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ORIGINAL ARTICLE

IMPROVED 5-YEAR DISEASE FREE SURVIVAL BY EXTENDED CLEARANCE OF THE PELVIS DURING RADICAL CYSTECTOMY FOR LOCALLY ADVANCED BILHARIZAL BLADDER CANCER "STAGE P_3 AND P_{4a}"

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Aim: *To reduce the possibility of local pelvic recurrence after radical cystectomy for stage P_3 and P_{4a} bilharzial bladder cancer by performing extended pelvic dissection in order to accomplish complete clearance of the anterior part of the pelvic cavity.*
Methods: *A prospective study which was done in the period between 1998 and 2000. Forty-one patients (38 males and 3 females) having stage P_3 – P_{4a} bilharzial bladder cancer underwent radical cystectomy (or anterior pelvic excentration in females) with extended pelvic dissection to include and remove the parietal endopelvic fascia to achieve complete clearance of the anterior part of the pelvic cavity. Five patients were excluded and 36 patients were followed up for 5 years.*
Results: *There was one post-operative mortality. Local recurrence occurred in 16.6% of these patients. Five patients with tumor invasion to the prostate developed early vertebral metastases. The 5 year Disease Free Survival for all patients in stage P_3 and P_{4a} was 55.6%. It was 67.9% for stage P_3 patients and was only 12.5% for stage P_{4a} patients.*
Conclusion: *A reduced incidence of pelvic recurrence could be achieved by a meticulaous and extended pelvic dissection to achieve complete clearance of the anterior part of the pelvic cavity.*
Tumor invasion to the prostate represents a major problem that could be studied and solved.

Keywords: *Urinary tract neoplasms, Schistosomiasis, Surgery.*

INTRODUCTION

Cancer of the bilharzial bladder defines a distinct clinico-pathological entity different from that reported in western countries. The tumor is usually localized to the bladder with a limited tendency to lymphatic and blood spread.[1, 2]

Local recurrences, which are the main causes of failure after radical cystectomy for bilharzial bladder cancer, are originally residual microscopic growths which progressively increase in size.[2] The local recurrence rate after radical cystectomy for bilharzial bladder cancer was 42%, 50 out of 119 P_2 – P_4 Patients.[3]

On treating locally advanced bilharzial bladder cancer by surgery (radical cystectomy) which is the mainstay and sole available treatment with intentive cure, it is logic that the surgeon must make every effort to decrease the possibility of local pelvic recurrence. In standard radical cystectomy, the loose fibro-fatty areolar pelvic tissues are left behind and are situated over the parietal endopelvic fascia. These tissues may harbor a residual microscopic disease, which is not seen and not palpable to the surgeon and this hidden residual microscopic growths will grow and increase in size to establish a detectable local recurrence. This postulated risk of undetectable residual disease at the time of surgery is expected to be higher in stage P_3 and P_{4a} bladder cancer. Complete clearance of the anterior part of the pelvic cavity will remove this possible hidden microscopic residual disease to the outside with the surgical specimen. Removal of the parietal endopelvic

fascia with the surgical specimen ensures complete extirpation of all areolar fibro-fatty-fascial tissues and hence achievement of complete clearance of the anterior part of the pelvic cavity. This work aims at achievement of complete clearance of the anterior part of the pelvic cavity in stage P_3 and P_{4a} bilharzial bladder cancer patients, and is based on standard anatomical facts, and causing no increase in surgical morbidity.

PATIENTS AND METHODS

A prospective study which was carried out during the period from January 1998 to December 2000 in Cairo National Cancer Institute hospital and in the Pyramid hospital in Cairo. Forty seven patients (42 males and 5 females) were explored with the intention of performing extended radical cystectomy (complete clearance of the anterior part of pelvic cavity) for cure of locally advanced bilharzial bladder cancer. Their mean age was 56.5 years (range 33–76y, SD12).

Pre-operative evaluation and patient selection: Preliminary diagnosis of schistosomiasis was based on past history or cystoscopic biopsy. Confirmation of this diagnosis is only valid when there is a histologic evidence of bilharziasis in the post-surgical specimen. All the patients were considered to have locally advanced bladder cancer on the basis of their clinical staging. The main items in staging were bimanual rectal examination and CT findings. All the patients were having a bladder mass with restricted mobility (T3–T4 explorable).

According to the American Joint Committee on Cancer 2002 TNM Bladder Cancer Staging[4]: T_3 means that tumor invades perivesical tissue (pT_{3a}: Microscopically, pT_{3b}: Macroscopically) and are expressed in the postsurgical pathological report as P_{3a} and P_{3b} . T_{4a}: tumor invades prostate, uterus, vagina and bowel. T_{4b}: Tumor invades pelvic sidewall or anterior abdominal wall, and are expressed in the postsurgical pathological report as P_{4a} and P_{4b}. In this work P_3 means histologic evidence of invasion of the perivesical tissue.

For all patients explored HB % should be above 10 gm% and serum albumin above 3 gm% and prothrombin concentration should be above 85%, blood urea should be less than 40 mg% and serum creatinine less than 1.5 mg%. Patients with tumor invasion to anterior abdominal wall were excluded from the study because they need adjuvant radiation therapy.

This operation of extended radical cystectomy which aims at complete clearance of the anterior part of the pelvic cavity includes (A+B+C) surgical steps:

A) The formal standard steps of standard radical cystectomy, as described by El-Sebai (1983) in the technique of standard radical cystectomy (Cancer of the bilharzial bladder, Vol 2, p 50-60).[2] It includes the removal of the bladder with its covering peritoneum, the median and lateral umbilical ligaments, closely related paravesical lymph nodes, fascial structures which enclose the bladder (visceral endopelvic fascia), pelvic areolar tissue which enclose the bladder, the areolar tissue in the cave of Retzius, a broad band of endoplvic fascia which is termed the vescio-vesculo-prostatico-rectal fascia (Denonvilliers fascia), the prostate, the seminal vesicles and as much as possible of the membranous urethra, the external iliac lymph nodes and their covering fascia (lateral chain, intermediate chain, medial chain including the obturator group and the group behind Poupart's ligament), the common iliac chain, and resection of the anterior division of the hypogastric artery (internal iliac a) with all its branches and the lymph nodes related to the artery and nodes related to its branches, all en masse, together with resection of the puboprostatic ligaments, posterolateral ligaments and the levator prostatae fibres of levator ani muscle. But in females the steps of anterior pelvic excentration were adopted.

B) Surgical steps which were described by El-Sebai (1983) in the technique of extended radical cystectomy (Cancer of the bilharzial bladder, Vol 2, p 63)[2]: En bloc resection of any infiltrated bowel and omentum.

C) Surgical steps which are additive (or extra) to the standard radical cystectomy are: dissection and removal of the parietal endopelvic fascia which lines the pelvic aspect of the true obturator fascia and removal of the parietal endopelvic fascia which lines the levator ani muscle (en bloc with the specimen). These fascia represent the outermost boundary of the pelvic cavity, beyond this layer lies the fleshy fibres of pelvic musculature. The aim of this surgical step is to accomplish complete clearance of the anterior part of the pelvic cavity. Removal of the parietal endopelvic fascia which lines the levator ani ensures complete extirpation of all pelvic fibro-fatty areolar tissue which lies over this fascial layer, while removal of the endopelvic fascia that lines the pelvic aspect of the true obturator fascia ensures complete clearance at this site. Dissection of the endopelvic fascia present on levator ani muscle was started from just anterior to the lateral ligament of the rectum and was continued distally to include all the tissues lying over the muscle. Meticulous dissection in the correct plane with counter traction on the elevated dissected part of the fascia will help further dissection and will avoid entery and injury to the venous plexuses and their emerging veins which lie above this fascial layer. Exposure is helped by a forward mobilization of the specimen after completion of the posterior dissection and by a forward traction on the rectum and to the contra-lateral side. It is noteworthy to mention that all the large vessels that seen related to the upper border of the greater

sciatic foramen lie posterior to the site of lateral ligament of the rectum and these vessels should be protected and left undisturbed. These vessels lie posterior (dorsal) to the proposed site of dissection of the endopelvic fascia lying over the levator ani muscle and outside the field of dissection.

(A+B+C) surgical steps were adopted as routine steps in every case in this current work.

The method of urinary diversion was the feasible and safe rectal bladder and a left iliac colostomy with liberal drainage of the abdomen. In three cases bilateral endcutaneous uretrostomy were done. The average resection time was 3 hours and the average blood loss was 1.5 litres.

The proper postoperative care was meticulously adopted and the patients were followed up for five years, to detect any local or distant recurrence of the disease.

RESULTS

1) Results of the surgery: Six patients were clinically understaged and proved to be inoperable on surgical exploration.(4 males and 2 females).

Forty one patients (38 males and 3 females) underwent the extended surgery.

Intra-operative complications: Intra-operative bleeding (1.5-2.5L), venous bleeding from the pelvic venous plexuses, occurred in three patients and managed by adequate replacement therapy and adequate control of the bleeding.

The post-Operative Period of 41 patients underwent the extended surgery:

Thirty Three patients passed a smooth postoperative period.

Postoperative complications have occurred as follow:

A) Minor urinary leakage (less than 300 ml/day) occurred in 3 patients out of 38 underwent rectal bladder diversion and were managed conservatively.

B) Skin wound sepsis occurred in 4 patients out of 41.

There was one Postoperative Mortality due to pneumonia in an old diabetic male.

2) ***Results of the histopathologic examination:***

Routine histopathological examination of the surgical specimens was performed according to standard procedure outlined in Appendix H p 2632 of Ackeraman's surgical pathology (8th edition).[5] In addition to routine tissue sections stated in this procedure, careful dissection of the perivesical tissue, and the pelvic fascia for any visible or suspected tumor involvement was done with sampling of such areas if any. In case no gross lesions were observed a random sample of the pelvic fascia was obtained as an additional safety margin (classical margins included urethral and ureteric margins).

The histopathologic examination of the post-surgical specimens showed a clear resection margin in 40 out of 41 patients. There was a positive urethral margin in one patient. The lateral resection margin was not involved in any of the forty-one patients as proved by examination (both grossly and microscopically) of perivesical fat clearance beyond tumor involvement as well as of the sampled endopelvic fascia.

The eligible patients for 5 years follow up should be bilharzial patients, having stage P$_3$ or P$_{4a}$ and treated by surgery alone in one setting.

On the basis of the histopathologic examination of the specimens, four patients were excluded from the study. Exclusion criteria were:

A) In 2 patients, the histopathologic examination showed capsular rupture of the resected iliac nodes that required post-operative radiation therapy.

B) One patient was clinically overstaged and proved to have P$_2$ stage.

C) In one male patient, there was a positive urethral margin, that required a perineal urethrectomy in another setting.

Out of 41 patients who underwent the extended surgery, only 36 (33 males and 3 females) patients were considered the eligible patients for 5 years follow up. Their mean age was 58.3y (range 33-75, SD 10.6).

In the current series (36 patients), the average tumor size was 5.2 cm (±2.02) with a median of 5 cm and size range was 3-10 cm. The average number of dissected lymph nodes per case was 7.5 lymph nodes (±4) with a median of 7 lymph nodes.

The histopathologic staging, typing, grading and nodal involvement in the postsurgical specimens of these patients are shown in Table 1.

28 patients were having stage P_3 and 8 patients were having stage P_{4a}. The sites of extravesical infiltration in stage P_{4a} patients are shown in Table 2.

Table 1. The tumor histopathologic characteristics of the eligible 36 patients.

Characteristics	Frequency	Percent
Pathological stage (P)		
P_3	28	77.78
P_{4a}	8	22.22
Total	36	100
Histology		
Squamous cell carcinoma	14	38.9
Transitional cell carcinoma	17	47.2
Adenocarcinoma	4	11.1
Undifferentiated carcinoma	1	2.8
Total	36	100
Grade		
1	1	2.8
2	29	80.4
3	6	16.8
Total	36	100
Nodal invasion		
+ VE	4	11.1
– VE	32	88.9
Total	36	100

Table 2. Sites of extravesical invasion.

Site of extention	Frequency	Percent
Colon	1	12.5
Prostate	3	37.5
Prostate + Intestine	1	12.5
Prostate + Seminal vesicle	1	12.5
	1	12.5
Small intestine	1	12.5
Vagina	8	100
Total		

The follow up schedule: The follow up schedule was clinical examination, laboratory and radiological investigations including pelvic CT. Follow up examination was done every 3 months for the first two years, then every 4 months in the third year and then every 6 months afterwards.

3) ***Results of the follow up:***

The mean follow up period for the eligible patients (36: 33 males and 3 females) was 42.2 months (SD: 22.05, range: 5-60, median: 54).

Two patients developed definite local pelvic recurrence (one female after 10 months and one male after 16 months). Both patients were having stage P4a of the disease. In both patients the site of local recurrence, as evidenced by pelvic CT, was central in the tumor bed related to anterior rectal wall.

Five patients developed vertebral metastases after a median time of 14 months (range9-17months). In these 5 patients, vertebral metastases occurred in the lower lumbar vertebrae but one of them developed also synchronous pelvic bone metastases. These five patients were having stage P4a with tumor invasion to the prostate. These five patients did not show clinical or radiological evidence of local pelvic recurrence.

Four patients missed the follow up after a median time of 6.5 months (range 5–8 months). Patients who missed the follow up were considered to be died from the disease.

Five patients died from other co-morbidity but were free from cancer till death. One of them died from heart disease and four patients died from renal failure, the median time to death was 48 months (range 36–51months). The cause of death and its time were determined by personal communications with their families, every death was considered attributed to the cancer in the calculation of the disease free survival even if a co-morbidity condition was found. Twenty patients were alive and free from cancer to the end of the study.

The 5 year Disease Free Cumulative Survival is shown in Table 3. The 5 year Disease Free Survival (DFS) for all patients in stage P_3 and P_{4a} was 55.6%. The 5 year DFS for 28 patients having stage P_3 was 67.9% while the 5 year DSF for 8 patients having stage P_{4a} was 12.5%. (Fig. 1) show the 5 year DFS for the patients with stage P_3 and P_{4a}.

Table 3. Show 5 year Disease Free Cumulative Survival.

Year	Cumulative Survival	SE
1	80.6%	6.6%
2	69.4%	7.7%
3	66.7%	7.9%
4	61.1%	8.1%
5	55.6%	8.3%

SE = Standard error

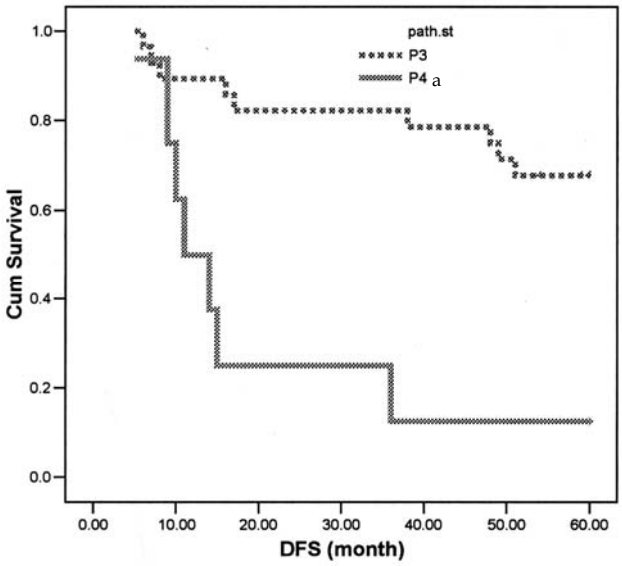

Fig 1. The 5-year Disease Free Survival for stage P_3 and P_{4a} patients.

DISCUSSION

In the present study two patients developed definite local recurrences. The five patients who developed vertebral metastases did not show evidence of local pelvic recurrence. The five patients who died from other co-morbidity were free from local recurrence till death. It is probable that the four patients who missed the follow up have experienced local pelvic recurrence. The sum of local recurrences is 6 out of 36 patients which equal 16.6% of all the treated patients.

The local recurrence rate reported by Ghoneim et al (1979) was 42%: 50 out of 119 P_2 – P_4 bilharzial bladder cancer patients.[3] For non-bilharzial transitional cell carcinoma of the urinary bladder, local recurrence occurred in 31 (20%) out of 154 patients (T1: 4.5%, T2: 31.2 %, T3: 51.9%, T4: 11.7%) treated by radical cystectomy and adjuvant chemotherapy.[6] Both studies had included patients with early stage and patients with advanced stage of the disease.

In the current work, the 5 year disease free survival (DFS) for all patients in stage P_3 and P_{4a} was 55.6%. The 5 year DFS for 28 patients having stage P_3 was 67.9% while the 5 year DSF for 8 patients having stage P_{4a} drops to only 12.5%.

The five year disease free survival was 32.5% for 120 patients, having different stages of bilharzial bladder cancer, treated by radical cystectomy, but it was 13% in patients having stage P_{4a} when intestine and omentum were involved and resected with the specimen.[2] There was no long term survival in basal tumors which invaded the prostate.[2]

The five year DFS was 32.6% for 138 patients (P1:2, P2:26, P3:90, P4:20) treated by radical cystectomy for bilharzial bladder cancer.[3]

The five year DFS was 48.1% for 1026 patients (P1:48, P2:142, P3:766, P4:70) treated by radical cystectomy.[7] It was 31% in 57 stage P3b patients (this ecompasses stage P3a and P3b in the current TNM staging). It was 19% in 70 stage P4a patients.[7]

Two schedules of postoperative radiotherapy were adopted after radical cystectomy (153 patiens stage P2-P4a): Conventional Fractionation (CF) and Multiple Daily Fractionation (MDF). The five year disease free survival rates were 49% and 44% in MDF and CF post-operative radiotherapy groups, compared to 25% in cystectomy alone group.[8] These figures are still lower than those achieved in the current work by extended surgery alone.

In the present study there were 5 patients with invasion of the prostate out of 8 patients having stage P_{4a}. The five patients developed lower lumbar vertebral metastases after a median time of 14 months (range 9-17 months) following surgery. The early development of lower vertebral metastases after radical cystectomy may be explained by two facts, the first is pathological and the second is anatomical.

Bilharzial infestations of the urinary bladder when severe or repeated leads to fibrosing its muscles, sclerosing its submucosa and narrowing its veins.[1] The blood vessels that lie within bilharzial infiltrations are prone to undergo thrombo-angitis or thrombo-phlebitis ending in partial or complete closure of their lumina.[1] Bilharzial affection of the prostate is less than the urinary bladder in both frequency and severity.[1] The percentage distribution of the eggs of Schistosoma haematobium among the endopelvic organs were: 90% in the urinary bladder, 80% in the seminal vesicles and 19% in the prostate.[9] The intensity of egg deposition in the tissues bears a similar correlation.[9]

From these pathological facts one can expect to find many cases with bilharzial bladder cancer but without bilharzial affection of the prostate. In these particular patients, when the bladder cancer advances and invades the non-bilharzial prostate, malignant emboli can spread to systemic circulation by passing through un-narrowed lumina of the prostatic veins and venous plexuses.

It was established that the internal vertebral plexus drains through the anterior sacral foramina into the lateral sacral

veins, and so into the internal iliac veins. There are no valves in this system. Sudden increase in abdominal pressure (as in coughing) may be momentarily more than the inferior vena cava can accommodate, and this drives blood backwards up the internal vertebral plexus, into posterior intercostal veins and by azygos veins into the superior vena cava, by-passing the diaphragm.[10,11] Emboli from disease of the pelvic viscera can thus find their way by occasional reflux blood flow into the vertebrae. In this way secondary carcinomatous deposits may appear in the vertebrae from primary growths in any of the pelvic viscera.[10,11]

So it is probable that during dissection and manipulations at surgery, malignant emboli are delivered to the prostatic venous plexus and can reach the internal iliac vein. In the mean time when the patient is under controlled ventilation, during general anaesthesia, there is rise of intra-thorathic pressure (during inspiratory phase) with concomitant rise of the pressure inside the inferior vena cava which impedes the venous return from the internal iliac veins, which results in reflux of the blood flow from the internal iliac veins backwards to reach the internal vertebral plexus (the same way described by Last, 1978 and Sinnatamby, 1999). It is probable that this mechanism of refluxed blood flow during surgery may play a role in the occurrence of vertebral metastasis in bilharzial bladder cancer patients when the prostate is infiltrated by cancer but not affected by bilharziasis. This point needs further study to verify and assess what really occurs, and to clearly know does it worth to perform early interruption of prostatic veins when the prostate is invaded in operable patients of bilharzial bladder cancer. Early interruption of these veins will be by early exposure of the internal iliac vein and ligation of the venous trunks which come out from the prostatic venous plexuses and drain into the internal iliac vein.

In conclusion, the extended radical systectomy technique may improve local control and hence disease free survival for patients with locally advanced bilharzial bladder cancer. A large prospective study including bilharzial and non-bilharzial bladder cancer patients would provide a more elaborate evaluation of the current findings.

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