Updates in Surgery (2018) 70:441–447
https://doi.org/10.1007/s13304-018-0592-7

ORIGINAL ARTICLE

Palliation with a multimodality treatment including hypoxic pelvic perfusion for unresectable recurrent rectal cancer: outcomes based on a retrospective study

Stefano Guadagni[1] · Marco Clementi[2] · Maria Bencivenga[3] · Shigeki Kusamura[4] · Caterina Fiorentini[5] · Francesco Masedu[6]

Received: 13 July 2018 / Accepted: 29 August 2018 / Published online: 6 September 2018

Abstract

Patients with unresectable recurrent rectal cancer that progresses after systemic chemotherapy and radiotherapy are candidates for palliation with hypoxic pelvic perfusion (HPP). The aim of this observational retrospective study was to evaluate if a multimodality treatment including HPP and targeted-therapy may be useful to prolong clinical responses and survival of these patients. From a cohort of 77 patients with unresectable recurrent rectal cancer in progression after standard treatments and submitted to HPP, 21 patients underwent repeat HPP using mitomycin C (MMC) at the dose of 25 mg/m^2. After the last HPP, 7 patients received a targeted-therapy with cetuximab according to overexpression of epidermal growth factor receptor in recurrence cancer cells. The median overall survival of these 21 patients from the diagnosis of unresectable recurrent rectal cancer was 23 months (iqr 18–24). After the first HPP, the median survival of the 21 patients until death or end of follow-up was 10 months (iqr 9–13). The 1-year and 2-year survival rates were 71.4%, and 4.8%, respectively. From the first HPP, age > 60 years, a recurrence shrinkage of at least 30% (partial response), and the addition of a post-HPP targeted-therapy with cetuximab significantly affected survival ($P < 0.04$). In conclusion, repeated MMC-HPP followed by targeted-therapy seems to be an effective palliative treatment for patients with unresectable recurrent rectal cancer in progression after systemic chemotherapy and radiation but the results of this study have to be confirmed by a larger phase III trial.

Keywords Unresectable recurrent rectal cancer · Hypoxic pelvic perfusion · Mitomycin C · Cetuximab

Introduction

The incidence of rectal cancer local recurrences after curative intent surgery varies between 2.4 and 10% in modern series [1]. The management of locally recurrent rectal cancer in high volume specialist centers is based on

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s13304-018-0592-7) contains supplementary material, which is available to authorized users.

✉ Stefano Guadagni
stefano.guadagni@univaq.it

Marco Clementi
marco.clementi@univaq.it

Maria Bencivenga
maria.benci@hotmail.it

Shigeki Kusamura
shigeki.kusamura@istitutotumori.mi.it

Caterina Fiorentini
caterina.fiorentini2891@gmail.com

Francesco Masedu
francesco.masedu@cc.univaq.it

[1] Department of Applied Clinical Sciences and Biotechnology, Section of General Surgery, University of L'Aquila, Via Vetoio, 67100 L'Aquila, Italy

[2] Department of Life, Health and Environmental Sciences, University of L'Aquila, 67100 L'Aquila, Italy

[3] General and Upper GI Surgery Division, University of Verona, Piazzale Aristide Stefani 1, 37126 Verona, Italy

[4] Fondazione IRCCS, Istituto Nazionale dei Tumori Milano, Via Venezian 1, 20133 Milan, Italy

[5] Division of Cardiology, Department of Medical Biotechnologies, University of Siena, 53100 Siena, Italy

[6] Department of Applied Clinical Sciences and Biotechnology, University of L'Aquila, 67100 L'Aquila, Italy

multidisciplinary modalities including extensive surgery, intraoperative and/or external irradiation, neoadjuvant and/or adjuvant systemic chemotherapy but, unfortunately, 30–50% of patients are unresectable [2] and several types of palliation are adopted [3]. Hypoxic pelvic perfusion (HPP) is a type of chemotherapy palliation based on the isolation of the pelvic circulation by blocking the blood flow in the aorta and the inferior vena cava with balloon catheters and at the level of the thigh with pneumatic cuffs [4]. The rationale of this loco-regional chemotherapy is based on the high tumor drug exposure in the perfused compartment and in the use of chemotherapeutic agents such as mitomycin C (MMC) who is 10 times more toxic to tumor cells under hypoxic conditions [5]. A median progression-free survival time of 6 months was reported at the beginning of the 2000s after one course of MMC HPP in patients with unresectable recurrent rectal cancer that had progressed after chemoradiotherapy [6]. HPP can be performed using a surgical or a percutaneous approach. A recent pharmacokinetic study demonstrated that the percutaneous approach is not significantly different from the surgical one in terms of tumor drug exposure when MMC at the dose of 25 mg/m^2 is administered; consequently, when perfusion must be repeated several times in the same patient, the percutaneous and surgical methods may be interchangeably adopted [7].

Based on the hypothesis that a multimodality treatment including HPP may be useful to prolong clinical responses and survival, a retrospective study has been done on a cohort of patients with unresectable recurrent rectal cancer that had progressed following radiotherapy and/or systemic chemotherapy.

Materials and methods

Patients eligibility

Patients eligibility criteria were as follows: (i) diagnosis of unresectable recurrent rectal cancer; pelvic sidewall involvement, growth into the sciatic notch, involvement of the first and/or second sacral vertebra, and/or encasement of the bladder or iliac vessels were the main criteria for unresectability, (ii) apparent increase of recurrence size for at least 3 months after radiation therapy or systemic chemotherapy, (iii) performance status of 0–3 based on the Eastern Cooperative Oncology Group (ECOG), (iv) leukocyte count > 2500 cells/mm^3 and platelet count > 50,000 cells/mm^3, (v) serum creatinine concentration ≤ 1.2 mg/dL, (vi) subjects with liver failure, deep venous thrombosis, severe atherosclerosis, or coagulopathy were not eligible.

Patients characteristics

This retrospective observational study was performed at the University of L'Aquila, L'Aquila, Italy, after approval from the investigational review board (n.10/CE/2018) and following the consideration that the patients had an unresectable disease with a predictable course outcome. In a cohort of 77 patients with unresectable recurrent rectal cancer in progression after radiotherapy and/or systemic chemotherapy and submitted to HPP, 21 patients underwent repeat HPP using MMC at the dose of 25 mg/m^2, from 2001 to 2017; 56 patients were excluded from this study because they were submitted to HPP using different drugs schedule. Written consent was obtained after they were given complete information about the disease and the implications of the proposed palliative treatment, in accordance with the ethical standards of the committee on human experimentation at our institution. Table 1 shows

Table 1 Characteristics of 21 patients with unresectable recurrent rectal cancer in progression after standard treatments

Gender	*N*	%
Female	10	47.61
Male	11	52.38
Age	Mean	± S.D. (years)
	64.13	± 13.98
	Median	Iqr (months)
Median elapse time from diagnosis of unresectable recurrent rectal cancer to first HPP	10	9–14
	N	%
Previous treatments		
Endovenous systemic chemotherapy	21	100.0
≥ 3 Systemic chemotherapy lines	17	81.0
< 3 Systemic chemotherapy lines	4	19.0
Radiotherapy	21	100.0
Re-irradiation	18	85.7
Radiation before diagnosis of unresectable recurrent rectal cancer	3	14.3
Surgery	12	57.14
Palliative	11	52.3
Extensive surgery	1	4.7
Other metastatic sites		
Not	5	23.8
Yes	16	76.2
EGFR overexpression	*N*	%
Yes	7	33.3
Not	14	66.7

SD standard deviation, *Iqr* interquartile range, *EGFR* epidermal growth factor receptor

demographic data. The median elapse time from the diagnosis of unresectable recurrent rectal cancer to the first MMC-HPP was 10 months (iqr 9–14).

Perfusions were repeated at intervals of approximately 8 weeks. The rationale and timing of repetition in patients obtaining partial response or stable disease were based on a previous pilot study [6] showing that progression was always observed in presence of residual tumor. In case of complete response, the treatment was not repeated. Treatments were not repeated if the patient did not consent, local recurrence progressed more than 20% in dimension, simultaneous distant relapses occurred, or the general condition of the patient worsened.

HPP techniques and MMC regimen

Before undergoing perfusion, patients received an angiography, or angio-CT, of the aorto-iliac tree and the inferior vena cava. Perfusions were performed under general anesthesia, using surgical or percutaneous approach as previously published [7]. When perfusion must be repeated more than 2 or 3 times in the same patient and the femoral vessels were surrounded by fibrous tissue, the surgical method could be done with iliac vessels exposure but the percutaneous puncture of femoral vessels is also feasible. Figure 1 shows a schema of the techniques.

MMC (25 mg/m^2), diluted in 250 mL of an isotonic sodium chloride solution containing 16 mg of dexamethasone sodium phosphate, was administered over a 3-min period at the beginning of HPP. Chemofiltration was always administered for 60 min at the end of HPP.

Post-HPP therapies

After the last HPP, 7 patients received a targeted-therapy with cetuximab at the dose of 250 mg/m^2 according to overexpression of epidermal growth factor receptor (EGFR) in recurrence cancer cells.

Criteria for responses and adverse events

Tumor responses were assessed using the Response Evaluation Criteria in Solid Tumors, version 1.1 [8] 30–45 days after each loco-regional chemotherapy treatment. Responses of patients treated before 2009 were retrospectively re-classified. Computed tomography (CT), Magnetic Resonance Imaging (MRI), and Positron-emission Tomography (PET) were used to evaluate responses. Pelvic pain requiring at least less than 50% of preoperative analgesic administration 30 days after perfusion was considered an objective pain relief. Adverse events were assessed by using Common

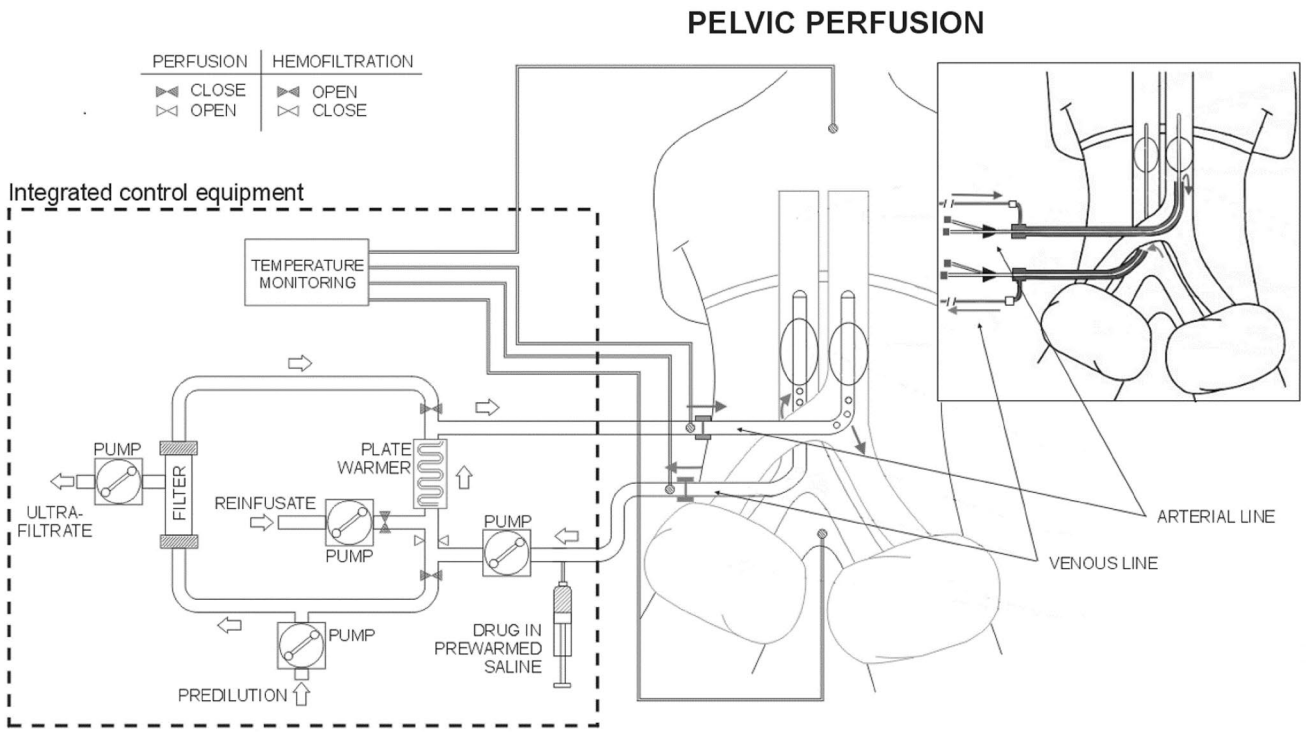

Fig. 1 Schema of the surgical and percutaneous (in cartouche) hypoxic pelvic perfusions with chemofiltration

Terminology Criteria for Adverse Events of the National Cancer Institute (CTCAE v4.03).

Statistical analysis

Descriptive statistics estimated with 95% confidence were provided. The means ± the standard deviation (SD) have been calculated. Survival was estimated by using the Kaplan–Meier product limit estimator. No patients were lost to follow-up. Survival times were stratified according to the clinical variables that can potentially affect survival. Log-rank tests were used to assess the significance of the differences between the groups. Hazard ratios were estimated by using a proportional hazard Cox regression model. Progression-free survival time (PFS) was calculated from the day of the first locoregional treatment. Statistical analysis was performed using STATA software, version 14 (StataCorp, College Station, Texas).

Results

The 21 patients underwent 44 HPP, 28 with the surgical approach, 16 with the percutaneous procedure. The mean HPP number per patient was 2.1 ± 0.1 (median, 2 perfusions). The length of hospital stay after the surgical procedure (mean, 10.2 ± 5.5 days) was significantly longer ($P = 0.01$; Mann–Whitney test) than that after percutaneous procedure (mean, 5.3 ± 2.7 days). This difference was due to iliac vessel exposures and to lymphadenectomies that were performed only in patients submitted to surgical procedure.

Tolerability and procedure-related complications

There were no technical, hemodynamic, or vascular complications during the 44 perfusions, and no perfusion-related postoperative deaths. Femoral cannulation was always possible. The cardiac evaluation with electrocardiography and echocardiography did not show any significant variation before and after perfusions. The complications registered in patients receiving the surgical procedure (which was associated with lymphadenectomy in 3 patients) were seroma (2 patients), persistent leakage of lymphatic fluid from incision (5 patients), and wound infection (1 patients). One patient receiving the percutaneous procedure had an inguinal hematoma (Table 2).

HPP with chemofiltration-related toxicity

Perfusion-related hematological toxicity was not relevant (Table 2). Among the 44 perfusions, the number (percentage) of grade 1, grade 2, and grade 3 toxicities was 5 (23.8%), 2 (9.5%), and 1 (4.7%), respectively. Patients with neutropenia received supportive therapy consisting of granulocyte colony-stimulating factor. Hematological toxicity stopped treatment in one (4.7%) patient. Two cases of grade 2 alopecia were registered, and grade 1–2 gastrointestinal toxicity was observed in 5 patients. Local toxicity, mainly manifesting as scrotum edema and pain, was registered in 2 patients.

Table 2 Procedure related complications and toxicity after 44 HPP in 21 patients with unresectable recurrent rectal cancer in progression after systemic chemotherapy and radiotherapy

	Grade	*n* (%)
Complications		
Seroma	1	2 (9.5)
Persistent leakage of fluid from the incision	2	5 (23.8)
Wound infection	1	1 (4.7)
Inguinal hematoma	1	1 (4.7)
Scrotum edema	1	2 (9.5)
Pelvic pain	1	4 (19)
Toxicity		
Bone marrow hypocellularity	1	5 (23.8)
	2	2 (9.5)
	3	1 (4.7)
Alopecia	2	2 (9.5)
Nausea and vomiting	1	5 (23.8)

n numbers of cases

Tumor and pain responses

The overall response rate after the first treatment was 38% with exclusively partial responses. 13 patients had stable disease (62%). There was no disease progression in the 30 days after the first treatment. No partial responses have been registered in the HPP courses following the first. Ten patients with pelvic pain showed a considerable decrease in pain and analgesic requirement within 36–48 h of the first treatment. Partial relief of pain was registered 1 month after HPP in 4 patients. In 10 patients a moderate improvement of the general conditions has been registered a month later HPP.

Survival

The median overall survival of these 21 patients from the diagnosis of unresectable recurrent rectal cancer was 23 months (iqr 18–24). All these patients underwent systemic chemotherapy, radiotherapy and surgery for the treatment of recurrence with a median elapse time from the recurrence diagnosis to the first HPP of 10 months (iqr 9–14). After the first HPP, the median survival of the 21 patients until death or end of follow-up was 10 months (iqr

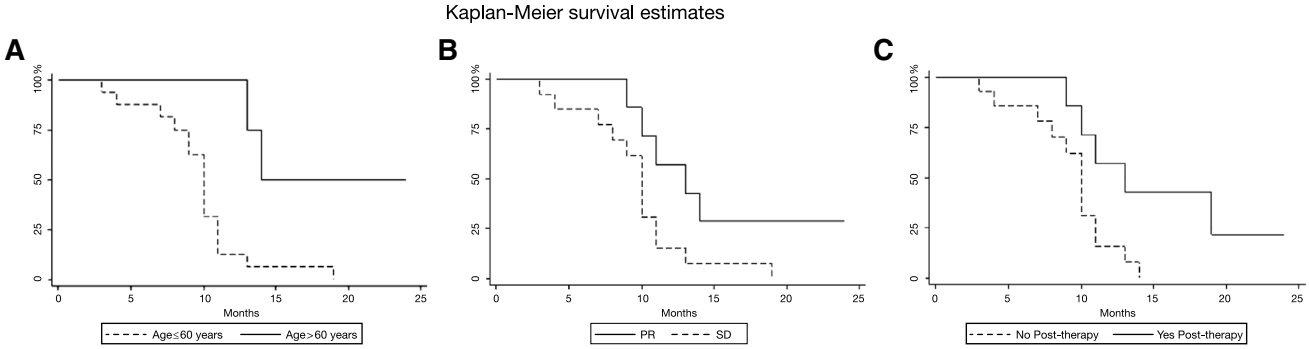

Fig. 2 Survival in 21 patients with unresectable recurrent rectal cancer in progression after systemic chemotherapy and radiotherapy submitted to repeated courses of MMC HPP. Stratification according to age lower or higher than 60 years (**a**), type of response (**b**), and post-HPP therapy (**c**)

9–13). The 1-year and 2-year survival rates were 71.4%, and 4.8%, respectively.

From the first HPP, age > 60 years, a recurrence shrinkage of at least 30% (partial response), and the addition of a post-HPP targeted-therapy affected survival (Fig. 2a–c), whereas gender, number of HPP and the presence of other sites of metastases did not. The MST was 14 months (mean, 14 ± 6.7 months) for patients aged more than 60 years and 10 months (mean, 9.7 ± 3.6 months) for patients younger than 60 years [$\chi^2 = 7.34$, $P = 0.007$, Cox hazard ratio = 5.79]. The median survival time (MST) of the patients who experienced a partial response after HPP treatments was 12 months (mean, 12.5 ± 5.5 months), at the contrary if the patients had a stable disease, the MST was 10 months (mean, 9.6 ± 3.9 months) [$\chi^2 = 4.1$ in the log-rank test, $P = 0.04$, Cox hazard ratio = 2.63]. The MSTs of the patients who received a targeted-therapy after the last HPP was 13 months (mean, 14.3 ± 5.4); without post-HPP therapy the MST was 10 months (mean, 8.9 ± 3.2) [$\chi^2 = 5.42$, $P = 0.02$, Cox hazard ratio = 3.27].

In the 21 patients, a median value of 6 months (iqr 5–7) for PFS has been calculated from the first HPP. A shrinkage of at least 30% (partial response) of the recurrent cancer, significantly influenced the PFS, whereas gender, age, number of HPP and the presence of other sites of metastases did not. The PFS of the patients who experienced a partial response after HPP treatments was 7 months (mean, 9.1 ± 5.3 months), at the contrary if the patients had a stable disease, the PFS was 6 months (mean, 5.6 ± 1.9 months) [$\chi^2 = 6.3$ in the log-rank test, $P = 0.01$, Cox hazard ratio = 3.87] (Table 3).

Follow-up

In 7 patients, targeted-therapy with cetuximab at the dose of 250 mg/m^2 was administered after the last HPP, with grade 2 dermatological toxicity in 3 patients. Among the 21 patients, 3 (14.28%) patients were alive at the end of follow-up, and 18 (85.71%) patients were dead because of relapse of rectal cancer. Interruptions after the first HPP treatment were due to refused consent in 6 cases and in 1 case for hematological toxicity. In 10 patients (47.61%) interruption of HPP treatments was due to disease progression, in 4 patients (19.04%) was due to worsening of general conditions. Site of progression was both distant and local in 20 patients (95.23%).

Discussion

As for other sites of rectal cancer relapse [9], the management of recurrent rectal cancer requires a multidisciplinary approach. When patients with locally unresectable recurrent rectal cancer were treated exclusively with radiotherapy, MST of 12 months was reported for palliative re-irradiation at the end of 1990s [10], but a similar median survival of 13 months has been very recently reported without apparent improvement of the therapeutic efficacy [11]. Our retrospective study on patients with unresectable recurrent rectal cancer that had progressed following radiotherapy and/or systemic chemotherapy demonstrated that a multidisciplinary treatment including repeated courses of MMC-HPP provides further MST of 10 months. When MMC-HPP is followed by targeted-therapy, the MST growth up to 13 months; in this sub-group of patients the overall median survival from the diagnosis of unresectable recurrent rectal cancer was 24 months (mean, 26.2 ± 7.2 months).

A survival ranging from 10 to 18 months have been previously reported after a single course of HPP in patients with unresectable recurrent rectal cancer that had progressed following radiotherapy or systemic chemotherapy [3, 6, 12, 13]. When HPP was routinely performed twice, a mean survival time of 24 months was reported in a Japanese study, adopting a drugs schedule with cisplatin (high dose escalated from

Table 3 Survival in 21 patients with unresectable recurrent rectal cancer in progression after systemic chemotherapy and radiotherapy submitted to repeated courses of MMC HPP

Variables (number of patients)	MST (months)	Log-rank χ^2	*P* value	Cox HR
Age				
< 60 (*n* = 16)	10			
≥ 60 (*n* = 5)	14	7.34	0.007	[5.79, 1.26–26.6]
Gender				
Female (*n* = 10)	10			
Male (*n* = 11)	10	0.06 (ns)	0.807	
Other sites of metastases				
Yes (*n* = 16)	10			
Not (*n* = 5)	10	0.01 (ns)	0.936	
Type of response				
PR (*n* = 8)	12			
SD (*n* = 13)	10	4.10	0.041	[2.63, 0.91–7.56]
Number of HPP treatments				
1 (*n* = 7)	10			
≥ 2 (*n* = 14)	10.5	0.74 (ns)	0.390	
Post-HPP therapy				
Not (*n* = 14)	19			
Yes (*n* = 7)	24	4.88	0.027	[3.27, 1.03–10.31]

Stratification according to age, gender, other sites of metastases stage, type of response, number of treatments, post-HPP therapy

MST median survival time, *HR* hazard ratio, *ns* not significant, *PR* partial response, *SD* stable disease

170 mg/m^2) and 5-fluorouracil (fixed dose of 1000 mg/m^2) [14]. This seems to support the hypothesis that repeated perfusions may be useful to prolong clinical responses and survival. In our study, using MMC monotherapy at the dose of 25 mg/m^2 in repeated courses of HPP, the mean survival time was 11.4 months. It was to be considered that the unresectable rectal cancer recurrences of the 21 patients included in this study had been heavily pre-treated with more than 2 lines of systemic chemotherapy plus re-irradiation for a mean of 11 months; moreover, 16 of 21 patients had distant metastases. This suggest that lack of patient homogeneity makes it difficult to compare retrospective observational studies. However, in our study, the MST of patients submitted to 1 HPP (10 months, iqr 5–13) was not significantly lower than that of patients who underwent 2 or more HPP (10.5 months, iqr 9–14). More than the repetition in self, the different chemotherapeutic schedule (platinum-based polychemotherapy versus MMC monotherapy) and dosage seem to play a relevant role in improving median survivals.

The most relevant aspect of this study was that a post-HPP targeted therapy have significantly improved the MST, suggesting an important role for the biomolecular characteristics of the recurrent cancer cells. The overexpression of EGFR has been utilized in these 21 patients to choose the targeted-therapy but recent observations suggest that also mutations in the family of RAF (Rapidly Accelerated Fibrosarcoma) kinases and human epidermal growth factor receptor 2 (HER2) amplifications should be always considered in colorectal cancer relapse targeted-therapy [9]. Biomolecular aspects, such as microsatellite instability, could explain the significantly higher survival registered in patients over than 60 years treated with a DNA-alkylating agent (MMC) of this series in comparison to those younger than 60 years.

As concerning tolerability of locoregional chemotherapy in terms of cytotoxic side-effects, this study confirms previously reported data [14, 15] about the efficacy of detoxifying treatments, such as chemofiltration or dialysis. Using chemofiltration after HPP, only 4.7% of treated patients experienced a G3 hematological toxicity. Moreover, a slow-flow HPP was adopted to reduce leakage and therefore to lower systemic toxicity because of a well-documented relationship [16] between the flow in the circuit and drug leakage to the systemic circulation.

A potential limitation of this study is that this is a phase II trial, and results must to be confirmed by a larger phase III study comparing different associations between locoregional chemotherapy and targeted-therapies.

Conclusions

In conclusion, MMC HPP seems to be an effective palliative treatment for patients with unresectable recurrent rectal cancer in progression after systemic chemotherapy and

radiation. This palliative treatment rapidly reduced symptoms in patients with pelvic pain and improved general conditions in a month; the symptoms response is a strong benefit in the palliative treatment of patients excluded from curative therapy. MMC HPP should be considered as a link of a chain in a multidisciplinary treatment based on recent observations of translational research.

Compliance with ethical standards

Conflict of interest The Authors declare that there is no conflict of interest regarding the publication of this paper.

Research involving human participants and/or animals The retrospective observational study was performed at the University of L'Aquila, L'Aquila, Italy, after approval from the investigational review board (n.10/CE/2018) and following the consideration that the patients had an unresectable disease with a predictable course outcome.

Informed consent Informed consent was obtained from all individual participants included in this study.

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