluded from the disease-free survival analysis due to their null hazard of developing cancer recurrence.
[b] Includes stroke, hypertension, arrhythmia and angina.
[c] Includes deep vein thrombosis and anemia.
[d] Includes ascites, bile leakage, liver absess, liver failure, perihepatic fluid collection, biliary fistula, seroma and hematoma.
[e] Data only available for PVE patients. Not included in the adjusted model due to this limitation.

count, neoadjuvant chemotherapy cycles, blood losses and operative times) that were significantly different from NoPVE participants. The proportion of PVE patients able to undergo a liver resection in our sample (80.3%) (82% if excluding the patient who refused surgery) was higher than the median rate of the literature (70%) [6]. Tumor progression was the most prevalent cause of non-resection (64%) but this rate was lower than was is currently suggested in the literature (84%) [6].

4.2. Impact of PVE on survival outcomes

In our multivariate-adjusted models, PVE had no statistically significant impact on ITT OS and DFS. The sole independent predictor of ITT OS and DFS was the total preoperative lesions count. Since PVE patients in our sample had a significantly higher median preoperative lesions count compared to NoPVE patients, adjusted models were definitely required to assess the impact of PVE on survival outcomes. In fact, every characteristics that were significantly different between PVE and NoPVE groups were included in the multivariate models. This result suggests that the intergroup variability between PVE and NoPVE patients may have a much stronger impact on the observed survival outcomes than the PVE intervention itself. Contrarily to our initial hypothesis, we did not observe a significantly lower OS nor DFS among PVE patients compared to NoPVE participants. In fact, the median DFS of the PVE patients who underwent liver resection was actually better than the one of NoPVE patients (33.2 months vs 23.4, $p = 0.991$). While this result may seem surprising at first, it is important to keep in mind that NoPVE patients receive an upfront surgery as soon as possible due to their acceptable FLR. For patients requiring PVE, there is waiting period due to the PVE intervention. During this waiting time, a proportion of PVE patients affected by an aggressive form of cancer suffer from a progression which render them inoperable. Since unresected patients have a null hazard of developing cancer recurrence, they are usually excluded from the DFS analysis. On the other hand, it is plausible that a proportion of NoPVE patients affected by aggressive cancers are operated rapidly but suffer from early recurrence soon after the liver resection. These patients are possibly lowering the DFS of the NoPVE group.

4.3. Observed survival outcomes vs literature

The median ITT overall survival of PVE patients was 44.7 months, which is higher than the median OS (ITT + resected patients only analysis) currently suggested in the literature (38.9 months) [6]. The median DFS of our PVE-resected patients (33.2 months) was also considerably higher than the DFS currently suggested in the literature (15.2 months) [6].

4.4. Study strengths and limitations

Our data are a substantial addition to the current literature. Considering the multiple significant differences between the characteristics of the PVE and NoPVE groups, there is a crucial need for model adjustment when comparing the clinical outcomes of both groups. In previous studies, several outcomes comparisons were performed on a univariate basis. Our adjusted models are an improvement over prior published data. It is also worth noting that the sample size of our PVE requiring group (n = 71) is the highest among any prior study comparing the survival outcome of PVE patients to NoPVE patients. This higher sample size gave us more flexibility in the multivariate models. Since an EPV (event per variable) of 10 is suggested as the rule of thumb for Cox regression analyses [16], we were able to include all variables expressing an effect of $p \leq 0.20$ in the OS + DFS univariates analysis in the multivariate models. While relevant and novel, our data are exposed to a risk of selection and attrition bias. These potential biases were taken into consideration during the results interpretation process. Since our non-resected patient sample size was small ($n = 14$), it was not possible for us to evaluate the predictors of post-PVE non-resection and/or PVE failure. This would be an interesting topic to assess in further researches.

4.5. Next steps

We think our results reinforce the premise that PVE is a safe and an essential part of a multimodal approach for CLM patients who are initially considered as unresectable. Since our conclusions are not fully in line with the current literature, we think more research is needed to evaluate the adjusted impact of PVE, especially on tumor progression. From our point of view, the indication for PVE is safe and clear for patients with an FLR under 30%. As suggested by Pamecha & al. [4], a randomized controlled trial including patients with a borderline preoperative FLR (> 30 to $< 40\%$) would be relevant in order to assess the impact of a broader usage of PVE on tumor progression, post-resection morbidity, and long-term survival. Since the expertise of our monocentric surgeon group might have an impact on our results, we also suggest that future research should be multicentric.

5. Conclusions

Patients requiring PVE in the context of CLM resection differ significantly from patients who can afford upfront surgery (NoPVE). PVE patients have significantly higher lesions counts, prevalence of bilateral disease, neoadjuvant chemotherapy cycles, blood losses during surgery and operative times compared to NoPVE patients. Despite those considerable intergroup variations, ITT overall survival and DFS are not significantly different between PVE and NoPVE patients. In the multivariate models, the sole significant predictor of OS and DFS was the preoperative lesion count. The proportion of patients experiencing post-PVE disease progression was lower than the one suggested in the current literature. The observed survival outcomes were also considerably better. Post-PVE survival appears to be improving quickly. The same prognosis and operative complication patterns can be provided with PVE to patients that are initially considered as inoperable. Additional studies might be relevant to assess the impact of a broader usage of PVE in borderline FLR cases.

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Data statement

Our full dataset has been uploaded in the data repository.

Ethical approval

Ethical Approval was given by the CHUM human research ethic board (12.106).

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Author contribution

All authors (Collin, Y., Paré, A., Belblidia, A., Létourneau, R., Plasse, M., Dagenais, M., Turcotte, S., Martel, G., Roy, A., Vandenbroucke-Menu, Frank. and Lapointe,R.) contributed to study conceptualization, paper writing and paper review.

Collin, Y., Paré, A. and Belblidia, A. were involved in data collection.

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Conflicts of interest

None to declare.

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Appendix A. Supplementary data

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