Bladder Preservation by Transurethral Resection and Radiotherapy in Invasive Bladder Cancer

Ahmed Hussin Adnan Mutter
Urology department, AL- Zahra Teaching Hospital, Baghdad, Iraq.

Abstract

Purpose: We evaluate the use of a transurethral resection with radiotherapy in the treatment of operable transitional cell carcinoma of the bladder with potential bladder preservation.

Materials And Methods: A total of 143 consecutive patients with T2-T3 bladder tumors underwent as complete transurethral resection as possible. They then received radiation therapy for 6-7 weeks. Following that, patients were reevaluated cystoscopically and ultrasound imaging. Of the 143 patients 92 have complete clinical response, undergo 3-6months cystoscopic examination for two years. 48 Patients had incomplete responses.

Results: Of the 143 patients 92 had no detectable tumor after induction therapy. 48 Patients who had incomplete responses, 11 of them were undergo an immediate radical cystectomy. 3 patients die during period of radiotherapy, and 12 patients, die during period of follow up and treatment. The mean age of our patients was 57 years, 106 male patients and 37 female patients

Conclusions: This study demonstrates a high rate of response to this combined radiation regimen in conjunction with a visibly complete transurethral resection. The results of bladder sparing approach for the treatment of muscle-invasive bladder cancer, using a combination of transurethral resection (TUR) and radiotherapy, are encouraging and increase the survival of patients treated by this method.

Introduction

Bladder cancer accounts for approximately 90% of cancers of the urinary collecting system (renal pelvis, ureters, bladder, urethra). Bladder cancer is the second most common cancer of the genitourinary tract [1]. Bladder cancer is most common in industrialized countries. It is the fifth most common type of cancer in the United States, the fourth most common in men and the ninth in women[2]. In Iraq, age-standardized death from bladder cancer per 100,000 inhabitants in 2004, was 15-16.5 [3]. Figure (1)

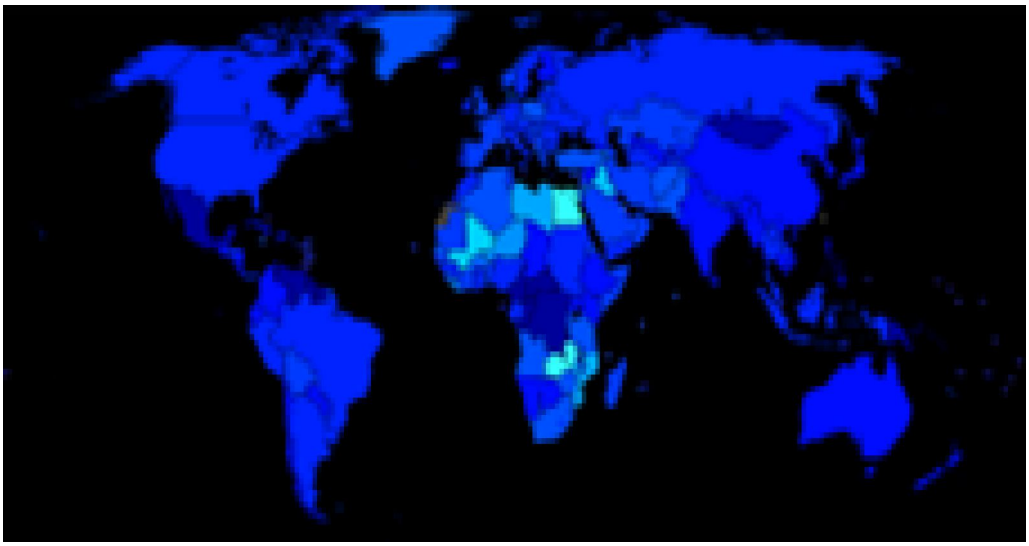

Figure 1 Age-standardized death from bladder cancer per 100,000 inhabitants in 2004.[3]

Each year, about 67,000 new cases of bladder cancer are expected, and about 13,000 people will die of the disease in the United state [4]. Bladder cancer affects three times as many men as women. Women, however, often have more advanced tumors than men at the time of diagnosis [5]. Whites, both men and women, develop bladder cancers twice as often as other ethnic groups. Bladder cancer can occur at any age, but it is most common in people older than 50 years of age. The average age at the time of diagnosis is in the 60s. However, it clearly appears to be a disease of aging [6]. Because of its high recurrence rate and the need for lifelong surveillance, bladder cancer is the most expensive cancer to treat on a per patient basis [7]. Approximately 75% of tumors are localized and 25% have spread to regional lymph nodes or distant metastasis at the time of presentation [2].

Risk factors:[8,9]

- Using tobacco, especially smoking cigarettes.
- Being 60 years or older, male, or white.
- Being exposed to certain substances, such as soot from coal, or chemicals used to make rubber, certain dyes, or textiles.
- Working as a dry cleaner or in places where paper, rope, twine, or clothing is made.
- Taking *A.* fangchi, a Chinese herb.
- Drinking water that has high levels of arsenic.
- Having a history of many bladder infections.
- Long-term use of urinary catheters.

- Past treatment with certain anticancer drugs or radiation therapy to the pelvis.
- Having a kidney transplant.
- Having an inherited disorder called hereditary nonpolyposis colon cancer .

Types of Bladder Cancer:

Bladder cancer usually originates in the bladder lining, which consists of a mucous layer of surface cells that expand and deflate (transitional epithelial cells), smooth muscle, and a fibrous layer. Tumors are categorized as low-stage (superficial) or high-stage (muscle invasive). In industrialized countries (e.g. United States, Canada, France), more than 90% of cases originate in the transitional epithelial cells (called transitional cell carcinoma; TCC). In developing countries, 75% of cases are sequamous cell carcinomas (SCC) caused by Schistosoma haematobium (parasitic organism) infection. Rare types of bladder cancer include small cell carcinoma, adenocarcinoma,

Diagnoses:

The following tests and procedures may be used:

- CT scan and ultrasound image.
- Intravenous urography (IVU).
- Cystoscopy:
- Biopsy: The removal of cells or tissues so they can be viewed under a microscope by a pathologist to check for signs of cancer. A biopsy for bladder cancer is usually done during cystoscopy. It may be possible to remove the entire tumor during biopsy.
- Urine cytology: Examination of urine under a microscope to check for abnormal cells [11].

Staging: The following stages are used by health care providers to classify the location, size, and spread of the cancer, according to the TNM (tumor, lymph node, and metastases) staging system [12,13,14,15].

Table 1 Primary Tumor (T)

TX	Primary tumor cannot be assessed.
T0	No evidence of primary tumor.
Ta	Noninvasive papillary carcinoma.
Tis	Carcinoma *in situ*: "flat tumor."
T1	Tumor invades sub-epithelial connective tissue.
T2	Tumor invades muscularis propria.
pT2a	Tumor invades superficial muscularis propria (inner half).
pT2b	Tumor invades deep muscularis propria (outer half).

T3	Tumor invades perivesical tissue.
pT3a	Microscopically.
pT3b	Macroscopically (extravesical mass).
T4	Tumor invades any of the following: prostatic stroma, seminal vesicles, uterus, vagina, pelvic wall, abdominal wall.
T4a	Tumor invades prostatic stroma, uterus, vagina.
T4b	Tumor invades pelvic wall, abdominal wall.

Table 2 Regional Lymph Nodes (N)

NX	Lymph nodes cannot be assessed.
N0	No lymph node metastasis.
N1	Single regional lymph node metastasis in the true pelvis (hypogastric, obturator, external iliac, or presacral lymph node).
N2	Multiple regional lymph node metastases in the true pelvis (hypogastric, obturator, external iliac, or presacral lymph node).
N3	Lymph node metastases to the common iliac lymph nodes.

Table 3 Distant Metastasis (M)

M0	No distant metastasis.
M1	Distant metastasis.

Treatment:

The four standard modes of treatment that are available for bladder cancer are **surgery, radiation therapy, immunotherapy, and chemotherapy** [16].

Treatment of bladder cancer depends on how deep the tumor invades into the bladder wall. Superficial tumors (cancer refers to Ta, T1, and Tis lesions of any grade those not entering the muscle layer) can be "shaved off" using an electrocautery device attached to a cystoscope transurethral resection (TUR). 80% of bladder cancer is superficial, but

70% of them will recur after TURT [2]. Tumor grade and stage clearly have an influence on tumor recurrence and progression. Low-grade Ta lesions recur at a rate of 50% to 70% and have approximately a 5% chance of progression, whereas high-grade T1 lesions recur in more than 80% of cases and progress in 50% of patients within 3 years. Tumor size, the number of lesions, the presence or absence of lymphovascular invasion, and the status of the remaining urothelium also provide predictive information regarding the behavior of superficial lesions. Careful follow up of patients with the superficial bladder tumor is mandatory. Periodic cystoscopy is suggested for all patients with the bladder cancer at three months interval is necessary for the first year, then annually for 5 years. After 5 years, the risk of recurrence has been estimated to be 22% and 2% for 10 years [17]. Radical TURT alone have a risk of leaving residual disease behind, as high as 40% to 75% of cases[18]. In many instances, there is persistent disease at the original site of resection, so TUR alone has rarely been used in the management of patients with the invasive bladder cancer, because of high risk of recurrence and progression.

Immunotherapy or biological therapy uses the body's own immune cells to fight the disease. To treat superficial bladder cancer, bacillus Calmette-Guérin (BCG) may be instilled directly into the bladder after TUR. BCG is a weakened (attenuated) strain of the tuberculosis bacillus that stimulates the body's immune system to fight the cancer. This therapy has been shown to be effective in controlling superficial bladder cancer. In the form of BCG instillation is also used to treat and prevent the recurrence of superficial tumors, BCG immunotherapy is effective in up to 2/3 of the cases at this stage [19].

Patients whose tumors recurred after treatment with BCG and invasive bladder tumor are more difficult to treat [20]. Many physicians recommend Cystectomy for these patients. If the cancer is large or is present in more than one area of the bladder, a radical cystectomy is done. The entire bladder is removed in this procedure, adjoining organs may also be removed. In men, the prostate is removed, while in women, the uterus, ovaries, and fallopian tubes are removed.

Chemotherapy uses anticancer drugs to destroy the cancer cells that may have migrated to distant sites. The drugs are injected into the patient intravenously or taken orally in pill form. Generally a combination of drugs is more effective than any single drug in treating bladder cancer. Chemotherapy may be given following surgery to kill any remaining cancer cells, called (neoadjuvant chemotherapy). Chemotherapy also may be given even when no remaining cancer cells can be seen (adjuvant chemotherapy). Anticancer drugs, including thiotepa, doxorubicin, and mitomycin, may also be instilled directly into the bladder (intravesicular chemotherapy) to treat superficial tumors after TUR. Instillations of chemotherapy, into

the bladder can also be used to treat BCG-refractory superficial bladder tumor [21].

The radiotherapy is one of the main stay for treatment of genitourologic malignant diseases, although aggressive surgery and chemotherapy have supplanted some of the uses of radiotherapy, radiation continue to play a major role in the management of bladder cancer [1].

The effect of radiation on tumor is mediated through induction of unrepaired double-strand break of DNA. Conventional EBRT (external beam radiotherapy), have been used in united state for more than 35years, other new technique use computed tomography has improved in ability to localized tumor and reconstruct pelvic anatomy, allowing more accurate design of treatment portals[2].

Radiotherapy EBRT 5000-7000 cGy, delivered in fraction over a 5 to 8 weeks period, is an alternative to radical cystectomy in patients with muscle invasive [21]. Radiation therapy that uses high-energy rays to kill cancer cells is generally used after surgery to destroy any remaining cancer cells. If the tumor is in a location that makes surgery difficult or if it is large, radiation may be used before surgery to shrink the tumor. In cases of advanced bladder cancer, radiation therapy is used to ease the symptoms such as pain, bleeding, or blockage [22].

Radiotherapy is divided into a number of sessions called fractions. Most people who receive external beam radiation therapy for bladder cancer are treated 5 days a week for 6 to 7 weeks as an outpatient. This standard regimens called Conventional Fractionation (dose-per-fraction 1.8-2Gy) were about 60-64Gy in 30-32 fractions over 6-7weeks [23]. Using small fractions causes less damage to surrounding normal cells but can still result in some side effects. There are other protocols which are used to decrease the complications like, Hyper-Fractionation(dose-per-fraction 1.5Gy or less) over 8 weeks, Accelerated-Fractionation were 60Gy in 32 fractions two fractions per day of 1.9Gy for 26 days but have high rate of intestinal toxicity [24] and Hypo-Fractionation (doses-per-fraction>2.5Gy) were 55Gy in 20 fractions(split 10+10 with a 2 week gap) [25].

Materials and Methods

A total of 143 patients with the bladder tumor, evaluated in AL-KUT general hospital from April 2002 to April 2008, ultrasound, CT scan, cystoscopy and EUA (examination under anesthesia) with histopathological examination done for all of them. From 143 patients 102 were stage T2 and 41 patients stage T3. All patients underwent complete transurethral resection TUR, then they received radiation therapy for 6-7 weeks in Baghdad Oncology Center by Conventional Fractionation method .Most patients who receive external beam radiation therapy are treated, 5 days a week for 6 to 7 weeks as an outpatient.

Following that, patients were reevaluated cystoscopically and ultrasound imaging.

Our study includes only transitional cell carcinoma (TCC) and excludes

sequamous cell carcinomas(SCC), superficial bladder tumor and advanced bladder tumor.

Results

A total of 143 patients with stage T2(102 patients) (71%) and T3(41 patients) (29%) bladder tumors admitted in AL-KUT general hospital from April 2002 to April 2008 underwent as complete transurethral resection as possible ,then they received radiation therapy for 6-7 weeks in Baghdad Oncology Center by Conventional Fractionation method. Following that, patients were reevaluated cystoscopically and ultrasound imaging. Of the 143 patients, 92(64%) have complete clinical response [82 stage T2 (80%) and 10 stage T3 (24%)], undergo 3-6 months cystoscopic examination for two years. 32 (35%) of 92 have recurrence and need other cession of TUR with intravesical chemotherapy [25 stage T2 (30%) and 5 stage T3 (50%)].

The radiotherapy complication which more common in stage T3 , old age, thin, poor performance status and male patients, were16(11%) (6 female and 10 male) have Gastrointestinal complications (diarrhea and enteritis) and 59(41%)(23 female and 36 male) have urological complications (severe cystitis ,clot retention ,frequency ,small capacity bladder ,dysuria and pyelonephritis). While 3 patients(2%) all of them male and stage T3 die due to bowel perforation (one) and sever enteritis and septicemia (two),

Fourty eight(34%) of 143 Patients who had incomplete responses 20 stage T 2(20%) and 28 stage T3 (68%), 11 of them were undergo an immediate radical cystectomy, one of them die postoperatively (male, stage T3) due to fecal fistula and septicemia, 4 of 48 patients end with nephrostomy as palliative measures and 33 of 48 patients need other modalities of chemotherapy ,11 patients of 33 die during the period of treatment and follow up (2 male stage T2 and 9 stage T3,7 male and 2 female)due to uremia and sepsis. The over all mortality in our series was 15(10%) within 24 months (2%in stageT2 and 32% in stage T3). Figure (2)

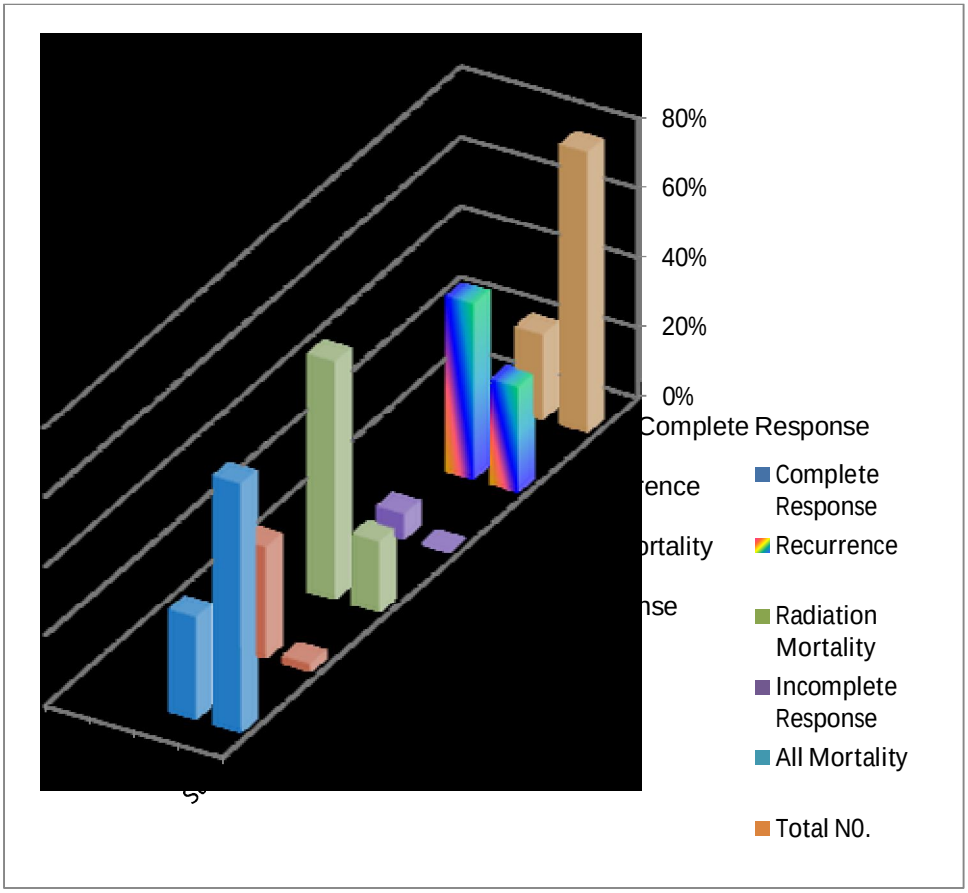

Figure 2 Percentage of our results

Discussion

In the past, complete removal of the bladder was the only way to treat bladder cancer. With advances in radiation therapy and chemotherapy, doctors are sometimes able to treat the cancer while preserving the bladder. This allows many patients to preserve normal urinary function [26].

Unavailability and expensiveness of chemotherapy and immunotherapy in our country, poor compliance of our patients for periodic cystoscopy follow up, patients dissatisfaction with the urinary diversion due to special concerns that arise for those who have undergone radical cystectomy, the patient will need to learn a new way to store and pass urine, is one of the most social and psychological problem after bladder removal [1]. Women who have had a radical cystectomy are not able to have children because their uterus has also been removed. Men who have had a radical cystectomy will become impotent if their prostate and seminal vesicles have also been removed. Therefore many patients refuse to undergo this life changing operation, and prefer to try novel conservative treatment options

before opting to this last radical resort [27]. Radiotherapy after TUR is such one option used to over come all above problem especially in our community .Bladder preservation allow freedom from an external appliance with the preserve sexual function [28]. External-beam radiation therapy (EBRT) is the primary treatment for invasive bladder cancer in some European countries [29].A recent study by Cancer Research UK scientists has found that survival rates among bladder cancer patients treated with radiotherapy in Leeds are the same as those associated with radical cystectomy ,the five-year survival rate for radiotherapy patients was 56.8 per cent, compared with 53.4 per cent of surgery-treated patients[30]. In our study we achieve 64% complete response and 42% no recurrence during follow up of 24 months, compares with other investigators how had treat invasive bladder cancer with the complete TUR followed by radiation. Shipely et al 1999 show complete response rate may be as high as 70% [29]. Zeitman et al 2001 show complete response rate about 60% initially with the 5 years survival rates approaching 50-60% [31] Figure(3). Using a combination of transurethral resection (TUR), and radiotherapy are encouraging, the survival of patients treated by this method is similar to the survival of patients treated by radical cystectomy [32].

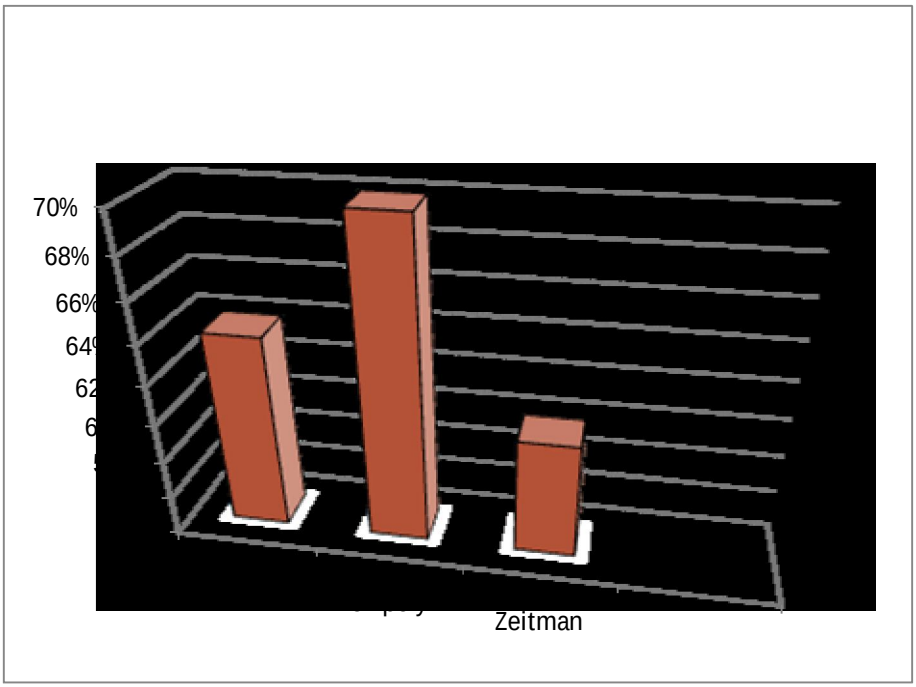

Figure 3 Comparsion of our complete response rate

The 6 to 7 weeks treatment-associated morbidity and mortality of radiotherapy which more common in stage T3, old age, thin poor performance status and male patients were 16(11 %) (6 female and 10 male) have Gastrointestinal complications (diarrhea and

enteritis), and 59(41%) (23 female and 36 male) have urological complications (severe cystitis ,clot retention ,frequency ,small capacity bladder ,dysuria and pyelonephritis). while 3 patients(2%) all of them male and stage T3 die due to bowel perforation (one) and sever enteritis and septicemia (two). The over all mortality in our series was 15(10%) within 24 months (2%in stageT2 and 32% in stage T3) Figure(4).This result was accepted as compared with stander mortality and morbidity of radiotherapy, Joycelyn et al show, acute enteritis and cystitis are frequent complication of radiotherapy, sever bone marrow toxicity is reported in 10% of organ preservation patients, decrease bladder capacity reported in up to 10% of patients, sever rectal and small bowel injury are reported in 3-4% and 1-2% respectively, mortality rate are 1% [22].Male patients have sever complication especially urological as clot retention, radiation cystitis and necroturia due to associated benign prostatic enlargement and few of them even can not complete the full protocol of radiotherapy. Most side effects will get better a few months after treatment has finished, although some patients still complaining of frequency and small capacity bladder. The standard regimens Conventional Fractionation used for all of our patients so no complication difference regard the type of protocol.

Predictors of poor out come after combined radical TUR and radiation for invasive bladder cancer includes advanced clinical tumor stage, presence of hydronephrosis, inability to complete the entire treatment protocol and poor performance status. In our study we found that high stage, old age, thin, poor performance status and male patients, have poor out come results.

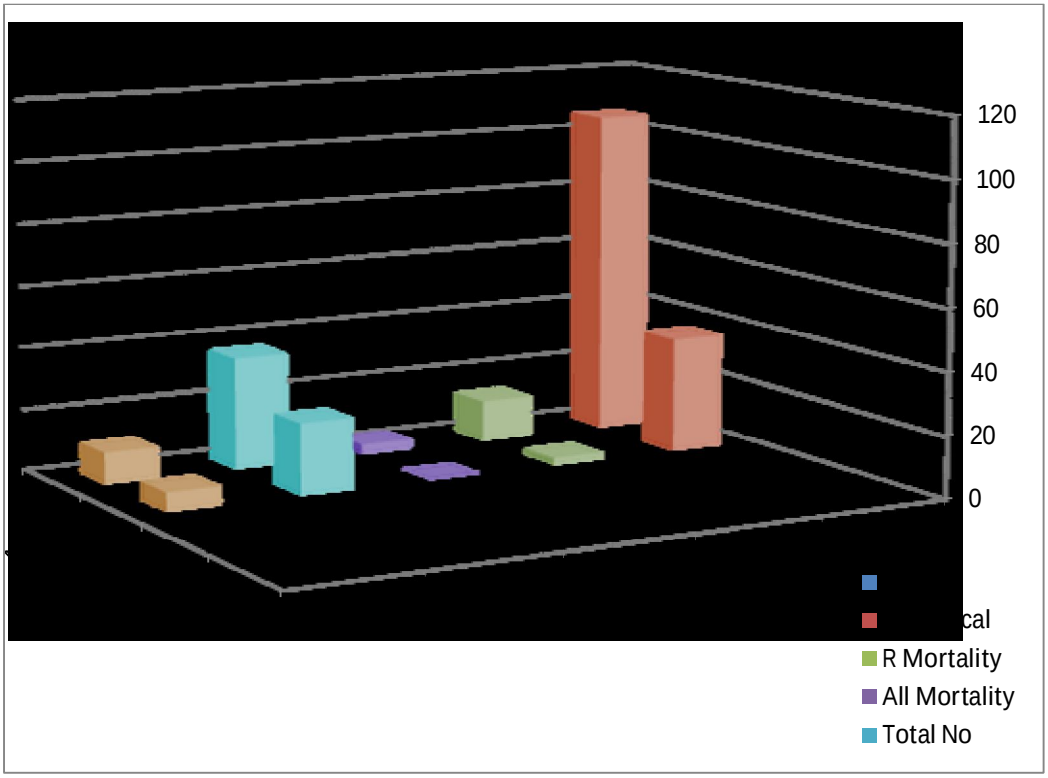

Figure 4 Morbidity and Mortality in Our Result

Conclusions

Owing to unavailability and expensiveness of chemotherapy and immunotherapy in our country, with the poor compliance of our patients for periodic cystoscopy follow up, and patients dissatisfaction with the urinary diversion after radical cystectomy for invasive bladder cancer, with the higher rate of response to combination of transurethral resection (TUR) and radiotherapy, we conclude that radiotherapy after TUR is such an option used to over come all above problem especially in our community.

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