

**Quality Assurance In Pelvic Radiotherapy
As Applied To Preoperative And
Postoperative Radiotherapy For Muscle
invasive And Operable T4 Bilharzial
Bladder Cancer**

Thesis

Submitted In Partial Fulfillment of the Doctorate Degree of
Radiation Oncology

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Abstract

This study is a prospective analysis for 100 eligible patients with operable bladder cancer between 2004 and 2007. Patients were treated by radical cystectomy and either pre-operative or postoperative radiotherapy. The average age of the patients was 54.8 ± 9.5 years. Male: Female ratio 2:1. The most commonly encountered pathological subtype was transitional cell carcinoma (51%), while squamous cell carcinoma was reported in 46% of cases. As regards the grade of the tumor, only 2% of the population had grade I tumor. Grade II and III were 81% and 17% respectively. The pathological stage was classified according to UICC classification system 1997, and the commonest pathological stage was P_{2b} which was encountered in 39.5% followed by P_{3b} 33.3% and P_{3a} 14.6% of the patients. Positive lymph nodes reported in 14 patients (15.4%) which was significant prognostic factor. Acute GIT radiation reactions are nearly the same in both groups. As regards late GIT radiation only 2 patients developed intestinal obstruction. Loco-regional recurrences were reported in 6 patients. Distant metastasis was observed in 12% of the preoperative group and in 22% of the post-operative group. The 3-year disease free survival rate was 47.4% and 34.1% for the pre-operative and for the postoperative groups respectively. The 3-year overall survival rate was 53.4% and 51.8% for the pre-operative and for the postoperative groups respectively. The difference in DFS and OS of both groups is statistically insignificant. Random sample of ten patients tested for set up accuracy with and without cast immobilization which did not add significant benefit.

Acknowledgement

I wish to express my deepest gratitude and sincerest thanks to **Dr. Hassan Abdel Moneim**, Professor of Radiation Oncology, National Cancer Institute, Cairo University for his honest supervision, fatherly guidance, and giving me his valuable advices and support throughout the whole work. A sincere appreciation is also expressed to **Dr. Alaa Younos** Professor of surgical Oncology, National Cancer Institute, Cairo University for his help in following the work to ensure its valuable level. Great thanks to **Dr. Manal El Baradie**, Assistant Professor of Radiation Oncology, National Cancer Institute, Cairo University for her unlimited help and guidance.

I would like to thank my family for their continuous and limitless love and support, my wife **Magda**, my daughter **Judy**, and my dear brother & sister. Needless to say, it then all comes back to the parents. Who can do without them? To them I am so grateful that I never ever needed to worry about anything.

I am also grateful to my patients, without their tolerance to this treatment protocol; this piece of work would have never seen light.

دراسة إكلينيكية لتأكيد الجودة في العلاج الإشعاعي للحوض كتطبيق في العلاج الإشعاعي قبل وبعد

طبيب/ ياسر محمد رجب

مدرس مساعد العلاج الإشعاعي بمعهد الأورام القومي

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Arabic Summary

Invasive bladder cancer, overview

Bilharziasis associated bladder cancer is the commonest form of cancer encountered in Egyptian males, 30% of all cancers in the NCI, Cairo (40% of male cancers & 14% of females cancers), (**Sherif, and Ibrahim, 1987**). It represented about 26.4% of all cancer cases documented in the pathology registry at NCI Cairo (**Mokhtar, 1991**). Recently the bladder cancer relative frequency decreased to 12% of cancer cases presented to NCI Cairo at the beginning of the 21st century (**El Attar, 2002**).

Bladder carcinogenesis is related to bacterial infections associated with bilharzial infestation rather than the parasite itself (**El Aasar, and El Merzabani, 1981**). Urinary bacteria is associated with,

- Production of carcinogenic nitrosamines
- Secretion of B- Glucuronidase which helps in yielding free carcinogens

Transitional cell type of bladder cancer accounts for nearly 90% of cancers reported in the West, **Sidransky et al, 1992** where as squamous cell type accounted 60-73% of cancers reported in Egypt till before the last two decades (**El Bolkainy et al, 1981**). Now probably due to the effect of anti-bilharzial treatment, both transitional & squamous cell types are nearly equal (**El Bolkainy et al, 1998**). The decline in the prevalence

of bilharziasis in Egypt was associated with significant changes in the pathology of bladder carcinoma. This was confirmed by time trend analysis studies of the frequency of bilharzial eggs and tumor type in two

large series of cystectomy specimens collected at different time intervals with 15 years period in between (**El Bolkainy, 1998**). This study demonstrated a significant decrease in bilharzial eggs in tissue, a decline in the relative frequency of squamous carcinoma. Table (1)

Table (1): Time Trend analysis of bladder cancer in cystectomy specimens.

	Series A (1976-1978) (1095 Patients)	Series B (1991-1993) (1256 Patients)
Bilharzia egg positivity	902 (82%)	741 (59%)
Squamous carcinoma (SC)	854 (78%)	665 (53%)
Transitional carcinoma (TC)	175 (16%)	452 (36%)
Other types	66 (6%)	139 (11%)
SC/TC ratio	4.7	1.5

Because symptoms of bladder cancer, viz: frequency, pelvic pain, haematuria, dysuria, and pyuria; differ a little from symptoms of chronic bilharzial cystitis, most of the cases present in advanced stage. **El-Bolkainy et al, (1972)** found that 81% of the operated patients had stages P3-P4 disease (UICC staging system). In another series of 1033 cases, the incidence of locally advanced disease, P3-P4, represented about 86.2% of cases (**Mokhtar, 1991**).

Radical treatment procedures used in muscle invasive bladder cancer are either bladder conserving or bladder none conserving. Radical cystectomy is generally the treatment of choice in USA & Egypt where as conservation is generally the treatment of choice in Europe (**Stein, 2003**).

Radical cystectomy entails the removal of the bladder with its perivesical fascia, peritoneal covering, the prostate, and the seminal vesicles together with the distal common iliac, external and internal iliac lymph nodes. In females, the bladder, urethra, uterus, and upper 2/3 of the vagina with pelvic cellular tissue and the above-mentioned lymph nodes are removed (**Ghoneim et al, 1976; EL Sebai et al, 1961; and 1978**).

If there is involvement of bladder neck or prostatic urethra total urethrectomy is indicated as the risk of subsequent urethral involvement in these patients exceeds 10 % (**Ghoneim et al, 1976**).

Urinary diversion procedures include: Rectal bladder which is the most frequent type with night incontinence is the main complaint. The ileal conduit that needs a good surgical skill. Uretrocolic diversion with its subsequent renal complications. Uretrocutaneous diversion is recommended in cases with substantial back pressure to shorten time of anesthesia.

Post operative mortality nowadays have been reduced due to gaining of experience and advances in anesthesia and intensive care. **Ghoneim et al, 1997** reported Post operative mortality of 4% in 1026 patients.

The overall 5 year disease free survival rate after RC amounts to about 48% (*Ghoneim et al, 1997*). The 5-year overall survival for bladder cancer patients treated by radical cystectomy in different series are shown in table (2).

Table (2): The 5-year overall survival for bladder cancer patients treated by radical cystectomy in different series.

Author	The 5-year overall survival in different series.
El-sebai (1977)	27%
Ghoneim (1976)	38.9%
Ghoneim (1997)	48.1%
Lerner (1992;1993)	45%
Stein (2001)	66%

Preoperative radiotherapy

The rationale for the use of preoperative radiotherapy in bladder cancer is to prevent intra-operative seeding of tumor cells and sterilization of the microscopic tumor deposits beyond the surgical field. The role of preoperative radiotherapy in bladder cancer remains uncertain.

El-Sebai 1983 reported that about 30% of local recurrences occurred during the first three months following cystectomy. **Wishnow et al, 1988** reported pelvic recurrence rate to be approximately 15%. The most likely benefit of preoperative radiotherapy is a reduction in the pelvic recurrence. Although pre-operative radiotherapy may be very useful in preventing local recurrence, the early emergence of distant metastasis would obscure this benefit in patients with bladder cancer.

Egyptian experience and Results of preoperative radiotherapy in bladder cancer

A prospective study by **Awwad et al, 1979** had aimed at investigating the value of moderate doses of pre-operative telecobalt irradiation; two dose-time regimens were compared: conventional fractionation and hyperfractionation. In either case a split-course technique was used. Forty eight patients with T3 bilharzial bladder carcinoma were considered eligible for radical cystectomy and were included in the trial and followed up for at least 2 years. The therapeutic groups included:

A. Radical cystectomy alone.**B. Split-course (SC) pre-operative radiotherapy group:**

Two courses were given with a gap of 1 week. Each course comprised 10 fractions of 200 cGy each, delivered over 14 days. Cystectomy was performed 15-20 days after the end of the second course.

C. Hyperfractionation (HF) pre-operative radiotherapy group:

Two courses also were given with a gap of 1 week. Each course consisted of 2 days treatment; on each day 17 fractions of 60 cGy each, were delivered at a rate of 1 fraction / hr,(low dose per fraction which was the same principle of brachtherapy) i.e., a total daily dose of 1000 cGy. Cystectomy was performed 15-20 days after the end of the last course.

The 1 and 2-year disease free survival rates in patients receiving pre-operative radiotherapy were 59±9% (19/32) and 53±9% (17/32) respectively (table 3), while in the surgery alone group it was, 25±11% and 19±10% respectively (P< 0.05). The survival rates did not differ significantly in the SC and HF groups.

Table (3): Disease free survival rates in patients receiving pre-operative radiotherapy in the SC and HF groups.

	Control	HF (low dose rate)	SC
No. of patients	16	16	16
Operative mortality	1	3	1
Cause	Peritonitis	-Peritonitis -Hemorrhage -Liver failure	Peritonitis
Alive and NED*			
1 year	4	8	11
2 year	3	8	9
Died of disease within 2 year	12	5	4
Died of other causes	0	0	2**
* No evidence of disease.			
** Hematemesis (portal hypertension; coronary heart disease)			

Awwad et al., 1979

These results were comparable with the results of **Ghoneim et al, 1985** where 96 patients with T3 bilharzial bladder cancer were randomized into 1 of 2 groups:

- *Radical cystectomy alone (49 patients)*
- *Cystectomy preceded by 400 cGy x 5 fractions /week (43 patients)*

Cystectomy was performed 1-2 days after the end of radiotherapy. There was improvement in survival after pre-operative radiotherapy (P3 and P4) tumors ($P < 0.10$) Table (4).

The survival rate of patients with low pathological stage tumors, irrespective of grade, appeared to be uninfluenced by pre-operative radiotherapy. On the other hand, patients with high stage tumors in whom pre-operative irradiation was used had better survival in each grade category. It is clear from the table that the low number of patients in P1 and P2 group might affect the statistical analysis.

Table (4): 5-year direct survival according to pathological stage (P) in 92 patients with T3 bilharzial bladder cancer.

	Cystectomy (No/Total)	Radiation and cystectomy (No./Total)
P1	3/3 (100%)	2/4 (50%)
P2	7/12 (58.3%)	5/9 (55.5%)
P3*	6/30 (20%)	9/20 (45%)
P4	0/1 (0%)	0/1 (0%)
Pts with positive nodes	0/3 (0%)	1/9 (11.1%)

Ghoneim et al., 1985.

* $P < 0.1$

They also reported improvement in the survival rate in high grade tumors after pre-operative radiotherapy. Table (5).

Table (5): Survival proportion by grade in 92 patients with T3 bilharzial bladder cancer.

	GROUP 1 Cystectomy (No./Total)	GROUP 2 Radiation and cystectomy (No./Total)
Low grade	15/35 (42.9%)	12/26 (46.1%)
High grade*	1/14 (7.1%)	5/17 (29.4%)
Total	16/49 (32.7%)	17/43 (39.5%)

Ghoneim et al., 1985.

*P<0.05

The survival benefit of preoperative radiotherapy had also been proved by **Abdel Moneim et al, 1982**, where 96 patients with T3 bilharzial bladder cancer were randomized into 1 of 3 groups:

- A. Radical cystectomy alone (23 patients)
- B. Split-course (SC) pre-operative radiotherapy (28 patients). Two courses were given with a gap of 1 week. Each course comprised 10 fractions of 200 cGy per fraction, delivered over 14 days. Cystectomy was performed 15-20 days after the end of the second course.
- C. Concentrated pre-operative radiotherapy (45 patients) two courses of a single dose of 650cGy with 1week gap. Cystectomy was performed 15-20 days after the end of the second course.

Patients assigned to concentrated pre-operative radiotherapy are rerandomized to:

- Radiotherapy alone (15 patients).
- Radiotherapy plus oral misonidazole: 3g/m² given 3-5 hours before each fraction. (18 patients).
- Radiotherapy plus intravesical misonidazole: 2.5g dissolved in 50 ml and kept 1-2 hours before each fraction. (12 patients).

The efficiency of split-course of pre-operative radiotherapy scheme was confirmed and a 2-year disease free survival rate of 54±9 % was achieved compared to 32±10 % for cystectomy alone group (P=0.03). However, the concentrated pre-operative radiotherapy regimens were less efficient with a 2-year disease free survival rate of 47± 7 % (**Abdel Moneim et al, 1982**).