Hypoxic Pelvic Perfusion With Mitomycin C Using a Simplified Balloon-Occlusion Technique in the Treatment of Patients With Unresectable Locally Recurrent Rectal Cancer

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Hypothesis: To evaluate the role of hypoxic pelvic perfusion in providing therapeutic options for palliation without relevant complications in a homogeneous group of patients with unresectable locally recurrent rectal cancer who are nonresponders or have disease progression after the standard treatments.

Design: Nonrandomized and noncontrolled phase II experimental study.

Setting: University hospital, L’Aquila, and the National Cancer Institute, Naples and Milan, Italy.

Patients: Eleven patients had symptomatic unresectable pelvic recurrent rectal cancer. The mean ± SD product of the 2 maximum perpendicular diameters of the recurrent cancer was 24.2 ± 11.0 cm² (range, 10-48 cm²). Tumor fixation to the pelvic side walls or proximal sacrum were the main criteria for unresectability. All patients were free from extrapelvic disease and had a life expectancy longer than 3 months.

Intervention: Patients were submitted to one course of pelvic perfusion with mitomycin C (MMC) (25 mg/m²) by means of a simplified balloon occlusion technique. A pharmacokinetic evaluation of the procedure was also performed.

Main Outcome Measures: Response rate and time to disease progression were the primary endpoints; overall survival was the secondary endpoint.

Results: Mean ± SD value of the ratios of pelvic MMC area under the plasma concentration curve (0 to 20 minutes) (AUC₀₋₂₀) to systemic MMC AUC₀₋₂₀ was 13.30 ± 6.52. During the procedures there were no technical, hemodynamic, or vascular complications, and no deaths occurred during surgery or in the postoperative period. The response rate was 36.3% (95% confidence interval [CI], 6.5%-66.1%). Pain response rate was 45.4% (95% CI, 16.6%-76.2%). Median survival was 12.2 months (range, 5.7-19.5 months). Median time to disease progression was 6 months (range, 3-8 months). Two-year overall survival was 9.1%.

Conclusions: Hypoxic pelvic perfusion with MMC is a safe and good palliative treatment for patients with unresectable locally recurrent rectal cancer. Further studies are necessary to establish if a different sequence in the multimodular treatment of these patients could be more useful.

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The incidence rate of local pelvic recurrence after standard “curative” surgery for rectal cancer varies widely according to the definition employed, accuracy of diagnosis, completeness of follow-up, and whether and how often postmortem examinations were performed.¹² In control groups included in prospective randomized trials or in epidemiological studies, the 5-year local recurrence rates vary from 20% to 30%.³ The value of adding radiotherapy to surgery in the treatment of patients with resectable primary rectal cancer has been demonstrated in trials using postoperative and especially preoperative irradiation.⁴ However, the treatment of local recurrence remains a challenge since, without surgical intervention, the reported survival rate of patients with local recurrence of rectal cancer is less than 4% at 5 years, and the median life expectancy is 7 months.⁵ Although 50% of recurrences are associated with disseminated disease,³ most patients die of local and/or regional progression of disease rather than of systemic metastases.⁶ Extensive resection (abdominal sacral resection with or without pelvic exenteration) gives the best chance of survival.⁷⁻⁹ Operative mortality varies from 0% to 10%, the 5-year survival rate varies from 20% to 30%, and the median life expectancy varies from 39 to 44 months.⁷⁻⁹ Results from such radical sur-
**PATIENTS AND METHODS**

**PATIENTS**

Written consent was obtained from 11 patients (9 men and 2 women) after they were given complete information about the disease and implications of the proposed palliative treatment, in accordance with the ethical standards of the committee on human experimentation at our institution (Table 1). Mean ± SD age of the patients was 58.18 ± 6.38 years; body weight, 64.2 ± 10.1 kg; and surface area, 1.70 ± 0.15 m².

All patients had symptomatic unresectable pelvic recurrent rectal cancer as measured by computed tomography (CT). Previous surgery was low anterior resection of the rectum in 8 patients and abdominoperineal resection in 3 patients, and the interval between operation and recurrence was less than 2 years (mean, 18.5 months). The mean ± SD product of the 2 maximum perpendicular diameters of the recurrent cancer was 24.2 ± 11 cm² (range, 10-48 cm²). The existence of arterial blood supply was confirmed in all tumors by CT. Before perfusion, patients had angiography of the aortoiliac tree and inferior vena cava. Tumor fixation to the pelvic side walls or proximal sacrum were the main criteria for unresectability. Previous treatments of recurrence were (1) radiation therapy in 8 patients (3 patients had been irradiated for the primary tumor with 60 Gy); and/or (2) systemic chemotherapy in 6 patients (5 patients had been submitted to systemic chemotherapy with 5-FU for the primary tumor); and/or (3) palliative surgery in 10 patients; (4) intra-arterial chemotherapy in 1 patient (Table 1). All patients were free from extrapelvic disease (based on CT evaluation), renal and liver failure, deep venous thrombosis, severe atherosclerosis, or coagulopathy. Patients had a life expectancy higher than 3 months and were able to function with some independence (Karnofsky score of at least 60). During the month preceding the pelvic perfusion, the subjects received neither radiotherapy nor chemotherapy.

This nonrandomized and noncontrolled phase II experimental study was performed at the University of L’Aquila, L’Aquila, Italy, after approval was obtained from the investigational review board, following the consideration that the patients, nonresponders, or those with disease progression after the standard treatments had a disease with a predictable course and invariably fatal outcome.

**ANESTHESIA**

Before perfusion, patients received a short-term bowel preparation and hydration. After an overnight fast, each patient received a single subcutaneous dose of 12500 IU of heparin calcium and a single intramuscular injection of 1.0 g of ceftaxime sodium. All patients were premedicated 45 minutes before surgery with an intramuscular injection of promethazine hydrochloride, 50 mg, and atropine sulphate, 0.5 mg. The induction of anesthesia was obtained with propofol at a variable dose from 1.5 to 2.5 mg after administration of 0.10 mg of fentanyl citrate 5 minutes before surgery. Endotracheal intubation and controlled mechanical ventilation were initiated after muscle relaxation with 1-mg/kg succinylcholine chloride. Maintenance of anesthesia was obtained with a mixture of oxygen and nitrous oxide at the rate of 1/3 to 2/3, isoflurane in concentrations that varied from 0.5% to 1.5%, and pancuronium bromide at a dose of 0.05 mg/kg. During the procedure, either 0.7-mg/kg urapidil or IV nitroglycerine at a dose of 0.006 mg/kg per minute were administered whenever arterial pressure levels exceeded 40% of baseline values. Both pH and PO₂ values were measured in blood samples taken from the extracorporeal circuit and from a peripheral artery 7, 14, and 17 minutes after the start of the infusion. The bladder was emptied before initiation of perfusion.

**HYPOXIC PELVIC PERFUSION TECHNIQUE**

The femoral artery and vein were exposed through a short longitudinal incision in the groin. After systemic heparinization (150 U/kg), a 3-lumen balloon catheter (PIM, Cologne, Germany) was introduced into the inferior vena cava via the saphenous vein and a second one into the aorta via the femoral artery; these were positioned under fluoroscopic control below the renal vessels and above the aortic and venous bifurcation using a guidewire. Both balloons were filled with isotonic sodium chloride solution, containing the radiopaque dye diatrizoate, and blocked. For isolation of the pelvis, 2 large-cuff orthopedic tourniquets, placed around each of the upper thighs just below the lower level of the femoral triangle, were inflated just before starting the perfusion.

The infusion channel of the arterial and venous stop-flow catheters were connected to a hypoxic perfusion set on a roller pump. The set was primed with an isotonic sodium chloride solution containing heparin (10000 U/L). Once flow was established (approximately 200 mL per minute), the drug therapy started. The drug, diluted in 250 mL of isotonic 

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Surgery seem to be optimized by applying multimodality approaches, including external beam radiotherapy, sensitizing chemotherapy, and intraoperative radiation therapy. The actuarial 2-year overall survival is approximately 50%, and the actuarial 5-year disease-free survival is approximately 35%. However, if the resected recurrent cancer does not have margins free on histopathologic examination, the actuarial 2-year survival rate is significantly lower (approximately 35%). Unfortunately, extensive surgery is not feasible in almost two thirds of patients with recurrent rectal cancer. In general, demonstration of 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 contraindicates surgery.

Although occasional cases of complete remission have been reported, radiotherapy alone or in conjunction with chemotherapy provides palliative benefit and extension of mean or median survival, but long-term survival (>2 years) is rare. Recent studies using radiotherapy alone have reported a median survival time of 17.9 months in a group of patients able to receive a dose of 50 to 60 Gy; on the other hand, after a mean dose of 30 Gy, a median survival time of 14 months has been observed in chemotherapy- and radiotherapy-naive patients, whereas a median sur-
sodium chloride solution, also containing 16 mg of dexamethasone sodium phosphate, was administered over 3 minutes. The extracorporeal circuit (Figure 1) also included both a hemofiltration system and a heater-cooler unit (Polystan, Vaerlose, Denmark). The hypoxic perfusion circuit was maintained over 20 minutes (mean, 22 ± 4 minutes). The temperature of the perfusate was 38.5°C.

After perfusion, both catheter balloons and pneumatic cuffs were deflated and the circulation restored. The extracorporeal circuit also was used in the hemofiltration section over 80 ± 20 minutes. A polyamide hemofilter (Hemoflux 20; Gambro, Lund, Sweden) with a surface area of 2 m² was used. Thereafter, the catheters were withdrawn and the vessels repaired.

CHEMOTHERAPEUTIC REGIMEN AND PHARMACOKINETIC STUDY

One course of perfusion was administered. Mitomycin C was administered at the dose of 25 mg/m². The dose of MMC and the duration of drug exposure (20 minutes) were determined based on results of previous in vivo and in vitro studies.40-43,48 We performed pharmacokinetic analyses of blood samples taken from the inferior caval vein 5, 7, 14, 17, and 20 minutes after the start of the infusion and from a peripheral vein of the arm 5, 7, 14, 17, 20, 25, 30, 45, 60, and 75 minutes after the start of the infusion. To evaluate the effectiveness of hemofiltration, we performed pharmacokinetic analyses of blood samples taken from the extracorporeal circuit (before and after the hemofilter) 25, 30, 45, 60, and 75 minutes after the start of the infusion. At the end of hemofiltration, the total volume of both urine and ultrafiltrate was recorded, and both urine and ultrafiltrate samples were collected for the analysis.

Mitomycin C was quantitated in plasma using high-performance liquid chromatography.39 A noncompartment pharmacokinetic analysis with intra-arterial input was fitted to the MMC concentration-time data by weighted (1/A²) nonlinear regression analysis using a computer program (TopFit 2.0; Gustav Fischer Verlag Publishers, New York, NY).30 Maximum plasma concentration (Cmax) was determined by visual inspection of the plasma concentration-time data. Terminal half-life (t₁/₂) was calculated from the equation t₁/₂ = 0.693/β. Terminal elimination rate constant (β) was calculated by means of log-linear regression with data points of elimination phase. The AUC from time 0 to the last measurable concentration was determined by trapezoidal estimation. The ratio of pelvic to systemic AUC of MMC, which gives the time-averaged enhancement of drug concentrations in the isolated circulation, was determined. The mean residence time (MRT), which applies only to drug molecules within the systemic circulation, was calculated by an algorithm similar to the one used to calculate AUC:

\[ \text{MRT} = \int_0^t C(t)tdt/AUC. \]

Systemic clearance (Cl_s) was calculated as dose/AUC. The apparent volume of distribution (Vc) in the central compartment of MMC was calculated as Cl_s/K₀₁₀, where K₀₁₀ is the elimination constant.

Clearance of MMC in the extracorporeal circuit (Cl_e) was estimated from venous and arterial drug concentrations using the following equation:

\[ Cl_e = Q \times \epsilon, \]

where Q is the average blood flow through the drug removal system and ϵ is the extraction ratio. ϵ was calculated as (A−V)/A, where A and V are the concentrations in the predetoxification and postdetoxification filter lines, respectively, corrected for mean hematocrit.

RESPONSE CRITERIA

Response was determined by CT 30, 60, and 90 days after baseline when clinically indicated, according to the following standardized criteria. Complete response was intended as complete disappearance of all directly or radiographically measurable disease; partial response defined a greater than 50% tumor regression (based on bidirectional measurements); tumor regression from 25% to 50% was defined as minor response, while nonresponse or stable disease ranged from 0% to 25% tumor regression; finally, a tumor growth greater than 25% indicated progressive disease.

Pelvic pain requiring at least less than 50% of preoperative analgesic administration 30 days after perfusion was considered as pain response. Serum carcinoembryonic antigen levels (nanograms per milliliter) were also measured preoperatively and at monthly intervals.

STATISTICAL ANALYSIS

Response rate and time to progression were the primary end points; overall survival was the secondary end point. The 95% confidence interval (CI) was calculated for all figures. Survival analysis was assessed by the Kaplan-Meier method. All calculations were performed by SAS/STAT software (SAS Inc, Cary, NC).

vival time of 12 months has been reported for palliative reirradiation.21

For patients with unresectable recurrent rectal cancer, neither intravenous (IV) systemic chemotherapy nor intra-arterial chemotherapy achieve desirable results in terms of pain control and tumor response.22-29 To improve clinical response, several methods of regional chemotherapy delivery have been suggested. One of these methods is regional pelvic perfusion. In 1958, Creech et al30 proposed the technique of isolated perfusion in which the blood supply of a body region was isolated: the aorta and the vena cava were occluded with vessel clamps and perfused by means of cannulae with thigh tourniquet application to reduce collateral circulation. Actually, the perfused compartment was not fully isolated. Pharmacokinetic evaluations of 5-fluorouracil (5-FU) in patients with pelvic recurrence of colorectal cancer31 showed that isolation perfusion was advantageous compared with intra-arterial or IV administration. This technique is still in use.32 The isolated perfusion incorporating laparotomic aortic and caval cannulation was modified by the use of femoral cannulation.33-38 In 1960, Watkins et al39 described a technique using balloon catheters to achieve the blockage of the aorta and inferior vena cava. In 1963, Lawrence et al40 reported a technique using balloon occlusion catheters and a large abdominal external tourniquet. In a 1987
A similar technique was reported by Turk et al41 in 6 patients with refractory pelvic cancer. In 1993, by means of balloon catheters and femoral cannulation and Smolin36 reported the occlusion of the great vessels of normothermic pelvic perfusion with the same regimen in 14 patients with unresectable and 5 with resectable recurrent rectal cancer. Both occlusion of the great vessels and perfusion were done with only 2 catheters, which were surgically introduced through the femoral vessels. The 2-year survival rate in the group of patients preoperatively treated with radiotherapy and/or chemotherapy was 35%. In 1994, Aigner and Kaevel43 presented the results of pelvic perfusion with MMC and melphalan in 41 patients with recurrent unresectable rectal cancer submitted to hypoxic pelvic perfusion of MMC by means of a simplified balloon occlusion technique. A pharmacokinetic evaluation of the procedure is also reported.

**RESULTS**

**TOLERABILITY AND TOXIC EFFECTS**

During the procedures there were no technical (ie, balloon rupture), hemodynamic, or vascular complications, and no deaths occurred during surgery. In the postoperative period, there were no deaths. Postoperative complications included neutropenia in 6 patients (grade 3 in 3 patients, grade 2 in 3 patients), requiring granulocyte colony-stimulating factor for a maximum of 5 days. Nausea and vomiting, despite aggressive management with antiemetics, were registered in 4 patients (grade 3 in all cases). No delayed postoperative complications (ie, deep vein thrombosis or cellulitis) occurred. Total hospitalization ranged from 6 to 14 days (median stay, 8 days).

**PHARMACOKINETIC EVALUATION**

Mean±SD value of 11 pelvic Cmax of MMC measured in the inferior cava vein blood during hypoxic pelvic perfusion was 54.8 µg/mL±20.2 (range, 28.9-105.8 µg/mL) with a 95% CI of 41.0 to 68.6 µg/mL. Mean value of the ratios of pelvic MMC AUC0-20 to systemic MMC AUC0-20 is presented in Table 2. The same Table also reports mean values of pH and P O2 measured in the blood samples taken in the extracorporeal circuit and mean study of hyperthermic pelvic perfusion with 5-FU, Wile and Smolin36 reported the occlusion of the great vessels by means of balloon catheters and femoral cannulation in 11 of 27 patients with refractory pelvic cancer. In 1993, a similar technique was reported by Turk et al41 in 6 patients with recurrent unresectable rectal cancer who underwent perfusion with 5-FU, cisplatin, and mitomycin C (MMC). In 1996, Wanebo et al42 published the results of normothermic pelvic perfusion with the same regimen in 14 patients with unresectable and 5 with resectable recurrent rectal cancer, respectively. In 1994, Aigner and Kaevel43 presented the results of pelvic perfusion with MMC and melphalan in 41 patients with recurrent unresectable rectal cancer. Both occlusion of the great vessels and perfusion were done with only 2 catheters, which were surgically introduced through the femoral vessels. The 2-year survival rate in the group of patients preoperatively treated with radiotherapy and/or chemotherapy was 35%. A similar technique using percutaneous catheters was later performed by Thompson et al44 in 7 patients with recurrent rectal cancer who underwent perfusion with MMC and 5-FU or cisplatin.

Microenvironmental alterations, including tissue hypoxia and low cellular pH, occur during isolated pelvic perfusion. Mitomycin C is 10 times more toxic to tumor cells in hypoxic conditions.45,46 Pharmacokinetics of MMC in peripheral and inferior caval vein blood were recently studied by our group47 in 4 patients with unresectable recurrent rectal cancer under different types of major vessel occlusion. For the type of pelvic perfusion corresponding to the method used by Aigner and Kaevel,43 the area under the plasma concentration-time curve (AUC) ratio for inferior caval vein blood vs systemic circulation was 11.7:1.

The aim of this study is to evaluate response rates and survival of a homogeneous group of patients with unresectable locally recurrent rectal cancer submitted to hypoxic pelvic perfusion of MMC by means of a simplified balloon occlusion technique. A pharmacokinetic evaluation of the procedure is also reported.

**Table 1. Characteristics of 11 Patients With Unresectable Locally Recurrent Rectal Cancer**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>1</th>
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<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex/age, y</td>
<td>M/54</td>
<td>M/61</td>
<td>F/58</td>
<td>M/65</td>
<td>M/50</td>
<td>M/62</td>
<td>M/60</td>
</tr>
<tr>
<td>Previous treatments</td>
<td>RT, 35 Gy; SC</td>
<td>S, palliative, laparotomy; SC</td>
<td>S, palliative, ceytrodulation; RT, 45 Gy</td>
<td>S, palliative, laparotomy; RT, 35 Gy</td>
<td>S, palliative, laparotomy; RT, 45 Gy</td>
<td>S, palliative, laparotomy; RT, 45 Gy; SC</td>
<td></td>
</tr>
<tr>
<td>Product of 2 maximum perpendicular diameters, cm²</td>
<td>21 (7 × 3)</td>
<td>28 (7 × 4)</td>
<td>10 (5 × 2)</td>
<td>18 (6 × 3)</td>
<td>24 (6 × 4)</td>
<td>18 (6 × 3)</td>
<td>12 (6 × 2)</td>
</tr>
<tr>
<td>Preperfusion serum CEA level</td>
<td>34</td>
<td>22</td>
<td>72</td>
<td>32</td>
<td>16</td>
<td>52</td>
<td>33</td>
</tr>
<tr>
<td>Pain, scale of 1-5†</td>
<td>1</td>
<td>1</td>
<td>4</td>
<td>3</td>
<td>3</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>

*RT indicates radiation therapy; SC, systemic chemotherapy with 5-fluorouracil; S, surgery; IAC, intra-arterial chemotherapy with 5-fluorouracil; and CEA, carcinoembryonic antigen.
†1 indicates least painful; 5, most painful.

![Figure 1. Scheme of hypoxic pelvic perfusion and extracorporeal circuit incorporating both hemofiltration system and heater-cooler unit.](image-url)
value of 11 MMC clearances in the extracorporeal circuit. More details of MMC concentrations during hypoxic pelvic perfusion in 11 patients with unresectable locally recurrent rectal cancer are reported in Table 3.

Mean ± SD value of MMC Cmax into the systemic circulation was 2.5 ± 1.19 µg/mL (range, 1.1-4.2 µg/mL); MMC t1/2, 33.1 ± 6.7 minutes (range, 22.4-42.2 minutes); MMC disposition MRT, 42.9 ± 8.5 minutes (range, 30.2-55.3 minutes); total body clearance of MMC, 365.9 ± 172.5 mL per minute (range, 190.0-671.0 mL per minute); MMC apparent volume of distribution (Vc), 17.4 ± 8.8 L (range, 8.3-34.4 L); MMC in urine, 630 ± 406 µg (range, 200-1300 µg); and MMC in ultrafiltrate, 2990 ± 1270 µg (range, 1280-4950 µg).

RESPONSES AND SURVIVAL

An objective response involving CT shrinkage of tumor by 50% occurred in 2 patients. Two patients obtained a minor response, and 4 patients, a stable disease. Response rate was 36.3% with a 95% CI of 6.5% to 66.1%. Disease progression occurred in 2 patients (Table 4). A reduction in serum carcinoembryonic antigen level occurred in 9 patients; an increase was recorded in the other 2 patients. Most of the patients showed a considerable decrease in pain and analgesic requirement within 36 to 48 hours of the perfusion. Partial relief of pain occurred in 5 patients (median duration, 6 weeks; range, 3 to 12 weeks). Pain response rate was 45.4% with a 95% CI of 16.6% to 76.2%. Five patients had no pain relief, and pain progression occurred in 1 patient. Median survival was 12.2 months (range, 5.7-19.5). Median time to disease progression was 6 months (range, 3-8 months). Two-year overall survival was 9.1% (Figure 2).

FOLLOW-UP

Two patients developed new pulmonary metastases and were treated with systemic chemotherapy. The remaining patients refused any kind of chemotherapy. One patient was found to have hepatic metastases. Two patients died of progression of local disease. Six patients developed extrhepatic abdominal disease. Six patients died of progression of local disease.

COMMENT

The focus of interest of this article is the demonstration of a new simplified technique of hypoxic pelvic perfusion that provides therapeutic options for palliation without relevant complications in a homogeneous group of patients with unresectable locally recurrent rectal cancer who are nonresponders or have disease progression after the standard treatments (radiation therapy and/or systemic chemotherapy). For patients with unresectable recurrent rectal cancer, particularly when the surgeon is unable to accomplish a gross total surgical resection of the recurrent cancer, administration of preoperative external irradiation plus continuous infusion chemotherapy, intraoperative irradiation, maximal surgical resection, and systemic chemotherapy are currently being studied in clinical trials.

The relative advantage of intra-arterial over IV chemotherapy (RD) is proportional to the increase of drug
concentration in the target organ or compartment (R_T) and to the reduction of drug concentration in systemic circulation (R_S), as quoted in the following equation

\[
R_n = \frac{R_T}{R_S} = 1 + \frac{C_{LT}}{Q} (1 - E)
\]

where \(C_{LT}\) represents the overall amount of blood detoxified in the whole body per minute (drug clearance in the whole body), \(Q\) represents the blood flow in the artery in which the drug is infused, and \(E\) represents the amount of drug cleared by or held by the organ or compartment in which the drug has been infused.\(^{52}\) The relative advantage of intra-arterial over IV chemotherapy (R_0) can be increased by reducing Q and increasing \(C_{LT}\) and E. Hypoxic perfusion with the balloon-occlusion technique can be an effective method for reducing Q. Hemofiltration of venous blood from the infused organ or compartment can increase \(C_{LT}\).

Hypoxic pelvic perfusion has potential therapeutic advantages over intra-arterial infusion of chemotherapy as recently demonstrated by a pilot study in which an approximately 10-fold superior MMC pelvic-systemic exposure ratio was measured for hypoxic pelvic perfusion in comparison to intra-aortic infusion in patients with unresectable locally recurrent rectal cancer.\(^{32}\) After IV push injection of 20 mg/m² of MMC, Door\(^{30}\) reported that the peripheral \(C_{max}\) was 6.0 µg/mL with an AUC of 73.3 µg/mL × minutes. In the present study, after intra-aortic administration of 25 mg/m² of MMC during hypoxic pelvic perfusion, the mean \(C_{max}\) in the pelvic compartment was 54.8 µg/mL, the mean peripheral \(C_{max}\) was 2.5 µg/mL, and the mean peripheral AUC was 50.2 µg/mL × minutes.

The efficiency of the simplified balloon occlusion technique used in this study to perform hypoxic pelvic perfusion has been demonstrated by the good mean pelvic-systemic MMC-AUC ratio (13.3:1) measured in our series of 11 treatments, this being higher than both the value of 9.0:1 recently reported by Wanebo et al.\(^{42}\) and the value of 4.4:1 reported by Turk et al.\(^{41}\) The high variability in the range of MMC-AUC ratio values (4.3:1 to 25.7:1), which is attributable in our opinion to the variability of conditions in different individuals (ie, anastomotic venous leak from the pelvic circulation to the systemic circulation), explains why both the type of tumor response and the extent of toxic effects in this kind of patient are not accurately predictable.

Several different chemotherapeutic regimes have been used in pelvic perfusions, often as part of a single study. In the treatments performed for recurrent rectal cancer, the agents more frequently have been used fluorouracil,\(^{36,41,42}\) MMC,\(^{41-43}\) and cisplatin\(^{36,41,42}\) in monotherapy or in polychemotherapy. Less frequently and often in small series, the use of nitrogen mustard,\(^{33,34,40}\) cyclophosphamide,\(^{40}\) methotrexate,\(^{37}\) 2'-deoxycytidine,\(^{40}\) melphalan,\(^{43}\) and mitoxantrone\(^{32}\) have been reported. The real value of pelvic perfusion in terms of tumor response is consequently difficult to ascertain. After a pilot study on hypoxic pelvic perfusion,\(^{37}\) we planned this phase II trial based on the use of single-agent MMC, which has been shown to be increasingly cytotoxic in a hypoxic environment.\(^{44,45}\) Although fluorouracil has been considered more effective than MMC against adenocarcinomas of the rectum also when administered by pelvic perfusion,\(^{41}\) fluorouracil was not selected for this study mainly because most patients had disease progression after systemic chemotherapy with this agent.

In the present selected series of patients, one course of hypoxic pelvic perfusion with 25 mg/m² of MMC resulted in an overall response rate of 36.3%. These results are comparable to those reported by Turk et al.\(^{41}\)approximately 30%, using fluorouracil (3000 mg/m²), cisplatin (25-75 mg/m²), and MMC (15 mg/m²). Aigner and Kaevel\(^{37}\) reported an overall response rate of 32% in a se-

Table 4. Responses After Hypoxic Pelvic Perfusion and Survival of 11 Patients With Unresectable Locally Recurrent Rectal Cancer

<table>
<thead>
<tr>
<th>Patient</th>
<th>1</th>
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<tr>
<td>CT response</td>
<td>PR</td>
<td>SD</td>
<td>SD</td>
<td>SD</td>
<td>PR</td>
<td>SD</td>
<td>PR</td>
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<td>PR</td>
<td>PD</td>
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<tr>
<td>Serum CEA level 30 days</td>
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<td>12</td>
<td>32</td>
<td>30</td>
<td>1</td>
<td>10</td>
<td>18</td>
<td>79</td>
<td>28</td>
<td>81</td>
<td>180</td>
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<td>Pain response</td>
<td>PR</td>
<td>SD</td>
<td>PR</td>
<td>SD</td>
<td>PR</td>
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<td>PR</td>
<td>SD</td>
<td>PR</td>
<td>PD</td>
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<td>Time to progression, d</td>
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<td>210</td>
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<td>360</td>
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<tr>
<td>Further therapy</td>
<td>S, Palliative</td>
<td>. . .</td>
<td>. . .</td>
<td>. . .</td>
<td>SC</td>
<td>. . .</td>
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<td>. . .</td>
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<tr>
<td>Site of progressions</td>
<td>Peritoneum</td>
<td>Local</td>
<td>Hepatic</td>
<td>Peritoneum</td>
<td>Lung</td>
<td>Local</td>
<td>Lung</td>
<td>Local</td>
<td>Local</td>
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<tr>
<td>Survival, d</td>
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<td>703</td>
<td>392</td>
<td>366</td>
<td>219</td>
<td>367</td>
<td>1004</td>
<td>154</td>
<td>172</td>
<td>94</td>
<td>197</td>
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</table>

*CT indicates computed tomographic; MR, minimal response; PR, partial response; SD, stable disease; PD, progressive disease; CEA, carcinoembryonic antigen; downward arrow (↓), reduction; upward arrow (↑), increase; ellipses, not applicable; S, surgery; and SC, systemic chemotherapy.
ries of 41 patients treated with MMC (12.5 mg/m²) and melphalan (12.5 mg/m²). Wile and Smolins reported an overall response rate of 40% in 17 patients treated with fluorouracil (750-1500 mg/m²) in hyperthermic perfusion. Based on these data, the response rate seems to be not significantly higher in patients treated with polychemotherapy than in those receiving monochemotherapy. Further studies are necessary to evaluate other drugs that are active in hypoxic conditions (ie, doxorubicin, tara-
pazamine), the role of hypertermia and oxygenation with prolonged isolated perfusion,
the use of agents modulating multiple-drug resistance. The 45.4% response rate of pain relief, which is due, in our opinion, not only to tumor shrinkage but mainly to neurotoxic effects, represents a good palliation in patients with severe local symptoms. This result, together with the local control of tumor growth (6 months of median time to disease progression), promotes an improving quality of life for these patients. Further studies are necessary to evaluate if the median time to disease progression can be improved by long-term administration of heparin.

Since its first description, despite several innovations and significant response rates, regional pelvic perfusion has not seen widespread use, first owing to its inherent complexity and second owing to serious adverse effects due to local and systemic toxic effects. In 1963, Lawrence et al reported a 70% occurrence of local toxic effects (30% of major local toxic effects) after pelvic perfusion with MMC at the dose of 1 mg/kg. With the dose of 25 mg/m² and the regional administration of dexamethasone sodium phosphate, no local toxic effects were registered in the present series. To reduce systemic exposure, low pressure and flow in the extracorporeal circuit with the aim to reduce leakage as well as hemofiltration were adopted in this study. It has been reported that chemofiltration reduces immediate cytotoxic effects and postpones cumulative toxic effects in patients treated with abdominal stop-flow infusion. We previously demonstrated that the bioavailability of MMC in the peripheral venous blood can be reduced using a safe hemofiltration for 60 minutes. Based on results of the present study, at the end of the procedure, approximately 10% of the administered MMC total dose can be detected in urine and ultrafilterate. However, the minor clinical consequences of the MMC systemic bioavailability are mainly related, in our opinion, to the use of granulocyte colony-stimulating factors, unfortunately not available in the 1960s.

In this study, hypoxic pelvic perfusion has been proposed as palliative treatment in patients with unresectable locally recurrent rectal cancer who are nonre-
sponders or have disease progression after the standard modalities. The median survival time (12.2 months) reg-
istered after one course of hypoxic pelvic perfusion is comparable to that obtained by irradiation or reirradiation in non-pretreated patients. Considering the vascular damage following radiotherapy, a different sequence in the multimodular treatment of unresectable recurrent rectal cancer could be more useful. Further studies are necessary to establish if hypoxic pelvic perfusion improves quality of life and survival of these patients if administered before radiotherapy with or without concomitant systemic chemotherapy. In conclusion, hypoxic pelvic perfusion is a good palliative treatment for patients with unresectable locally recurrent rectal cancer, but it should be considered as a link of a chain in a multimodular approach.

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