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CLINICAL MANAGEMENT OF PERITONEAL METASTASES FROM COLORECTAL CANCER

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Peritoneal metastases (PM) from colorectal cancer (CRC) were traditionally associated with bad prognosis. Only recently, cytoreductive surgery (CRS) with hyperthermic intraperitoneal chemotherapy (HIPEC) has resulted in survival improvements. We reviewed the currently available literature regarding the clinical management of colorectal PM. The most relevant and recent studies were selected and their findings were discussed. From these series, the weighted median overall survival was 31,6 months (range 16–51). Major morbidity was 17,6–52,4% (weighted average 32,6%). Mortality was 0–8,1% (weighted average 2,9%). Additional relevant topics, such as CRC-PM prevalence, results by systemic therapies, preoperative work-up, and technical aspects were summarized through a narrative review. The recent literature suggests that CRS/HIPEC is gaining acceptance as standard of care for selected CRC-PM patients. Refinement of selection criteria, and rationalization of comprehensive systemic and local-regional management is ongoing. Prevention and early treatment of PM are new and promising options.

Keywords: *colorectal cancer, peritoneal metastasis, cytoreductive surgery, hyperthermic intraperitoneal chemotherapy, HIPEC, liver metastasis.*

Introduction

Colorectal cancer (CRC) is the third most common tumor worldwide [1]. Recent advances, such as early diagnosis by colonoscopy, highly effective systemic chemotherapy (sCT), and targeted agents, have significantly improved patient prognosis. The use of surgery and local-regional therapies to treat metastatic tumor regionally confined to specific organs (such as liver or lung) has resulted in further improvements [2].

Peritoneal metastases (PM) from CRC has been traditionally regarded as end-stage disease only amenable to palliative sCT, or supportive care [3]. In recent years, better knowledge of the natural history has evolved into the current understanding of PM as a local-regional disease. Aggressive cytoreductive surgery (CRS) has been combined with intraoperative/perioperative intraperitoneal chemotherapy to eradicate microscopic residual disease [3–4].

Despite a randomized trial, and a growing body of retrospective data suggesting survival benefit over historical non-randomized controls [5–6], criticism still centers on the scarcity of high-quality controlled studies, high rates of life-threatening complications, and lack of standardization of treatment protocols [3]. We reviewed the relevant literature regarding the clinical management of CRC-PM.

Epidemiology of colorectal peritoneal metastases

PM from CRC are relatively common. In a population-based study collecting 11 124 patients in Stockholm County during 1995–2007, the prevalence of synchronous PM was 4,3%, and the cumulative incidence of metachronous PM was 4,2%. Independent predictors for metachronous PM were right-sided colon cancer (P=0,002), pT4 stage (P=0,001), pN2 stage with <12 lymph-nodes examined (P<0,001), emergency surgery (P<0,001), and non-radical surgery (P<0,001) [7]. In the Eindhoven Cancer Registry (1995–2008), 3,8% of patients were diagnosed with synchronous PM, and 3,5% with metachronous PM. The peritoneum was the second most common single site of metastasis, after the liver [8–9]. In surgical series, PM were diagnosed in 4-19% of patients after curative surgery, and up to 44% at reoperation for recurrent CRC. In autopsy studies, PM prevalence is 40–80% [10].

Treatment by systemic chemotherapy

There are poor literature data on sCT in CRC-PM patients, and no randomized trial has been conducted in this clinical setting. Median survival exceeding 30 months has been recently obtained in all-type metastatic CRC by modern combinations such as FOLFOXIRI (oxaliplatin, irinotecan, 5-fluorouracil, and folinic acid) and bevacizumab, or doublets plus anti epidermal growth factor receptor (EGFR) in K-RAS wild-type tumors [11]. However, it remains unclear if such results are replicable in PM.

Historically, median survival of CRC-PM was only 5,2-7 months in unselected series treated with supportive care, outdated 5-fluorouracil-based sCT, and/or palliative surgery [12–14]. In a randomized study, median survival of selected patients with potentially resectable PM was 12,6 months with 5-fluorouracil-based sCT [5]. Recent data suggest only limited improvements. Survival results appear to depend on patient selection and increasingly aggressive sCT. Oxaliplatin/irinotecan-containing combinations are associated with median survival ranging from 10,1 to 15 months. The use of monoclonal antibodies against VEGF and EGF receptor may result in further improvements (median 15,2-18-2 months) [15–21]. Chua reported median survival of 23 months with oxaliplatin/irinotecan-containing sCT plus biologic agents, 15 months with the same chemotherapies without biologic agents, and 11 months with 5-fluorouracil-based sCT [17].

The Peritoneal Surface Disease Severity Score (PSDSS) is a recently developed score to stage patients with PM, based on symptom severity, disease extent, and primary tumor histopathology [16–17]. Peltz stratified outcomes of different systemic treatments according to PSDSS in 167 patients treated before 2006. In stage I and II patients, which may be assumed to be potential surgical candidates (good clinical conditions, limited/moderate PM extent, moderate tumor aggressiveness), median survival was 16 months with supportive care, 16 months with 5-fluorouracil-based sCT, and 28 months with oxaliplatin/irinotecan-containing sCT ± biologic agents [16].

Two studies have demonstrated that modern systemic treatments result in lower survival benefit in CRC-PM, as compared with non-PM metastases. Franko analyzed 2101 patients included in two randomized trials of the North Cancer Central Treatment Group (N9741 and N9841). Overall, 364 patients with PM were individuated (17,4%). Patients were treated with 5-fluoruracil, folinic acid, plus oxaliplatin or irinotecan, oxaliplatin plus irinotecan, or irinotecan alone. Median survival was 12,7 months in patients with PM and 17,6 months in those without PM (P=0,001) [18]. In the retrospective analysis of two pooled Dutch randomized studies (CAIRO and CAIRO2), median survival was decreased in patients with PM, as compared with those without PM [19].

Principles of cytoreductive surgery and perioperative intraperitoneal chemotherapy

Cytoreductive surgery may be seen as a tool to maximize response to intraperitoneal chemotherapy, because locally delivered drugs penetrate in tumor tissue not more than few millimeters. CRS must aim at removing all visible tumors. Near complete cytoreduction, leaving behind millimetric residual tumor, may only be pursued to

preserve minimal postoperative organ functions. On the other side, the role of local-regional chemotherapy is to preserve the macroscopically complete surgical response by eradicating microscopic residual disease [3–4].

Cytoreductive surgical procedures have been formalized by Sugarbaker [4]. Diaphragmatic, anterior abdominal wall, omental bursa, and pelvic peritonectomy, greater and lesser omentectomy are usually combined with visceral resections, as needed. Because visceral peritoneum is more intimately attached to underlying structures, tumor implants on visceral surfaces require organ resections [22].

The extent of peritoneal involvement is rated during the abdominal exploration using the peritoneal cancer index (PCI), a semi-quantitative score that rates lesion size from 0 to 3 (no tumor, ≤5 mm, >5-50 mm, or >50 mm) in 13 abdominal-pelvic regions, resulting in a numeric score (PCI 0-39) [32]. The completeness of cytoreduction (CCR) is classified according to Sugarbaker, as CCR-0 (macroscopically complete); CCR-1 (residual disease ≤2,5 mm in any region); CCR-2 (residual disease >2,5 mm and ≤25 mm) and CCR-3 (residual disease >25 mm) [23].

Timing of gastrointestinal anastomoses and need for protective ostomies are still controversial issues. In our center, anastomoses are performed before HIPEC because both in the literature and our experience there is no evidence of increased risk for anastomotic complications, or isolated recurrence on suture lines. On the contrary, heat and drug-induced bowel edema can make anastomosis completion technically difficult. Our policy is to perform protective ostomies only in cases at high risk for anastomotic leakage [22]. However, some authors recommend a more liberal approach to ostomies.

Local-regional chemotherapy is performed either as hyperthermic intraperitoneal chemotherapy (HIPEC), or normothermic early postoperative intraperitoneal chemotherapy (EPIC) [24]. The pharmacological rationale of intraperitoneal administration relies on the dose intensification originated by the presence of a semi-permeable plasma-peritoneal barrier. Intraperitoneal delivery allows higher local-regional concentration with minimal systemic toxicity [25].

Intraoperative/early postoperative time setting allows optimal distribution throughout the abdominal cavity before postoperative adhesions develop, and tumor cells entrapped in scar tissue give rise to disease recurrence [25–26]. Mild hyperthermia (41–43°C) has a direct cytotoxic effect by several mechanisms, including DNA repair impairment, protein denaturation, oxidative metabolism inhibition, and increased apoptosis. Also, it increases the efficacy of antiblastic agents, such as mitomycin-C, and platinum compounds, and their penetration into tumor tissue [25].

HIPEC techniques vary widely among centers, in terms of close- versus open-abdomen techniques, drug(s), drug dosage, target temperature, duration, and carrier solutions. The choice of antiblastic drugs is based on their clinical efficacy and pharmacokinetics. The perfect agent should be hydrophilic, with a high molecular weight to limit its passage through the peritoneal-plasma barrier, high plasma clearance, and mechanisms of action potentiated by hyperthermia. Cell-cycle phase non-specific agents are indicated for this single-shot treatment. Currently, two schedules are widely used: open-abdomen oxaliplatin ± irinotecan with concurrent intravenous 5-fluorouracil and folinic acid, and open- or close-abdomen mitomycin-C, alone or in combination with other drugs [27–29].

EPIC consists of the administration of normothermic antiblastic agents through peritoneal Tenckhoff catheters or subcutaneous ports, starting immediately after surgery and continuing for 1–5 days. Drugs with high rate of hepatic extraction and no significant heat enhancement may be used, such as 5-fluoruracil, doxorubicin, or taxanes [25–26].

Patient selection for CRS/HIPEC

Given the technical complexity, economic costs, and relatively high rates of postoperative complications, knowledgeable selection of surgical candidates is essential to optimize oncologic outcomes of CRS/HIPEC with acceptable treatment-related morbidity [30–31]. Patients have to be fit to deal with a 8–14 hour surgery, extensive peritoneal stripping, multi-organ resections, and local-regional chemotherapy under hyperthermic conditions [4]. Older age, poor performance (World Health Organization score >2), significant co-morbidities, impaired renal, cardio-vascular, respiratory, hepatic, and bone-marrow functions represent exclusion criteria.

Multidetector computed tomography (CT) scan with oral and intravenous contrast medium represents the current standard to select patients amenable to potentially complete CRS. However, CT-scan still suffers from some limitations in identifying small peritoneal implants (<5 mm) [32–33]. Magnetic resonance imaging has been suggested to have better accuracy than CT-scan, but it needs to be read by experienced radiologists [34]. Positron-emission tomography is useful to detect systemic metastases [32].

Radiological features that predict failure to obtain complete CRS are extensive small bowel and mesenteric involvement, massive sub-hepatic disease, biliary and ureteral obstruction, bowel obstructions, pelvic/retroperitoneal nodal involvement, severe ascites, extra-peritoneal disease (except for limited and resectable spread through the diaphragm, and limited LM) [32–33]. It is increasingly clear from the literature that peritoneal disease extent has a major prognostic impact, with a threshold beyond which complete CRS/HIPEC is not beneficial. Various PCI cut-offs have been proposed for patient selection (PCI>20, PCI>16, or PCI>14), but this issue is still a matter of clinical research [35–36].

Regarding histo-pathologic features, undifferentiated/poorly differentiated, and signet-ring cell neoplasms are associated to poor prognosis [37]. Poor response to prior sCT is an exclusion criterion in many centers [38–39], while other authors have reported that it does not necessarily carry a negative prognosis [40].

Laparoscopy is useful to obtain pathological diagnosis, predict surgical resectability, quantify peritoneal involvement, and assess response to previous therapies, thus avoiding unnecessary laparatomies. Laparoscopic CRS/HIPEC has been shown to be technically feasible and safe in patients with low tumor load [41].

Results of treatment by CRS/HIPEC

The study published in 2003 by Verwaal still remains the only randomized trial in this setting [5]. 105 patients were randomly assigned to either standard fluorouracil-based s-CT (-leucovorin) with or without palliative surgery (n=51), or an experimental arm with CRS/HIPEC, followed by the same sCT (n=54). After a median follow-up of 21,6 months, median survival was 12,6 months in the standard arm, and 22,3 months in the experimental arm (P=0,032). Treatment-related mortality in experimental arm was 8%.

Of great relevance is the multi-institutional series by Elias including 523 patients who underwent CRS/HIPEC-EPIC in 23 institutions. Median overall survival was 30,1 months, and 5-year survival was 27% [38]. Two major prognostic factors were highlighted: completeness of surgical cytoreduction, and peritoneal disease extent. Median survival was 33 months after CCR-0 cytoreduction (n=439), 20 months after CCR-1 cytoreduction (n=53), and 7 months after grossly incomplete cytoreduction (n=22). Median survival was 40 months for PCI=1-6, 29 months for PCI=7–12, 25 months for PCI=13–19, and 18 months for PCI>19. Both CCR score and PCI, together with negative lymph-nodes, and the use of adjuvant sCT were recognized as independent prognostic factors. The authors' conclusions were that HIPEC is only justified after complete CRS, and for PCI<20, because survival rates in patients with incomplete CRS or PCI≥20 are similar to those obtained with sCT alone.

Two comparative non-randomized trials shared a common study design. The American study compared patients undergoing CRS/HIPEC (+sCT) with controls treated with modern sCT only, because CRS/HIPEC was not available in the centers where they were referred, despite their potential eligibility. Controls were highly selected to ensure comparability with CRS/HIPEC group [15]. Median survival was 16,8 months in 38 controls, and 34,7 months in 67 patients treated with CRS/HIPEC (P<0,001). In a similar multi-institutional French study, strict selection criteria (good performance status; limited, asymptomatic, completely resectable PM; no LM; no disease progression under previous sCT) resulted in the better survival ever reported with CRS/HIPEC (median 62,7 months), and an advantage over comparable controls treated with sCT (median 23,9 months; P<0,5) [39].

Selected recent studies are listed in table 1. These series collected a mean of 148 patients (median 101; range 48–660). The mean percentage of optimal (CCR0/1) cytoreduction, was 86,7% (range 53–100%). Median survival ranged from 16 to 51 months (weighted average 31,6 months), and five-year survival rates from 22% to 50,5% (weighted average 31,0%;) [5, 15, 38–40, 42–55].

Three studies compared different HIPEC regimens. In a Dutch series, mitomicin-C-based HIPEC was equivalent to oxaliplatin-based HIPEC [51]. In an international registry, both regimens were equivalent in the overall population, but mitomicin-C was superior among PSDSS stage I-II patients (54,3 vs. 28,2 months; P=0,012) and correlated to longer survival at multivariate analysis (P=0,042) [49]. Finally, oxaliplatin plus irinotecan was equivalent to oxaliplatin alone in terms of survival, but worse in terms of toxicity [54].

Two studies compared different strategies: in patients with synchronous PM undergoing primary tumor resection and simultaneous HIPEC, survival and complication rates were similar to those of patients in which primary resection was performed before HIPEC (two-stage procedure). However, the data suggested that early referral may prevent extensive secondary bowel resections, decrease anastomotic leakage and permanent colostomy rates [52]. In another bi-institutional series, survival and complication rates do not differ between patients with acute vs. elective presentation of synchronous PM, suggesting that CRS/HIPEC is effective and safe in patients requiring emergency surgery [50].

Treatment of peritoneal and liver metastases

The presence of LM has been traditionally considered a contraindication for CRS/HIPEC, even if a complete CRS could be obtained. A multi-institutional series of 506 patients demonstrated a worse prognosis in patients with liver metastases surgically resected at the same time of CRS/HIPEC [54]. Recent series confirmed the negative prognostic impact of LM [48, 55], while other series did not [38, 44]. Neither a systematic meta-analysis answered the question, showing only a trend towards lower overall survival for patients with PM and LM undergoing CRS/HIPEC (pooled HR=1,24, 95%CI=0,96–1,60) [56].

Investigators of the Institute G. Roussy (Villejuiff, France) have tried to define the selection criteria for simultaneous treatment of LM and PM. Based on a series of 24 patients undergoing CRS and LM resection, followed by HIPEC or EPIC, they suggested that patients with ≤2 easily resectable LM (not requiring major anatomical liver resections), and limited PM might be good candidate to comprehensive treatment, although LM affected negatively prognosis [57]. In their most recent update, 37 patients with PM and LM were matched with 61 patients

with PM alone. Three-year survival was significantly lower in patients with PM and LM: 40% vs. 66% (P=0,04). Three prognostic groups were identified: patients with PCI<12 and no LM (median survival 76 months); patients with PCI<12 and ≤2 LM (median 40 months); and patients with PCI>12 or ≥3 LM (median 27 months) [58].

Prevention and early treatment of peritoneal metastases

Two strategies for the prevention and early treatment of CRC-PM using local-regional chemotherapy have been proposed. The G. Roussy group tested a systematic second-look approach after curative resection and adjuvant s-CT in 41patients selected according to the following criteria: synchronous PM completely resected during primary surgery, synchronous ovarian metastases (also completely resected), and perforated primary tumors. PM were found and treated with complete CRS plus HIPEC in 23 patients (56%) without any clinical, biochemical or radiological evidence of recurrence. The remaining patients underwent complete abdominal exploration and systematic HIPEC. Five-year overall survival was 90%, with one operative death and 10% complication rate [59].

A different strategy is performing HIPEC at the time of primary surgery. Sammartino reported lower peritoneal recurrence rate, better disease-free, and overall survival, by comparison with 50 retrospective controls [60]. Baratti reported a prospective series of 22 patients without systemic metastases who had HIPEC simultaneously with curative surgery, plus adjuvant sCT (oxaliplatin/irinotecan-containing ± biologics), based on primary tumor-associated criteria: resected synchronous ovarian or minimal peritoneal metastases, primaries directly invading other organs, or penetrating the visceral peritoneum. A control group retrospectively included 44 matched (1:2) patients undergoing standard treatments and no HIPEC during the same period. The 5-year cumulative PM incidence was 9,3 % in the HIPEC group and 42,5 % in the control group (P=0,004). Kaplan-Meier estimated 5-year overall survival was 81.3 % in the HIPEC group versus 70,0 % in the control group (p= 0,047). Major morbidity rates were not different between groups (P = 0,75) [61]. Finally, adjuvant laparoscopic HIPEC at 6–8 weeks from primary surgery was demonstrated to be feasible and safe in a Dutch pilot study and is being evaluated in a prospective trial [62].

Treatment-related morbidity and quality of life

Patients with PM are often referred with massive tumor load or after extensive surgical and medical treatments. Their definitive management involves further demanding surgical and comprehensive procedures. Also, there is a steep learning curve in performing these complex procedures [63]. Although impressive reductions in complications have occurred in high-volume centers with increasing experience, high operative risk may be expected and needs to be carefully weighed against the potential benefit of this aggressive approach [31].

Among the series listed in table 1, major morbidity rates of CRS/HIPEC were 17,6–52,4% (weighted average 32,6%); mortality was 0–8,1% (weighted average 2,9%). In a recent review, morbidity was 12–52% and mortality 0,9–5,8% in 10 international high-volume centers (including our institution) treating all-type peritoneal malignancies. These figures are similar to other major gastrointestinal operations, such as duodenopancreatectomy and esophagectomy [31].

The fundamental purpose of cancer therapy is to maximize both survival and quality of life (QOL). An aggressive treatment approach, such as CRS/HIPEC, may impact post-operative QOL. A recent systematic review and a meta-analysis have assessed the available QOL data [64–65]. Despite a relevant heterogeneity in primary tumors, HIPEC protocols and methodologies to assess QOL, the published studies consistently reported that physical, functional and emotional scores drop at 3–4 months after CRS/HIPEC, before becoming similar or better, compared to pre-operative levels, at 12 months. Nevertheless, even when QOL have restored to baseline, depression symptoms may persist after 12 months. This highlights the importance of QOL implications in selecting appropriate candidates, and the need for psychosocial support to help patients to deal with survivorship issues [65].

Conclusions

During the last years, several accomplishments have greatly contributed to the progress of peritoneal oncology: i) epidemiology of CRC-PM has been addressed in population-based studies [7–9]; ii) large retrospective series have strongly suggested that sCT and targeted therapies are less effective in treating CRC-PM than hematogenous metastases [18–19]; iii) strict selection criteria have been definitively accepted as absolute requirements for successful treatment; iv) simultaneous treatment of PM and LM may be offered to selected patients with limited peritoneal and hepatic disease [55–58]; v) large randomized trials have been undertaken, and their results will be available in the next future.

Future developments are expected by better understanding of the mechanism of peritoneal seeding. A molecular signature of the propensity for peritoneal vs. systemic failure would ideally help to individualize both prophylactic and established disease treatment plans. Prospective trials are needed to define which drug, or drug combinations, are more effective local-regionally, as the available retrospective data are mainly inconclusive [75, 79]. Finally, better knowledge of patient- and treatment-related factors predicting operative complications will improve both early and long-term outcomes [34, 67].

Table 1. *Selected series of CRS/HIPEC for colorectalperitoneal metastases*

Center (ref.)	Publ. year	Pts (n.)	CRS	HIPEC	Follow-up (mos.)	Median OS (mos)	5-year OS (%)	P value	Major morb. (%)	Death (%)
Amsterdam, ND [5]	2003	54	81.2% CCR0/1	MMC	21.6	22.3		0.032	–	8%
		51	No CRS	No HIPEC, only s-CT		12.6			–	–
France* [39]	2009	48	100% CCR0/1	OXL ± IRI	63.0	62.7	51.0	<0.005	–	–
		48	No CRS	No HIPEC, only s-CT	95.7	23.9	13.0		–	–
France* [38]	2010	523	83.9% CCR 0	Various	45	30.1	27.0		33.8	3.3
Pittsburgh, PA [15]	2010	67	84.2% CCR0/1	MMC	NR	34.7	–	>0.001	–	–
		38	No CRS	No HIPEC, only s-CT	NR	16.8	–		–	–
Italy* [43]	2011	146	100% CCR 0/1	Various	19.0	21.0	36.0		27.4	2.7
Villejuiff	2011	43	74.4% CCR0	OXL-based HIPEC	48.5	40.8	41.8	NS	34.9	2.3
Montpellier, FR [54]		103	97.1% CCR0	OXL + IRI-based HIPEC		47.0	42.4		52.4	4.9
Lyon, FR [40]	2012	131	86.1% CCR 0/1	MMC + OXL or IRI	58.5	36.3	33.0		21.8	3.8
Belgium* [48]	2012	48	100% CCR 0/1	OXL	22.7	NR	88.7 [5]		52.1 [2]	0
The Netherlands* [46]	2013	660	80% CCR 0[1]	MMC or OXL	41[1]	33.0 [1]	31.0 [1]		34.5 [1]	3.3 [1]
Osaka, JPN [47]	2013	146	76.1% CCR 0	MMC + CDDP	NR	24.4	23.4		17.6	0.7
Eindhoven, ND [52]	2013	52	100% CCR0/1	Synchr. PM; early HIPEC	NR	–	46.0 [2]	NS	32.8	
		20	100% CCR0/1	Synchr. PM; delayed HIPEC	NR	–	48.0 [2]		35.0	
Ghent, BE [43]	2014	166	87.3% CCR 0/1	MMC or OXL	18	27.0	NR		34.9	2.4
Wake-Forest, SC [44]	2014	93	100% CCR 0	MMC or OXL	89	33.6	26.0		23.0	5.4
Milan, IT [45]	2014	101	98% CCR 0/1	MMC + CDDP	44.9	32.0	43.2		23.8	3. 0
Eindhoven, ND [42]	2014	133	96% CCR 0	MMC	22.9	27.0	NS		24.8	0.8
Villejuiff, FR [35]	2014	139	100% CCR 0/1	OXL ± IRI	NR	39.0	39.0		21.6	5.8
International* [49]	2014	418	94.2% CCR0/1	MMC-based HIPEC	NR	32.7	–	0.042	–	–
		166	93.4% CCR0/1	OXL-based HIPEC	NR	31.4	–		–	–
Amsterdam, NL	2014	39	100% CCR0	MMC-based HIPEC	33	37.1	54.0	0.32	48.7	–
Leuven, BE [51]		56	100% CCR0	OXL-based HIPEC	61	26.5	41.1		35.7	–
Nieuwegein	2014	36	97.2% CCR0/1	Synchr. PM; acute present.	16.2	32.1	–	NS	25.0	0
Eindhoven, NL[50]		113	97.3% CCR0/1	Synchr. PM; elective present.		36.1	–		22.1	1.8

CRS: cytoreductive surgery; HIPEC: hyperthermic intraperitoneal chemotherapy; OS: overall survival; CCR 0:: no visible residual disease; CCR 1: residual disease ≤2.5mm; 5FU: 5-fluorouracil; MMC: mitomycin-C; CDDP: cisplatin; OXL: oxaliplatin; IRI: irinotecan; NR: not reported; NS: not significant; *: multi-institutional trial; [1]. calculated in the overall series of 996 patients with either colorectal or appendiceal tumor; [2]: all-grade complication rate; [7]: median OS was 48 in 27 patients with CCR 0/1 and PCI>15, and 15 months in 23 patients with CCR 2/3 or PCI>15.

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