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Results of systematic second-look surgery plus hipec in perforated or pt4 colon cancer. Case series

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ABSTRACT

Background: Perforated or pT4 colonic tumors have a bad prognosis with a high rate of relapse, including peritoneal relapse (20–30%). Our aim is to analyze the effectiveness of Second Look surgery (SLS) + hyperthermic intraperitoneal chemotherapy (HIPEC) in these patients for early treatment of peritoneal relapse (PR) or for preventing it.

Patients and methods: Patients previously operated for colon cancer, either pT4 or perforated (M0), with no evidence of disease at any level after adjuvant chemotherapy, who undergo systematic SLS + HIPEC (Oxaliplatin 30 min) one year after the initial surgery.

Results: Since February 2014 to July 2018, we performed SLS + HIPEC in 42 patients with M0, either pT4 (n = 33) or perforated (n = 9) colon cancer. Although during SLS there were suspicious lesions in 15 cases (37.5%), they were histologically confirmed in only 4 (9.5%). Histologically confirmed peritoneal relapse (PR) rate at SLS was 6% in pT4 (2/33) and 22.2% in perforated tumors (2/9). Prophylactic HIPEC was performed in all the cases. There was no postoperative mortality. Grade III-IV morbidity occurred in 19% (8/42). With a median follow-up of 33.8 months after primary tumor surgery, 6/42 patients (14.3%) presented peritoneal relapse (PR). 3-year peritoneal disease free survival was 86%, with 3-year disease free survival of 78.6% and 5-year overall survival (OS) of 97.4%.

Conclusion: Peritoneal relapse and survival rates are remarkable in these groups of, a priori, very bad prognosis, which could suggest a beneficial effect of HIPEC.

1. Introduction

Peritoneal relapse (PR) occurs in 2.3–19% of patients after curative surgery for colorectal cancer (CRC) [1–6], is present in 19–35% of all relapses [7–9] and is the second more frequent after liver recurrence for some authors [10]. PR could be even higher because of the inaccuracy of imaging techniques, reaching up to 40% in autopsies of patients died for CRC [2]. Metachronous peritoneal metastases (PM) have a higher incidence in colonic rather than rectal tumors (especially for right colon cancer), in pT4 or N2 stages, in mucinous tumors and in the poorly differentiated ones [1,3–6]. In case of peritoneal or ovarian synchronous metastases resected during the primary tumor surgery (stage IV), the occult peritoneal relapse rate is estimated on 54–71% [11,12].

Attending to the high risk criteria for PM, in the last years there have been several proactive strategies described, either to treat early or even occult metachronous peritoneal metastases with SLS + HIPEC, or to prevent them (adjuvant or prophylactic intraperitoneal chemotherapy) [13,14]. In this proactive way, the first studies were carried on with SLS in selected risk groups (perforated primary tumor or resected either peritoneal or ovarian disease at the primary tumor surgery), finding occult PM in up to 56% [11,15]. As pT4 tumors have a higher PR rate, as described in literature [1,3,4,6,16], up to 36% in 3 years, there have been several clinical trials recently designed using adjuvant HIPEC for T4 cases, either at the time of the primary tumor surgery [18,19] or some weeks after it [20]. After an exhaustive review, we found no publication supporting SLS for pT4 tumors. We present our results of SLS + HIPEC in a group of patients previously operated for pT4 or perforated colon cancer with curative surgery, in a prospective clinical trial carried on in our high volume Peritoneal Surface Disease Unit, with 100 cytoreduction + HIPEC procedures per year.

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1.1. Hypothesis

Second look Surgery + HIPEC allows us to treat peritoneal disease at an earlier stage when present, and gets better peritoneal disease free survival rates.

The primary outcome is peritoneal disease free survival.

2. Patients and Methods

2.1. Study design

SLS + HIPEC is performed in our Center, a University Hospital, since 2012, after Elias et al. [11] initial results, in a prospective study approved by the Ethics Committee of our center, in which all the patients were informed of the aim of it and given written consent to join. The complete series of SLS + HIPEC includes 74 patients who had undergone a colorectal cancer curative surgery, without peritoneal nor regional disease in the follow-up, but with any of the following high risk factors for PR: pT4, perforated tumor, resected synchronous peritoneal disease (RSPD), resected synchronous ovarian metastases (RSOM) or positive cytology. We analyze the results of the systematic SLS + HIPEC in the group of patients previously operated for a pT4 or perforated tumor (M0).

This is a prospective single center series of consecutive cases; the protocol can be accessed at the Institution.

This work has been reported in line with the PROCESS Guideline [45].

The database is registered in a publicly accessible database, with this unique identifying number: 2020-10-30T12:27:09Z. Hyperlink: https://hdl.handle.net/20.500.12530/54279.

2.2. Procedures

After primary tumor surgery, patients received adjuvant systemic chemotherapy (CT) for 6 months. In those with good performance status and no evidence of disease at any level after adyuvant CT, we proceed to SLS + HIPEC around 1 year after the initial surgery, either by laparotomy or laparoscopy (if previous surgery was perfomed by laparoscopy). In the SLS we performed adhesiolisis as needed, resection of peritoneal suspicious lesions if found, stoma closure if present, and resection of target organs (omentectomy, appendectomy and adnexectomy in postmenopausal women). Were suspicious peritoneal lesions found, surgical PCI (Peritoneal Cancer Index) was calculated, but it was not considered definitive until confirmed by the histological study (pathological PCI = *gold standard*). HIPEC (either open or closed with CO_2 recirculation) was performed using Oxaliplatin 460 mg/m^2 at 42 °C during 30 min, with intravenous infusion of 5-fluouracil (400 mg/m^2) and leucovorin (20 mg/m^2) 30 min before starting the HIPEC.

In the postoperative period major morbidity at 90 days (Dindo-Clavien classification [21]) and length of hospital stay were recorded. After discharge patients were followed-up with thoraco-abdomino-pelvic CT scan and tumor markers every 3–4 months for the first 2 years, and every 6 months for the next 3 years (oncological protocol of our Institution). If an intra or extraperitoneal relapse occurred, patients were treated according to the decision of the MDT of our Institution, with curative surgery (even a second cytoreductive surgery + HIPEC in case of PR) in those with appropriate criteria. No patient was lost in the follow-up. All the surgeries were performed by the Surgeons in the Peritoneal Disease Unit, experienced in this technique.

2.3. Statistical analysis

Qualitative variables are described using distribution frequencies and are compared with Pearson χ [2] or Fischer's exact tests. Quantitative variables are described by its median and interquartile range (IQR) or total range, and compared with Student T test or Mann-Whitney *U* test. Survival analysis is done with the Kaplan-Meier method and the curves are compared with the log-rank test. All the statistical analysis were done using SPSS 25.0. Statistical significance was set at a p value less than 0.05.

3. Results

Since February 2014 through July 2018 we performed 42 SLS + HIPEC in patients who had previously undergone curative surgery for pT4 (n = 33) or perforated (n = 9) colon cancer, with no evidence of disease in the follow-up, one year after the initial surgery (median 10.6 months; range 7–23). Data were analyzed in February 2019.

Characteristics of the primary tumor are as shown in Table 1. There are only 2 rectal tumors, both above peritoneal reflection. 7 patients (16.6%) had stoma, all done in urgent primary tumor surgery either for perforation (n = 4) or other complication in pT4 tumors (n = 3).

3.1. Second Look surgery (SLS)

Surgical approach was laparotomy in 31 patients (22 pT4, 9 perforated) and laparoscopy in 11 (1 of them converted; all pT4, and all of them had had the primary tumor surgery also done by laparoscopy).

During SLS we found suspicious lesions (surgical peritoneal carcinomatosis = SPC) in 15 cases (35.7%), but they were histologically confirmed (pathological peritoneal carcinomatosis = PPC) only in 4 patients (9.5%). The rate of +PPC was 6% in pT4 (2/33) and 22.2% in perforated tumor (2/9) (Table 1), with no statistical significance (p = 0.14).

Median PCI in the 4 +PPC cases was 10 (range 2–33). In 2 patients, one in the pT4 group and another in the perforated tumor group, there was high volume PC found, despite negative preoperative image test, the first one being considered unresectable (PCI 33), and managing to achieve complete cytoreduction in the second one (PCI 16).

At the end of surgery we performed HIPEC in all the patients except in the one with unresectable PC (though we have analyzed all the cases by intention to treat). Median length of surgery was 281 min (range 120–450), with no statistical difference between + SPC (300 min) and -SPC (260 min) (p = 0.21).

Table 1
Characteristics of patients and incidence of PPC.

	pT4 (n = 33)	Perf tum (n = 9)	TOTAL (n = 42)
Median age	61.8	60.5	61.6
Sex (M/F)	16/17	3/6	19/23
Primary tumor site			
Right	14	1	15
Left-sigmoid	18	7	25
Upper rectum	1	1	2
Primary tumor pT			
pT3	0	2	2
pT4	33	7	40
Primary tumor pN			
pN0	12	3	15
pN1-2	21	6	27
Hystological grade/type			
Well/mod diff	23	8	31
Poor/indif	5	1	6
Mucinous	3	0	3
Signet Ring Cell	2	0	2
Stoma closure	3	4	7
+PPC in SLS: n(%)	2* (6%)	2 (22.2%)	4* (9.5%)

* one of them with unresectable PPC.
PPC: pathological peritoneal carcinomatosis. Perf tum: perforated primary tumor. SLS: Second Look surgery.

4. Morbidity and mortality

There was no postoperative mortality. Major complications (Dindo-Clavien grade III-IV) occurred in 19% (8/42), no statistical significance between + SPC (13.3%) and +SPC (22.2%) (p = 0.48). 81% of the patients had no major complications in the postoperative course.

Median length of stay was 7.5 days (range 1–44) and 1 day in ICU/PACU (IQR 2), no statistical significance between + SPC (9 days; range 1–44) and -SPC (7 days; range 4–26) (p = 0.25).

5. Follow-up, peritoneal relapse and survival

5.1. Median follow-up after the primary tumor surgery is 33.8 months (range 7–68). No patient has been lost in the follow-up

5.1.1. Global and peritoneal relapse

Gross rate of recurrence at any level (not only peritoneal) is 23.8% (10/42), showing no difference between both groups pT4 (24.2%) and perforated tumor (22.2%). Table 2 shows the site of the recurrences (all of them are either peritoneal or hepatic) and the surgical rescue (in 100%). There was no relapses othersites.

Gross rate of PR is 14.3% (6/42). 4 of the 6 PR (66.6%) were diagnosed at the time of the SLS (2 in the group pT4, one of them being unresectable, and 2 in the perforated tumor group), and the rest in the follow-up (both in the group of pT4, they underwent CRS + HIPEC, but one of them was non-resectable).

5.1.2. Survival

As shown in Table 3, 3-year Kaplan-Meier survival rates were: PR 14%, peritoneal disease free survival (PDFS) 86%, disease free survival (DFS) 78.6% and overall survival (OS) 97.4%. Despite the difference in PR and PDFS between both groups, there is no statistical significance (p = 0.46).

DFS and PDFS are estimated until the first relapse, but it can be confusing as 100% of the relapses (either liver or peritoneal relapses, even the 4 +PPC found in the SLS) have been surgically rescued (Table 2) (radical surgery in all the 4 peritoneal and the 4 hepatic ones).

6. Discussion

Either pT4 pathological stage and perforated tumor are clear bad prognosis factors in CRC and have been linked to higher peritoneal relapse (PR) rates. A considerable part of pT4 develop metachronous peritoneal metastases (PM) [3,4,6,16,22] (estimated rates of 15.6% at 1 year and 36.7% at 3 years [17]), and survival rates described in literature for non-metastasic pT4 tumors are 5-year OS of 60% and 5-year DFS of 50% [23] (even though recent series [24] present 5-years cancer-specific survival of 65.4% for pT4a and 78.2% for pT4b, and 5-year DFS of, respectively, 61.8% and 65.4%). Perforated CRC happens in 1.6–5.4% of all the cases [25], and is as well known as a bad prognosis factor [26], having a 5-year OS of 37% [25], and a 1-year hidden PR incidence of 27% [11], similar to that in our series (22.2%). However, the rate of +PPC in the SLS for pT4 tumors in our series is very low (6%). In fact, since May 2018 we stopped including patients with pT4 tumors in the SLS program as we found a very low number (13.3%) in the preliminary analysis [27], having into account the potential morbidity of the process, which in that time was 15.2% and now is 19%. While you may expect a lower morbidity when the CRS + HIPEC is performed in these cases with no peritoneal radiological findings, it is always present a risk dued to the necessary adhesiolisis, as well as the peritoneal or visceral resections in those + SPC patients and the stoma closure (16.6% in our series), with long surgeries required (median 281 min) and the risk of intestinal complications.

Median time between colon resection and diagnosis of metachronous PM is 11–18 months (range 2.5–88 months) [6,16], so we perform the SLS around one year after the initial surgery. However, the results can not be extrapolated to the global group of pT4 and perforated tumors, as this period of time excludes the patients who have a recurrence before the SLS is performed, about a quarter of the whole group [28]. On the other hand, adjuvant HIPEC during the primary tumor surgery, based on the seemingly good results of intraperitoneal chemotherapy in previous trials [29], could be performed in the supposed high risk patients, considering that it does not require an additional procedure [30]. But this approach has also inconvenients, as the fact that it is not available in every Hospital where oncological colorectal surgery is performed, that it can not be performed in an urgent surgery for perforated tumor (not even in the Centers that usually perform HIPEC), and that it adds a risk of overtreating, dued to the low reliability of image tests for preoperative diagnosis of T4 [31]; around 40% of the patients classified as cT4 are pT2-3 [32], and a big part of pT4a tumors are only diagnosed postoperatively. So, SLS + HIPEC could be a more appropriate option for daily practice, being our results surprising for these groups, both pT4 and perforated tumors.

The results of our series (3-year PDFS 86%, 3-year DFS 78.6% and 5-year OS 97.4%) are remarkable in a group of patients of, a priori, bad prognosis (not expected DFS >65% nor OS >70% at its best [24]), and might indicate benefit from SLS + HIPEC, improving the prognosis due to an early treatment of occult PR (even if it is only found in 9.5% in our series) or preventing future PR. However, the negative results of three recent studies on different CRC scenarios (all of them also using Oxaliplatin 30 min) have arisen doubts on the efficacy of HIPEC, in spite of all the gathered data during the last two decades about CRS + HIPEC in selected patients with established CRC PM [33] and the initial enthusiasm about the proactive approach for early treatment and/or prevention of PR in high risk patients [11,29]. However, although some authors have tried to reject the HIPEC [34,35] based on those studies,

Table 2
Recurence and surgical rescue.

	Total recurence	Recurence/surgical rescue		
	Gross rate n (%)	peritoneal	hepatic	TOTAL
Whole series (n = 42)	**10 (23.8%)**	**6/6***	**4/4**	10/10*
pT4 (n = 33*)	8 (24.2%)	4/4	4/4	8/8
Perforated (n = 9)	2 (22.2%)	2/2	0	2/2

*includes the 4 +PPC (2 in each group), considering the SLS as surgical rescue (one of them non-resectable in the pT4 group).

Table 3
Peritoneal relapse and survival from primary tumor surgery.

		pT4 (n = 33*)	Perforated (n = 9)	Whole series (n = 42)
Peritoneal relapse	**GROSS RATE**	4 (12.1%)	2 (22,2%)	**6 (14.3%)**
	1 year	3%	11.1%	4.8%
	18 months	3%	22.2%	7.1%
	3 years	11.7%	22.2%	**14%**
PDFS	**median**	NR	NR	**NR**
	1 year	97%	88.9%	95.2%
	18 months	97%	77.8%	92.9%
	3 years	88.3%	77.8%	**86%**
DFS	**median**	55.6 months	NR	**55.6 months**
	1 year	97%	88.9%	95,2%
	18 months	90.9%	77.8%	88.1%
	3 years	79.1%	77.8%	**78.6%**
OS	**median**	NR	NR	**NR**
	1 year	100%	100%	100%
	18 months	100%	100%	100%
	3 years	96.8%	100%	97.4%
	5 years	96.8%	100%	**97.4%**

* one of them with unresectable PPC at SLS. Median follow-up 33.8 months.
PPC: pathological *peritoneal carcinomatosis; PDFS: peritoneal disease free survival; DFS: disease free survival; OS: overall survival; NR: not reached.*

their detailed analysis reveal some limitations that make us read the results with caution, even with the intraperitoneal 30 min Oxaliplatin protocol.

In the PRODIGE-7 [36] there was no difference on 5-year OS with or without HIPEC (39.4 vs 36.7%) after the resection of stablished PM (DFS 14.8 vs 13.1%). Nevertheless, there have been some critics, as the short time exposure to Oxaliplatin, the inclusion of patients with PCI >20, the overestimation of the effect of HIPEC on OS (18 months) for the sample size and the election of OS as the main end-point (as HIPEC could reduce the PR, while the OS is affected by the systemic treatment received by these patients) [37]. It is neither clear to what extent preoperative Oxaliplatin-based systemic chemotherapy may cause a degree of tumor resistance which might decrease the effect of intraperitoneal Oxaliplatin based chemotherapy [38].

In the same way, in the PROPHYLOCHIP trial (NCT01226394) [39] over SLS + HIPEC vs surveillance in high risk patients for PR (different inclusion criteria from those in our series), 3-years DFS was similar in both groups (44 vs 51%; p = 0.75). PDFS, the one that could be improved with HIPEC, is not analyzed, though they publish the PR gross rate, being very surprising, as even if it is 52% in the group of SLS + HIPEC (with 32% of PR in the follow-up), in the surveillance group it is only 33%.

The Dutch clinical trial COLOPEC (NCT02231086)[22] has been recently published, with an intermediate strategy of adjuvant HIPEC, carried on 5–8 weeks after the primary tumor surgery in most of the patients (91%), considering as high risk criteria exclusively T4 (80%) or perforated tumors (20%), as in our study (Table 4). PDFS, 18 months, was similar in both groups, with or without adjuvant HIPEC (80.9% vs 76.2%; p = 0.28), with a PR gross rate of 21%, which highlights the topic. The main barrier of the study is the masking of the potential effectiveness of adjuvant HIPEC, as almost half (47%) of the PR in the HIPEC arm were diagnosed early and unexpectedly before receiving it (in the surgery for HIPEC deferred administration at 5–8 weeks), even if they are all analyzed by intention to treat to ensure the design of the study. In fact, the rate of PR in the patients that did receive HIPEC was only 10%. One more limitation of the study is the delay of the onset of adjuvant systemic chemotherapy in the arm of HIPEC (median 10 weeks vs 6 weeks in the control group), which is nowadays considered as suboptimal treatment [40]. COLOPEC figures can not be extrapolated to all the T4 or perforated tumors, as the exclusion criteria take off the analysis to all the patients with serious comorbidities or those with primary surgery complications that interfere with HIPEC at 8 weeks [20].

So these three clinical trials, despite its undoubted worthiness, have their limitations and in some points they arise more questions than answers, so their conclusions can not be taken as definitive. In fact, the first two ones have not been published yet despite the time elapsed (presented in June 2018), so it is not possible to analyze the methodological details or their possible biases [41]. That is why, despite the results of PRODIGE7, it seems to be early to change the clinical practice before a complete peer reviewed publication [42,43], and in fact, most of the groups, even the French one, keep on considering the use of HIPEC (changing to Mitomycin-C) as the option [44]. As far as for our study, not being of high grade of evidence (no control group), it is prospective and it honestly shows our daily practice, the surprisingly low rate of post-SLS PR (only 2 cases with a long follow-up) and the really high 3-year PDFS (86%, when it was not expected to be higher than 70%) suggest a positive effect of HIPEC despite the data of the three mentioned trials, which we do not consider as definitive.

However, our current recommendation on the use of prophylactic HIPEC, waiting for the publication of the ongoing trials (highlighting the Spanish study HIPEC-T4[18]) is that it should be only carried on in the context of clinical studies approved by the Ethics Committee and exclusively in high volume Units. Further studies could be focused on using a different drug for the HIPEC, different dosage, …

Table 4
Comparison with the COLOPEC study (adjuvant HIPEC).

	our series SLS + HIPEC	COLOPEC	
	n = 42	Surveillance (n = 102)	adj HIPEC (n = 100)
PR gross rate	14.3% (6/42)	23%	19%
PR Kaplan-Meier 18-months	7.1%	19.1%	15.2%
PDFS 18-months	92.9%	76.2%	80.9%
DFS 18-months	88.1%	69.3%	69%
OS 18-months	100%	94.1%	93%

SLS: Second-Look surgery; adj HIPEC: adjuvant HIPEC; PR: peritoneal relapse; PDFS: peritoneal disease free survival; DFS: disease free survival; OS: overall survival.

Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

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Ethical approval

The study was approved by the Ethics Committee of the Institution.

Provenance and peer review

Not commissioned, externally peer-reviewed.
Not previously presented at any conference or meeting.

Author contribution

Á Serrano del Moral: study design, data collection, writing, data analysis. E Pérez Viejo: data collection. I Manzanedo: data collection. F Pereira: supervising.

Registration of research studies

- Name of the registry: 2nd look T4 y perforados sin metástasis.xlsl.
- Unique identifying number or registration ID: 2020-10-30T12:27:09Z.
- Hyperlink to your specific registration (must be publicly accessible and will be checked): https://hdl.handle.net/20.500.12530/54279.

Guarantor

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Declaration of competing interest

No conflict of interest to declare by any of the authors.

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