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# Isolated Chemotherapeutic Perfusion as Neoadjuvant Therapy for Advanced/Unresectable Pelvic Malignancy

*Harold J Wanebo[1]*, Giovanni Begossi[2], James Belliveau[1] and Eric Gustafson[1]*

[1]*Department of Surgical Oncology, Boston University, USA*

[2]*Alta Bates Summit Medical Center, Canada*

## Abstract

**Introduction:** Previous chemo radiation (CRT) usually precludes neoadjuvant therapy for advanced pelvic malignancy. Neoadjuvant isolated pelvic perfusion (IPP) provides higher tissue drug levels with less toxicity than systemic therapy and may enhance resectability of advanced pelvic malignancy. We have performed 113 IPP in 75 such patients (pts) 59 for pre operative therapy and 16 palliative.

**Methods:** There were 50 pts with advanced, irradiated recurrent rectal cancer (34 pre-op and 16 palliative), 8 pts had advanced anal squamous cancer (SCC), 6 pts with pelvic sarcoma; 4 pts with pelvic/perineal melanoma (MEL), and 7 other advanced cancers (endometrial (2), ovarian cancer (3), and bladder cancer (BC) 2 pts. Hyperthermic IPP for (60 minutes) utilized regimens targeted to malignancy type. High dose IPP with stem cell support was utilized in 3 advanced chemo resistant pts.

**Results:** Neoadjuvant IPP in 26 recurrent rectal cancer pts rendered 15 potentially resectable achieving a complete path CR in 2 patients and facilitating curative pelvic resection in 7 pts. The remaining 8 pts were non-resected because of disease/medical status (5 pts) or patient refusal (3 pts). Median overall survival (OS) post IPP was 24 mos in 15 resectable pts, 30 mos in the 7 resected pts (2 survived >5 yrs) and 8 mos in 11 non-resectable pts. It was 23 and 8 mos (resected vs. non resected) months in 8 advanced SCC anal pts and 28 and 24 mo in advanced gyn cancer pts (endometrial/ovarian), 13 mos in 4 advanced melanoma pts and was only 5 mos in 6 sarcoma pts (only 1 resectable). High dose IPP with stem cell support induced significant regression (with resection) in 2 of 3 pts with advanced chemo resistant (Endometrial/Melanoma) malignancy. Overall of 59 neoadjuvant pts, 34 (58%) responded to IPP, 21 (36%) were resected, and the remaining 25 pts (42%) were considered reasonably palliated.

**Conclusion:** IPP has promise in augmenting resectability (or palliating) selected patients with advanced pelvic malignancy not amenable to p or previously treated with conventional chemo RT. IPP responsive tumors included recurrent rectal and anorectal cancers, and localized gyn cancers and melanoma, whereas sarcomas were quite resistant. Biologic therapy or stem cell supports are viable future options to enhance outcome of IPP.

**Keywords: Pelvic malignancy as neoadjuvant therapy; Pelvic Perfusion; Neoadjuvant; Perfusion; Chemoperfusion**



***Correspondence:***
*Harold J Wanebo, Department of Surgical Oncology, Boston University, 206 Cass Avenue, Woonsocket, Rhode Island 029895, Tel: 401-529-5275; Fax: 401-767-1508;*
*E-mail: hwanebo@landmarkmedical.org*

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## Synopsis

Isolated pelvic perfusion was performed as planned neoadjuvant therapy in 59 pts with advanced pelvic malignancy of which 38% responded and 36% were resected and the remaining reasonably palliated (74%).

## Introduction

Preoperative chemo radiation therapy for advanced pelvic malignancy is often precluded by previous radiation exposure or chemo resistant progression. Isolated pelvic perfusion (IPP) provides high tissue drug exposure without the toxicity of high-dose systemic therapy and may benefit patients with advanced malignancy. We have performed 113 IPP in 75 patients (16 for palliation, and 59 with pre op intent) using a simplified groin accessed balloon occlusion technique.

Creech and Associates introduced isolated regional perfusion in 1958 [1] to treat advanced

**Table 1A:** Chemotherapy data for IPP.

| **Pelvic Perfusion** | | | | |
|---|---|---|---|---|
| **Patient Perfusions** | **Taxol** | **5FU** | **Cisplatin** 100 mg/m² | **Oxaliplatin** 15 mg/m² |
| Ano-Rectal Cancer | 30mg/m² | 1500mg/m² | 100 mg/m² | 150 mg/m² 5-15 mg/m² |
| **II. Sarcoma** | Paclitaxel | Adriamycin | Cisplatin | Iflosfamide |
| 4 pts | 40 mg/m² | 70-90 mg/m² | 200 mg/m² | 200 mg/m² |
| 4 pts | 40 mg/m² | 90 mg/m² | 100 mg/m² | |
| **III. Melanoma** | | | | Phenylalanine Mustard |
| 2 pts | 50 mg/m² | --------- | --------- | 110 mg/m² |
| 2 pts | 60 mg/m² | --------- | --------- | 110 mg/m² |
| **IV. Endometrial Cancer** | | | | |
| 2 pts | 60 mg/m² | --------- | 100 mg/m² | 110 mg/m² |
| **Ovarian Cancer 2 pts** | 60 mg/m² | 1500 mg/m² | 100 mg/m² | |
| | 400 mg/m² | 1500 mg/m² | 100 mg/m² | |

**Table 1B:** Pharmacokinetics-neoadjuvant perfusion.

| | **5 Flourouracil** | **Cisplatin** | **Oxaliplatin** | **Mitomycin C** |
|---|---|---|---|---|
| Maxiumum | 317 ± 45ug/ml | 37 ± 4 ug/ml | 29 ± 4 ug/ml | 5.3 ± 0.8 ug/ml |
| Pelvic | N = 30 | N = 30 | N = 6 | N = 30 |
| Plasma | | | | |
| Concentration | | | | |
| N = Pts | | | | |
| Pelvic | 8.4 : 1 | 6.0 :1 | 7.3 :1 | 9.0 : 1 |
| System Ratio | | | | |

Data on each individual drug was developed over different time periods (1990-2006) with 5 FU and Mitomycin C, and in more recent time periods with Cisplatin (1992-2002) and Oxaliplatin (2001-2006) [6].

extremity melanoma, based on pioneering efforts by Klopp with regional intra arterial therapy with nitrogen mustard in 1950 [2], and experimental perfusion studies by Ryan [3]. Initial studies demonstrated regional therapy achieved local drug levels of 6-10 times higher than achieved by systemic therapy with minimal tissue edema/local toxicity. The Tulane group initially focused on perfusion therapy for advanced extremity melanoma but subsequently treated a variety of cancers of limbs, head and neck, pelvis and liver combining perfusion with surgical resection [4,5].

Austen et al. [6] pioneered treatment of malignant pelvic tumors by extra corporeal perfusion and obtained a clinical response in 4 of 7 pts with advanced cancers [6]. They accessed the vascular circuit intra abdominally effort and obtained pelvic isolation utilizing an abdominal tourniquet with groin inserted catheters in 7 pts [6]. Watkins obtained pelvic isolation by placing groin accessed balloon catheters placed 2-3 cm above the aortic bifurcation for isolated perfusion with pump oxygenator [7]. Lawrence conducted pelvic perfusion in 34 pts (5 open), via intra vascular balloon technique with use of an inflatable abdominal tourniquet [8]. Dedrick 1984 (NIH) utilized chemo filtration with charcoal column to detoxify the circuit as demonstrated in successful studies of isolated perfusion of the head in Rhesus Monkeys [9]. Pharmacokinetics and clinical monitoring of regional therapy was addressed by Collins who described a regional therapeutic index as ratio of drug concentration in the tumor (Area under Curve in the Tumor (AUCT) versus the Systemic drug concentration (AUCS) [10]. The therapeutic advantage (Rd) is expressed as Rd=AUCT/AUCS. Rd depended on the potential for metabolizing the drug (i.e. liver) and the fractions of drug removed during single pass through target tissue. The pharmacology of regional cancer therapy by isolated perfusion vs. regional infusion is detailed in many review articles from this group [11-18].

## Patient data

A total of 113 IPP was performed in 75 patients including 59 neoadjuvant and 16 palliative, irradiated and resected rectal cancer pts prior to plan pelvic resection. Eight additional patients had IPP therapy for recurrence after previous extended resection (4 ABSR, 4 APR) with a major focus on symptomatic tumor relief and palliation, but with consideration of resection in selected responding pts. Not included in the neoadjuvant effort was a previous group of 16 pts who had palliative IPP for recurrence post conventional APR/AR. Additional patients included 8 pts with advanced anal canal squamous cancer, 6 pts with pelvic sarcoma, 4 pts with advanced melanoma of proximal lower extremity and perineum and 5 advanced gynecologic cancers (2 endometrial and 3 ovarian pelvic recurrences), and 2 advanced bladder cancer pts. A total of 113 Isolated pelvic perfusions for 60 minutes utilized 5FU Paclitaxel 30-40 mg/m$^2$, 5FU (1,500-2,000 mg/m$^2$), cisplatinum (100 mg/m$^2$) or Oxaliplatin 150 mg/m$^2$) and mitomycin (10-20 mg/m$^2$) for epithelial cancers and selected agents (Adriamycin, Ifosamide, DTIC, Phenyl Alanine Mustard for the other cancers) (Table 1).

## Surgical technique

IPP was carried out under fluoroscopic control using the occlusion and infusion catheters placed into inferior vena cava and aorta via the femoral vein and artery as accessed through the groin [13,14,18]. Proximal large-cuff orthopedic thigh tourniquets were placed at the

**Table 2:** Pelvic Perfusion for Advanced Malignancy.

| Pelvic Perfusion for Advanced Malignancy*<br>Planned Neoadjuvant Threrapy for Advanced "Unresectable" Pelvic Malignancy | | | | | | | |
|---|---|---|---|---|---|---|---|
| **Tumor Type** | **Total** | **Responded to IPP*<br>Yes<br>No** | **Resectable** | **Resected** | **Resected<br>OS (mos)** | **Palliative<br>**** | **Mos<br>OS** |
| Recurrent Rectal Cancer | 26 | 15 (58%<br>11 (42%) | 15 | 7/15 (47%) | 30 | 18 | 8**, 23*** |
| Recurent Post ABSR | 4 | 2 PR 40% | 0 | 0 | 0 | 4 | 12 (5-18) |
| Post APR | 4 | 1 (PR) 33% | 0 | 0 | 0 | 3 | 6 (4-10) |
| Anorectal<br>Epidermoid Cancer | 6<br>2 | 5 PR 80%<br>1 PR 50% | 6<br>0 | 5<br>0 | 32<br>(110-119) mos | 2<br>2 | 2 (3-5) |
| Sarcoma | 6* | 3 PR (50%) | 3 | 1 | 11 | 5 | 4 mos<br>(4-5) |
| GYN (Endometrial) | 3* | 2 PR 100% | 2 | 3 | 7, 48 | | |
| GYN (Ovarian) | 3* | SD | 0 | 0 | 0 | 3 | 24<br>(11,28,33) |
| Bladder | 2* | 1 PR | 1 | 1 | 14 mos | 1 | 3 mos |
| Melanoma | 4* | 4 PR | 4 | 4 | 13 (6-20) | 0 | 0 |
| | 59 | 32 PR (54%) | 29(49%) | 21 (36%) | | 37 (63%) | |

groin level to limit the perfusion to the pelvis. On-table arteriograms and venous dye injections facilitated placement of balloon occlusion catheters above the bifurcation of aorta and IVC and below renal artery (technique described in detail (3+5). Patients are heparinized (initially with 5000 units of heparin) and have an additional heparin (25,000 units) given during the 60 minute perfusion.

### Technical/clinical considerations

Subjects for IPP require careful pre operative assessment by CT or MRI and more recently by PET scan in addition to relevant tumor biomarkers. Cardiovascular assessment included clinical and radiologic assessment of aorto iliac and venous flow circuit. Pts receiving thrombotic prophylaxis would be converted to IV heparin infusion (stopped 4-6 hours prior to perfusion).

### On table procedure

A fluoroscopic compatible operating table permits continuous monitoring of aorto iliac circuit and venous circuit via frequent (5 minute reviews of balloon occlusion catheter. There is potential for balloon leak or rupture (rare event) from aortic wall plaques which may require replacement of the balloon catheter during procedure. The anesthesiologist provides proximal venous access by venous and arterial catheters for CVP and arterial pressure monitoring. Vascular access for perfusion was obtained via balloon occlusion catheters and perfusion in the aorta above the biforcation (below renal artery) the location being confirmed fluoroscopically with dye injection. The perfusion canula are inserted in the same way and attached to perfusion circuit. The aorta and IVC are balloon occluded and bilateral thigh tourniquets are inflated to 50 mm above mean arterial pressure, and the perfusion circuit is completed and initiated via cannula connectors to the extracorporeal bypass pump. On table monitoring of balloon occlusion catheter is done by fluoroscopic imaging over mid-lower abdomen (every 5 minutes during IPP). In general the anesthesiologist maintains the mean arterial pressure 10-20 mm above the perfusion pressure to minimize "bleeding of drug" into the systemic circuit. The perfusion utilizes a pump set to deliver hyper oxygenated perfusate (blood plus chemotherapy at 39-41°) at 750-1000cc per minute. Drugs are given at time intervals (1/3 dose) every 5 minutes in a programmed manner, terminating with a planned wash out of saline or blood in pelvic circuit (500-700cc) at 60 minutes with equivalent systemic replacement.

At completion of perfusion the balloon occlusion catheters are released first in the venous circuit and then the aortic circuit with close monitoring of blood pressure with subsequent arterial and venous suture repair. Distal pulses are measured to ensure no thrombo occlusion. Pt is observed in an overnight, I.C.U. and transferred to med-surg unit for longer term observation in hospital or as outpatient daily hematologic monitoring to ensure stable WBC and to detect signs of neutropenia (greater risk at post op days 9-12). Neupogen is started on first post op day at 480 mcg/day (dose 5-7 mcg/kg) to maximize the WBC. Patients are initially given subcutaneous heparin 5000 ug 8 hr and then started on Coumadin once WBC is stable to continue for 30 days post operatively.

## Results

The various drug combinations for IPP of different tumors are listed in Table 1. Table 1B outlines selected pharmacokinetic results regarding commonly used drugs for epithelial cancers, anorectal adenocarcinoma or squamous carcinoma (5FU, Cisplatin, Oxaliplatin, Mitomycin C). The linearity of drug dose with mean pelvic exposures is shown in. The mean AUC pelvic to systemic drug level ratios for ano rectal cancers are demonstrated in Table 1B. The levels include 5FU 8.4:1, Cisplatin 6.0:1, Oxaliplatin 7.3:1, and Mitomycin C 9.0. The relation of drug dose to mean pelvic exposure is illustrated in.

Of 50 advanced/recurrent rectal cancer pts, 26 received neoadjuvant therapy prior to planned resection for pelvic recurrence by ABSR, 8 pts received neoadjuvant therapy prior to planned resection of advanced rectal cancer by ABSR/APR, and 16 pts were treated for advanced pelvic cancer (non resectable) by palliative IPP.

Neoadjuvant IPP in 26 rectal cancer pts induced an objective response in 15 pts by clinical/imaging assessment and was considered resectable. Two patients had a pathologic complete response (one had an open sacral re biopsy (negative) and planned resection was cancelled. The other pt had a path CR demonstrated at extended APR resection. Seven of 15 pts considered resectable were resected (6 required ABSR, and 1 an extended APR). Among the remaining 8 pts (2 were medically inoperable, 2 developed distant metastases, 3 resectable pts refused surgery and the patient with a negative sacral rebiopsy was cancelled). Of 11 non resectable pts, 9 had palliative therapy and 2 were treated with implanted infusion pump. The

survival data for the potentially resectable and the palliative groups. Outcome data of 8 previously treated pts who were in the previous extended resection group by ABSR (4 pts) APR (4 pts) (median survival was 7 mos (4-20 mos). Eight pts had IPP for recurrent squamous cancer. Six pts responded, and were resected (ABSR 2 pt, Extended APR 4 pts, whereas 3 were not resectable.

Among the other patient groups, there were 6 sarcoma pts of whom 3 of whom responded to IPP but only 1 was resected (required extended hemi pelvectomy (Table 2). The other pts were compromised by development of distant disease (3 pts) or were medically unfit for extended resection (Table 2). All 4 melanoma pts responded, and 4 had limited resection with major focus on limiting disease spread rather than attempting total tumor control, with median survival of 13 months. The Gyn cancer pts included 2 with endometrial cancer, 1 of whom had a near complete response post IPP with stem cell support for an extensive recurrence within pelvis and abdomen and had resection of all residual cancer surviving 48 months NED and finally dying from non cancer related drug use) a second patient had a near CR but survived only 7 months. The 3 ovarian cancer pts with bulky pelvic disease responded to IPP, but refused follow-up retrieval surgery. Of 2 recurrent bladder cancer pts, one responded to neoadjuvant IPP and survived 14 mo post cystectomy. The other patient had para iliac nodal mets and survived only 3 mo. Among the total group of 59 pts an overall response (PR- 50% regression) was observed in 32 pts (54%) of whom 29 were considered resectable and 21 (36%) were resected. The survival of each group is noted in Table 2. Palliative therapy only was delivered in 37 pts (63%).

### IPP with stem cell support

Three pts underwent high dose IPP with stem cell support (patient details in Table 2). This included a 65 yo female with advanced endometrial cancer whose disease had progressed following surgery and chemo therapy and was able to have a re resection following tumor regression by IPP with stem cell support and survived NED for 48 months before succumbing to renal failure secondary to non cancer related drug use. A second patient with extensive penile melanoma and had refused amputation underwent IPP with stem cell support and had a 90% regression of extensive disease, was able to have degloving resection of the penile melanoma and proceeded to planned marriage although he succumbed to metastatic melanoma 6 months later. A third 63 yo male with advanced peri anal squamous cancer who had failed the Nigro protocol and two subsequent resections with development of new pelvic and nodal disease. He underwent high dose chemo therapy via pelvic perfusion with stem cell support and had nodal and pelvic regression of target lesions with documented reduction in mitotic rate and K.67-nuclear count. The pt unfortunately developed subsequent recurrence, disease progression and succumbed at 90 days post IPP.

There was limited surgical toxicity (one required femoral artery reconstruction) the other problems centered on edema or minor groin hematoma. The most significant toxicity was hematologic with grade III anemia (12%), thrombocytopenia 9% and neutropenia (18%) requiring hospital support in pts with neutropenia until counts were restored. Three mortalities in the overall group of 75 pts included an in-house acute renal failure in a 73 year old female post IPP. Two deaths occurred from neutropenia at day 8 and 9, in patients who had left the institutional area and developed unrecognized neutropenic sepsis which was diagnosed late before initiation of treatment in their home community. These events prompted a future policy of demanding that pts stay in the institutional area until restoration of adequate leukocyte and neutrophil counts.

## Discussion

Isolated Pelvic Perfusion (IPP) was performed as planned neoadjuvant therapy in 59 patients with advanced pelvic malignancy. The majority of pts were local failures of surgery for primary rectal cancer having had resection by conventional LAR or APR (26 pts) in addition to chemo radiation pre or post primary resection. An additional 8 pts had secondary recurrence or persistence of disease post previous extended resection by abdominal sacral resection (4 pts) or extended APR in 4 pts. These pts were selected on basis of potential for re operative surgery in event of an adequate response or who had good potential for prolonged "pain free" palliation from IPP. Among the neoadjuvant category of 26 evaluable pts 15 (54%) were responders on basis of clinical/radiologic exam and considered candidates for resection. Of the 15 responders 8 were resected by ABSR in 7 pts and extended APR in 1 pt. One pt had a path CR of a previously biopsied sacral recurrence at re-exploratory laparotomy after two IPP and the planned ABSR was cancelled. Another path CR occurred in a pt in the resected groups who had a re resection APR with lymphnode resection. Three pts were candidates for ABSR but refused surgery and 2 became medically inoperable and, 2 pts had an excellent pelvic response but developed distant metastases. The overall survival was 32 mo in the resected group (2 of 8 pts were 5 year survivors), vs. 23 mo in the non resected responders, and 8 mos in the non responders. Among the previously resected pts for recurrence (ABSR 4 pts, APR (extended) in 4 pts), a PR response was registered in each sub group and one pt had a localized resection of a repeat recurrence in the symphysis. None of the other pts in this group were amenable to resection but most had excellent reduction in symptoms (and survival 4-20 mos post IPP). Among the 8 pts with recurrent anorectal squamous cancer following initial chemo radiation the Nigro protocol, 6 considered resectable had RO resection with long term disease free survival of 119 mos in 1 pt and mean OS in 5 pts all of whom ultimately recurred. Two additional pts were amenable to palliateive IPP only.

Isolated Pelvic Perfusion showed moderate value in the 4 melanoma pts with perineal-pelvic melanoma recurrence (requiring IPP rather than isolated extremity perfusion). There was minimal benefit in the sarcoma group. There appeared to be retrieval value in a small number of gynecologic pts (60-80% tumor regression), including advanced disease in 2 endometrial cancer pts. Three ovarian cancer pts with bulky pelvic recurrence were considered potential candidates for resection (but all refused further surgery). Their survival of 11 mo, 28 and 33 months post IPP suggested potential for re-operative resection in selected ovarian cancer pts with bulky disease who are IPP responders.

Of interest combination of high dose IPP chemo (Phenylalanine mustard and paclitaxel) with stem cell support was very beneficial in 2 of 3 pts studied. One patient with advanced and metastatic endometrial cancer had a very high level of response with total abdominal isolated perfusion (above and below renal artery) with stem cell support and had RO resection of remnant abdominal disease surviving NED over 48 mo. A young pt with advanced penile melanoma (refused amputation) underwent IPP with stem cell support which induced >90% regression of the melanoma and was able to have conservative degloving surgery, (although ultimately succumbed to metastatic melanoma at 6 months). A third pt with extensive/recurrent peri

anal squamous cancer (failed multiple resections/chemotherapy) had an initial excellent response to IPP with stem cell support but subsequently had recurrence with death at 90 days post IPP.

Overall of 59 pts in this multi disease group with pelvic malignancy 32 responders (54%) of whom 29 (49%) pts became resectable and resection was possible in 19 (32%) pts with OS survival post IPP (and resection) of 30 mos median (average) (2 of 8 were 5 year survivors). Among 40 pts whose IPP was considered palliative (68% of total group) the mean OS was 11.7 months.

Isolated perfusion has been utilized in a variety of sites but the greatest experience is in the limb perfusion data for melanoma and sarcoma (reviewed by Kroon and Hoekstra) [19,20]. Because of achievability of good isolation of the extremity perfusion circuit there is potential to safely add other agents to mephalan such as tumor necrosis factor (TNF) to enhance anti tumor effects with alpha modification. The regional perfusion technique has been simplified by use of the isolated limb infusion which is a simpler, less invasive technique may be an equivalent method of delivering high dose extremity chemotherapy with minimal drug leak and side effects [21,22]. The technique is repeatable and may provide a workable palliative approach for advanced extremity tumors.

A modification of IPP with extra corporeal chemo filtration (IPPEC) may also have potential for future adoption [23]. This approach utilizes percutaneous pelvic perfusion with extra corpeal chemo filtration for advanced uterine cervical carcinoma. Percutaneous catheters are placed in the uterine arteries bilaterally for infusion and a specialized balloon catheter permits balloon occlusion of the IVC with intra catheter communication for channeling blood for dialysis and return to the circulation filtrated blood to the systemic circulation. Activated carbon in the filtration unit was used to remove the infused cisplatin. The pre filter vs. post filter free platinum levels in this showed reduction from the prefilter range72-122 ug/ml to post filter (peripheral) blood levels of 2.1-3.6 ug/ml and peripheral blood 1.0-3.8 ug/ml. Treatment of pts with stage III to IV (FIGO) uterine carcinoma was demonstrated with an excellent tumor response by MRI including CR (complete response) in 13%, PR (partial response) in 74% and MR (minimal response) or NR (no response) of 13%. Follow-up surgical resection was done in 18 of 19 pts (78%), with negative margin (RO resection) in 16 of 18 pts (89%). The 5 yr survival was 74% in 18 pts treated by IPPEC vs. 58% in 5 pts treated with Radiation alone and 43% in patients treated by conventional therapy [27]. Azuma et al. [24] utilized a similar approach for bladder cancer. In a randomized trial which compared balloon occluded arterial infusion of cisplatin, with hemo dialysis. Combined with concurrent radiation for advanced bladder cancer pts followed by cystectomy compared to cystectomy alone. The experimental regimen was resulted in a measurable response in 69/77 (86%) of pts with locally invasive bladder cancer. The 5 yr OS was 91% in this group vs. 59.8% with cystectomy alone $p< 0.0001$. There were no Gr 3/4 severe toxicities. In contrast in the cystectomy group 50% had suffered disease progression and death from tumor at 5 years post cystectomy.

These modifications in regional therapy of pelvic cancer may have value in selected pts with high risk primary pelvic cancers. Whether this approach would be effective in pts with recurrent pelvic cancers in this report i.e. recurrent rectal adenocarcinoma or anorectal squamous cancers, or melanoma, sarcoma is less obvious because of the extensive pelvic anatomy involved by tumor. A major problem with pelvic IPP is the significant systemic leak (~30%). Perhaps selective chemo filtration of out flow perfusion in conjunction with maintenance of low mean arterial perfusion pressure, might produce higher tissue-tumor drug concentrations with potential for increased (anti tumor response and reduced systemic toxicity). The use of stem cell support to enhance outcome with high dose chemo infusion may also merit further exploration.

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