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Pelvic stopflow infusion (PSI) and hypoxic pelvic perfusion (HPP) with mitomycin and melphalan for recurrent rectal cancer

K. R. Aigner, K. Kaevel

Department of Surgical Oncology, Asklepios Paulinen Klinik, Wiesbaden, Germany

Abstract. 41 patients with locally advanced and invasive, non-resectable pelvic recurrences from rectal cancer underwent pelvic stopflow infusion (PSI, n = 28) or hypoxic pelvic perfusion (HPP, n = 13) with Mitomycin (MMC). 6 patients had been preirradiated and 14 patients had had radiotherapy and chemotherapy prior to regional chemotherapy (RCT).

Isolation of the pelvis was achieved with aortic and caval double lumen balloon catheters and upper thigh pneumatic cuffs. Enhancement of MMC tumor toxicity through hypoxia was the special feature of this study.

The overall pain response was 69% (30% CR, 17% PR, 22% MR) , histologic response 69% (15% CR, 23% PR, 31% MR), tumor marker response 35% (12% CR, 19% PR, 4% MR), CT-response 32% (4% CR, 14% PR, 12% MR).

There was no significant difference in survival between PSI and HPP. One year survival was overall 55%, two year survival 47% (PSI) and 39% (HPP), respectively.

In patients without distant metastases (n = 23) one year survival was 73% and two year survival was 60%. In patients with distant metastases (n = 18) the overall survival including PSI and HPP was 33% at one year and 22% at two years. Patients with previous radio- or radiochemotherapy had a 50% one year survival versus 70% in those without pretreatment. At two years those survival figures were 35% and 59% respectively. Side effects were minimal and overall quality of life was improved by the procedure.

Key words: Recurrent rectal cancer – Mitomycin – Stopflow – Pelvic perfusion – Hypoxia

Address for correspondence: Prof. Dr. Karl R. Aigner, Asklepios Paulinen Klinik, Geisenheimerstraße 10, 65197 Wiesbaden

Substantial parts of this manuscript are from the thesis of K. Kaevel

Introduction

Rationale of the study: Bulky pelvic adenocarcinoma of colon or rectum or extensive pelvic recurrence of colon and rectum carcinoma present a distressing and difficult problem in cancer management. Systemic chemotherapy and radiotherapy of rectal cancer has failed due to high chemo-/radioresistance and poor vascularisation of colorectal tumors, showing that relief is at the best incomplete and transient and pain management becomes the only effective treatment option.

In-vitro concentration-response curves demonstrate that, to be effective, the level of tumor toxic concentration must be at least 10-times that which can be achieved with systemic chemotherapy [7]. This problem can be overcome by administration of the total drug into the isolated tumor bearing area. Activity of mitomycin against colorectal cancer tested in cell culture shows enhanced effectiveness under hypoxic conditions [15]. It was therefore postulated that isolated perfusion of mitomycin under hyoxic conditions should increase its tumortoxic effect.

Material and methods

Patients' characteristics

41 patients were entered into the trial. All had recurrent rectal cancer, invading surrounding tissues like bladder, ureters, sacrum, small bowel loops, vagina and in some cases penetration of the perineum. All patients had pelvic pain, 23 patients reported intractable pain, being therefore under morphine medication most of the time.

In 23 patients the disease was confined to the pelvis, 18 patients also had extrapelvic disease such as peritoneal seedings, positive abdominal lymphnodes, liver- and/or lung metastases.

20 of the 41 patients had previously been treated for pelvic recurrence. 6 patients had had previous pelvic irradiation up to 70 Gy with only temporary effect on local pain but without reduction of tumor mass. 14 patients had had combined radio-chemotherapy without tumor response and were being given strong medication for intractable pain.

Therapeutic Protocol

Patients were treated with two cycles of PSI or HPP at four weeks intervals. 7 patients had a 3rd cycle for relapse of pain. As a standard after the second perfusion an aortic bifurcation catheter (Jet Port Allround, PfM Cologne) was implanted via the formerly cannulated femoral artery with its tip located right above the aortic bifurcation and the port placed subcutaneously lateral to the groin incision. In case of pain relapse 5-FU was infused while the upper thighs were blocked intermittently with pneumatic cuffs (4 x 1000 mg 5-FU/1 hour).

Surgical Technique

The femoral artery and vein are exposed through a short longitudinal incision in the groin. Under systemic heparinization with 150 I.U./kg BW of heparin double lumen stopflow balloon catheters (PfM Cologne), (Fig. 1) are introduced and inserted until the balloon tip is located approximately 5 cm above the aortic and venous bifurcation. Both balloons are blocked (Fig. 2). For complete isolation of the pelvis two pneumatic cuffs placed as high as possible around the thighs are inflated.

Pelvic Stopflow Infusion (28 patients)

In this trial 20 mg Mitomycin and 20 mg Melphalan, diluted in 500 ml saline are administered through the infusion channel of the aortic catheter. In smaller patients of 50-70 kg body weight the total volume is reduced together with the total dose in order to keep the drug concentration at approximately the same level. Thus the entire arterial supply of the pelvis, including the femoral lymphnode area is filled with a drug solution containing both 40 pg/ml of MMC and 40 pg/ml of Melphalan. While venous outflow occlusion is accomplished with the vena cava balloon, the drug solution is kept in place over 15 minutes (Fig. 3). Thereafter the stopflow system is opened by releasing first the venous, then the arterial balloon and deflating the pneumatic cuffs. The catheters are withdrawn, and the vessels repaired with running prolene sutures.

Hypoxic Perfusion (13 patients)

The same procedure is applied as in the stopflow technique. The infusion channels of the arterial and venous stopflow catheters are connected to a saline primed hypoxic perfusion set on a roller pump (Fig. 4) and the hypoxic perfusion circuit is maintained over 15 minutes. In a later study combining pelvic stopflow and hypoxic perfusion the

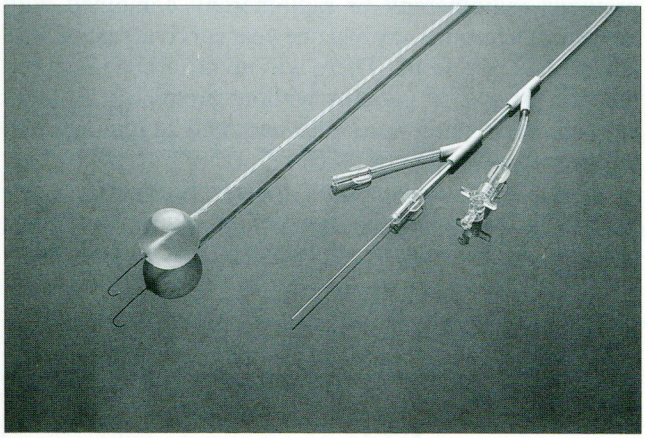

Fig. 1: Double lumen stopflow balloon catheter (PfM Cologne, FRG). The guide wire is introduced through a third channel

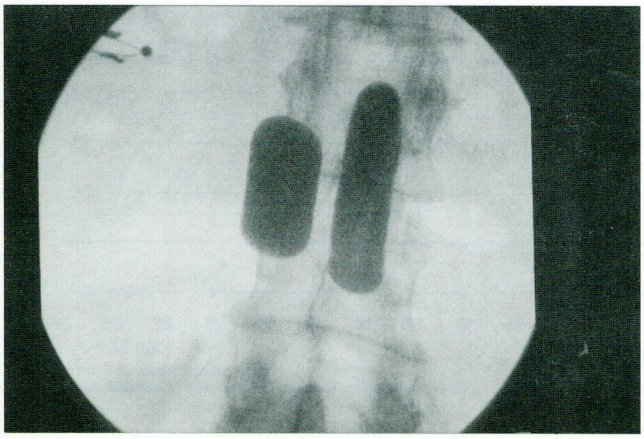

Fig. 2: Balloons in aorta and vena cava, inflated with contrast medium

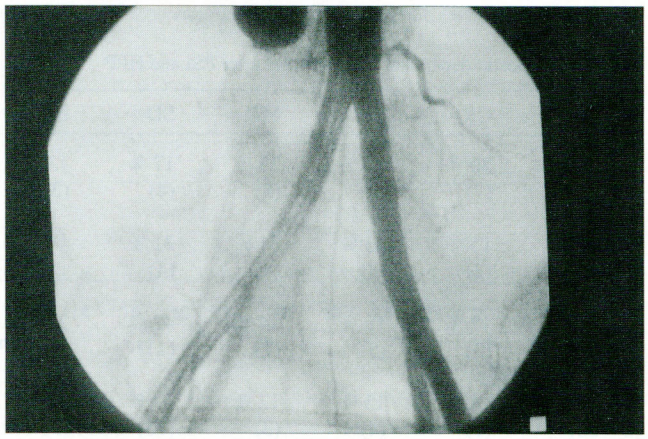

Fig. 3: Pelvic stopflow infusion. The correct position of the blocked balloons is controlled with contrast medium injected through the infusion channel of the aortic catheter.

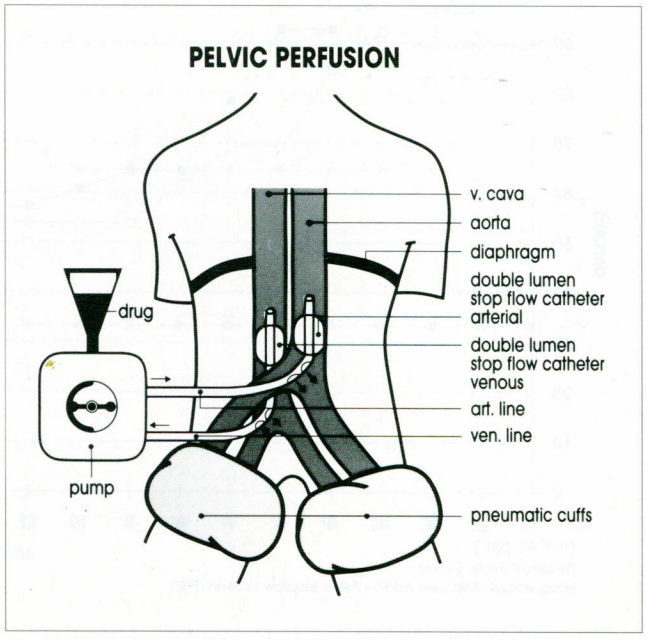

Fig. 4: Scheme of hypoxic pelvic perfusion

hypoxic exposure time was increased to 20 minutes without adverse reactions [2].

Results

Response was subclassified into pain response and clinical response (Tab. 1).

The overall pain response with substantial decrease or immediate resolution of pain the day after perfusion or stopflow was 69%. 7/23 patients with intractable pain became pain free (30% CR). The remainder required significantly reduced pain medication after therapy (17% PR, 22% MR). 13/41 patients underwent second look surgery with removal of bulky disease considered as R 1 and R 2 resections.

Tab. 1: Diagnostic-dependent responserates after PSI and HPP

%	CR	PR	MR	SD	NR
Pain (n = 23)	30 % (7)	17 % (4)	22 % (5)	17 % (4)	13 % (3)
Histology (n = 13)	15 % (2)	23 % (3)	31 % (4)	31 % (4)	-
TU-Marker (n = 26)	12 % (3)	19 % (5)	4 % (1)	42 % (11)	23 % (6)
CT % (n = 26)	4 % (1)	15 % (4)	12 % (3)	57 % (15)	12 % (3)

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Histological evaluation of resected tumors from these 13 patients showed response in 9/13 (69%) patients (15% CR, 23% PR, 31% MR). Overall tumor marker (CEA, CA 19-9) response was 35% (12% CR, 19% PR, 4% MR).

Response in CT scan was ranked according to the remaining tumor volume, where complete disappearance was classified CR, PR was reduction of the volume by 50% and MR by at least 30%. Complete or partial disappearance of intrapelvic masses in CT scan was never observed. This was only seen after treatment when completely necrotic lesions in the perineum drained externally and therefore diminished in size. Thus the overall CT response was 31% (4% CR, 15% PR, 12% MR).

Survival: There was no difference in survival between the two treatment groups (Fig. 5). One year survival was 55%. At two years there was a 47% survival rate in the PSI group and 39% in the HPP group.

Patients with extrapelvic metastases (n = 18) at commencement of therapy, however, had a significantly shorter life expectancy of 33% at one year and 22% at two years compared with patients without extrapelvic lesions (n = 23), where the survival rate was 73% at one year and 60% at two years (Fig. 6). Patients who had had previous radiotherapy or radiotherapy combined with systemic chemotherapy had one year survival rate of 50% and 35% at two years. There was no difference between the two groups. In patients without pretreatment, however, survival rates were 70% and 59% at one and two years, respectively (Fig. 7).

Complications and side effects: Side effects are usually mild. Stomatitis, diarrhea or severe bone marrow-toxicity have not been observed. This may be due to

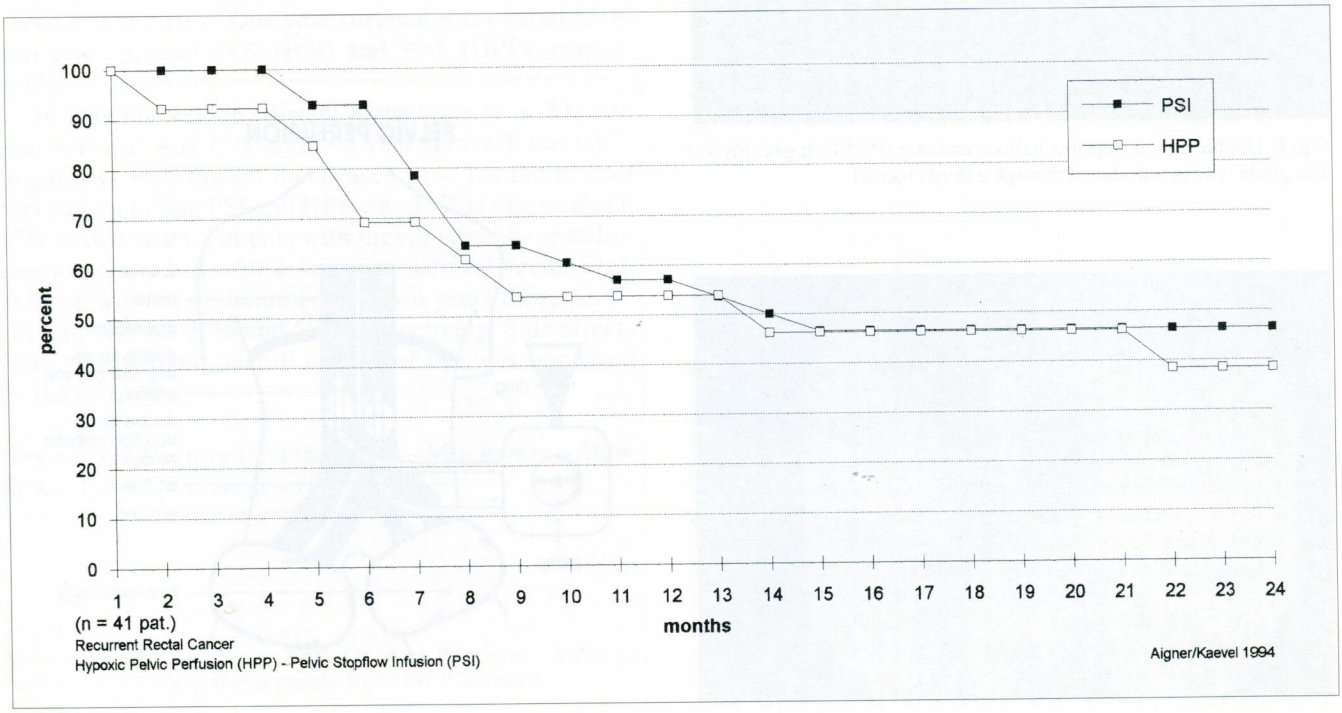

Fig. 5: Two years survival following PSI and HPP

partial tissue uptake of the drug during perfusion. Perforation of iliac vessels is a risk factor when rigid double lumen catheters are used. It has never occured in this study, where catheters with an additional guide wire channel were used. In early experience of these techniques the major complications were lymphfistulas in the groin. These may prolong wound healing. They can be avoided and were avoided in this study by exposing the femoral vessels directly beneath the inguinal ligament.

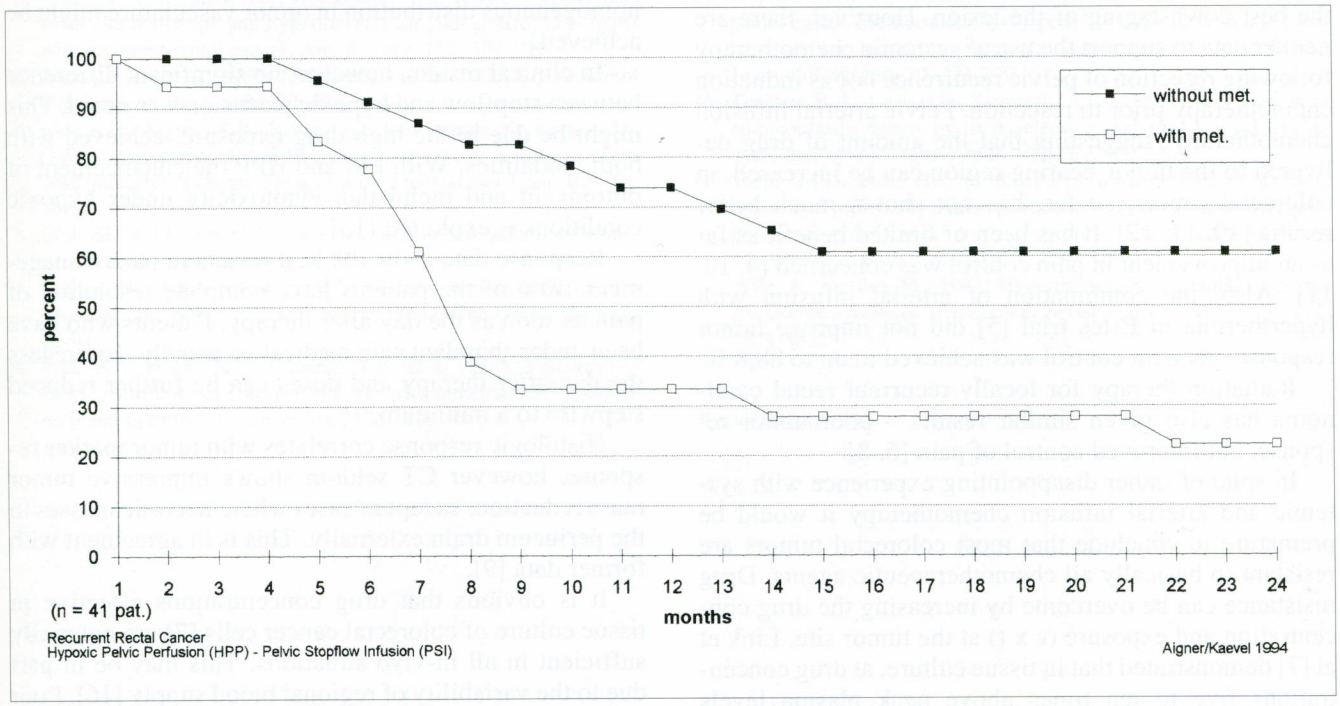

Fig. 6: Survival in patients with and without extrapelvic metastases after PSI and HPP

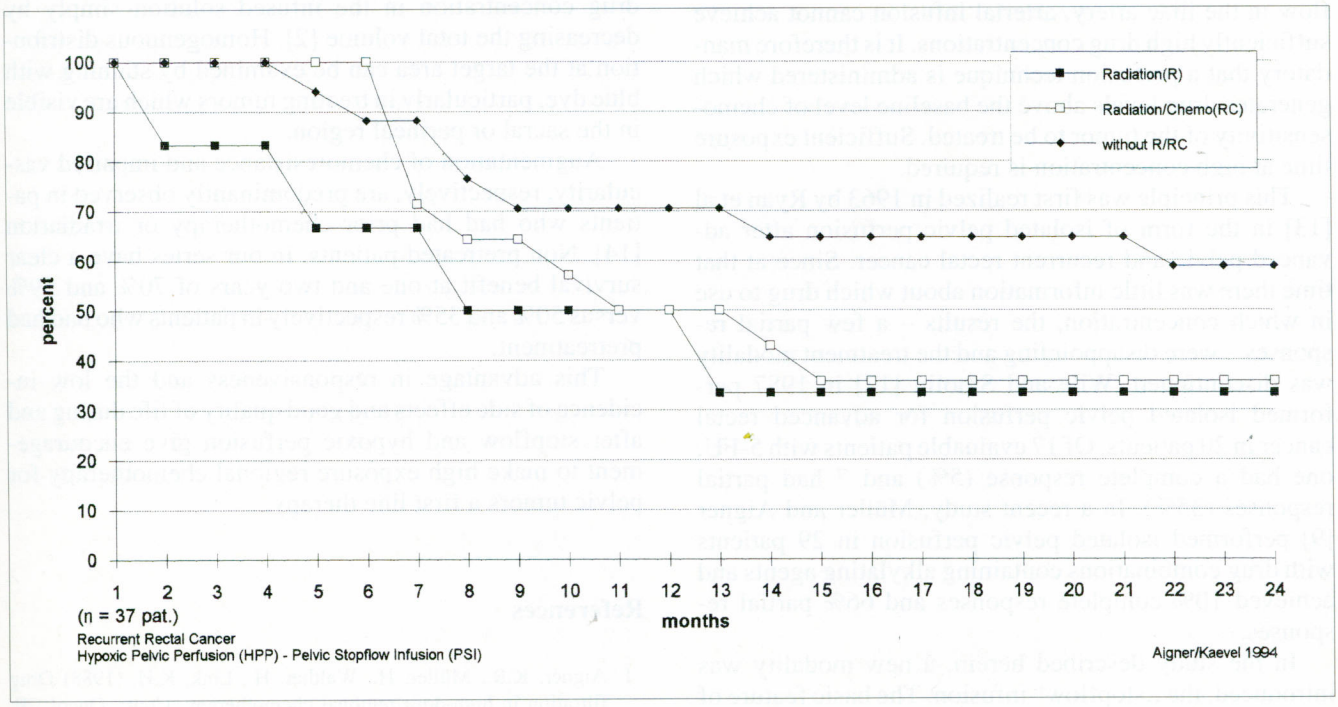

Fig. 7: Survival in patients with and without radio-chemotherapy prior to PSI and HPP

Discussion

Local recurrence in the pelvis is the most common site of failure after curative resection of rectal cancer. At diagnosis in only 10 % of such patients is recurrent colorectal cancer resectable [3]. This dismal prognosis has prompted efforts to use adjuvant or induction chemotherapy in order to achieve at least stable disease, or, at the best downstaging of the lesion. However, there are neither data to support the use of systemic chemotherapy following resection of pelvic recurrence nor as induction chemotherapy prior to resection. Pelvic arterial infusion chemotherapy, suggesting that the amount of drug delivered to the tumor-bearing region can be increased, in colorectal cancer, so far, has not shown much better results [10, 11, 12]. It has been of limited benefit as far as an improvement in pain control was concerned [4, 10, 11]. Also, the combination of arterial infusion with hyperthermia in Estes trial [5] did not improve tumor response, yet pain control was achieved in up to 88,8 %.

Radiation therapy for locally recurrent rectal carcinoma has also given similar results – poor tumor response, but improved control of pain [6, 8].

In spite of rather disappointing experience with systemic and arterial infusion chemotherapy it would be premature to conclude that most colorectal tumors are resistant to basically all chemotherapeutic agents. Drug resistance can be overcome by increasing the drug concentration and exposure (c x t) at the tumor site. Link et al [7] demonstrated that in tissue culture, at drug concentrations five to ten times above peak plasma levels achieved with systemic chemotherapy, colorectal tumor cells become sensitive to almost the entire range of chemotherapeutic agents. With regard to the high blood flow in the iliac artery, arterial infusion cannot achieve sufficiently high drug concentrations. It is therefore mandatory that a perfusion technique is administered which generates drug levels above the baseline level of chemosensitivity of the tumor to be treated. Sufficient exposure time at high concentration is required.

This principle was first realized in 1963 by Ryan et al [13] in the form of isolated pelvic perfusion after advanced pelvic and recurrent rectal cancer. Since at that time there was little information about which drug to use in which concentration, the results – a few partial responses – were disappointing and the treatment modality was discontinued. Wile and Smolin [17] in 1987 performed isolated pelvic perfusion for advanced rectal cancer in 20 patients. Of 17 evaluable patients with 5-FU, one had a complete response (5%) and 7 had partial responses (35%). In a recent study, Müller and Aigner [9] performed isolated pelvic perfusion in 29 patients with drug combinations containing alkylating agents and achieved 10% complete responses and 66% partial responses.

In the study described herein, a new modality was introduced, the „stopflow" infusion. The basic feature of this technique is to stop the aortic blood flow and vena cava outflow with a balloon catheters. Therefore all pelvic vascular branches can be filled with a precalculated volume and drug concentration which is kept in place over the required time interval of ten to twenty minutes (in our study fifteen minutes). The double channel balloon catheters, while connected to an external pump, allow rotation of the total volume in the form of a so-called hypoxic perfusion. In that way theoretically a more homogenuous distribution in tumor vasculature might be achieved.

In clinical results, however, no significant difference between stopflow and hypoxic perfusion was noted. This might be due to the high drug exposure, achieved with both modalities. With PSI and HPP the enhancement of mitomycin and melphalan cytotoxicity under hypoxic conditions is exploited [15].

Response data show the best results in pain management. 30% of the patients have complete resolution of pain as soon as the day after therapy. Patients who have been under abundant pain medication usually require less the day after therapy and doses can be further reduced stepwise to a minimum.

Histologic response correlates with tumor marker response, however CT seldom shows impressive tumor mass reduction, except in cases where necrotic masses in the perineum drain externally. This is in agreement with former data [9].

It is obvious that drug concentrations effective in tissue culture of colorectal cancer cells [7] are not really sufficient in all in-vivo situations. This may be in part due to the variability of regional blood supply [16]. Poor vascularity of colorectal tumors [1], besides low chemosensitivity, determines the responsiveness to chemotherapy. Therefore it may be of benefit to further increase the drug concentration in the infused solution simply by decreasing the total volume [2]. Homogenuous distribution at the target area can be examined by staining with blue dye, particularly in treating tumors which are visible in the sacral or perineal region.

Augmentation of chemoresistance and impaired vascularity, respectively, are predominantly observed in patients who had had prior chemotherapy or irradiation [14]. Non pretreated patients, in our series have a clear survival benefit at one and two years of 70% and 59% versus 50% and 35% respectively in patients who had had pretreatment.

This advantage in responsiveness and the low incidence of side effects and good quality of life during and after stopflow and hypoxic perfusion give encouragement to make high exposure regional chemotherapy for pelvic tumors a first line therapy.

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