Recent Advances in Management of Invasive Bladder Cancer

Essay

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بِسْمِ اللّهِ الرّحمَنِ الرّحيمِ

[...رَبِّ أَوزِعنِي أَن أَشكُرَ نِعمَتَكَ
الَّتِي أَنْعَمْتَ عَلَيَّ و عَلى والِدَيَّ
و أَنْ أَعْمَلَ صَالِحاً تَرْضَاهُ و أَدْخِلْنِي
بِرَحْمَتِكَ فِي عِبَادِكَ الصَّالِحِينَ]

صدق الله العظيم

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Mohamed Sobhi Ali Ali

I would like to dedicate this Essay

to my **Father**, *to my* **Mother**
to my **Brothers** *and my only* **Sister**

to them I will never find adequate words
to express my gratitude.

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List of Abbreviations

ABC	: Advanced Bladder cancer meta-analysis collaboration
AJCC	: American Joint Committee on Cancer
ATP	: Adenosine triphosphate
BC	: Bladder cancer
BT	: Brachytherapy
CALGB	: Current Cancer and Leukemia Group B
CBC	: Complete blood count
CIS	: Carcinoma in situ
cIScA	: Cisplatin, cyclophosphamide, and adriamycine
CM	: Cyclophosmamide - methotrexate
CMV	: Cyclophosmamide - methotrexate – vincrstine
CT	: Computed tomography
CTV	: Clinical Target Volume
EAU	: European Association of Urology
EBrT	: External beam radiation therapy
ECOG	: Eastern Cooperative Oncology Group
EGFR	: Epidermal growth factor receptor
EorTc	: European Organization for research and Treatment of cancer
ESMO	: European Society for Medical Oncology
FAcT	: Functional Assessment of cancer Therapy
FDG-PET	: Fluorodeoxyglucose -positron emission tomography
FISH	: Florescence in suit hybridization
GC	: Gemcitabine,Cisplatin
Gy	: Gray
hAL	: Hexaminolaevulinate
hrQoL	: Health-related quality of life
IArc	: International Agency for research on cancer
IHC	: Immunohistochemistry
mAbs	: Monoclonal antibodies
MIBC	: Muscle-invasive bladder cancer
MRI	: Magnetic resonance imaging

List of Abbreviations *(Cont...)*

MVA(E)c	: Methotrexate-vincrstine- adriamycin (epirubicin) -cyclophosmamide
NCCN	: National Comprehensive Cancer Network
NcI	: National cancer Institute
NmIBc	: Non-musle invasive bladder cancer
OAR	: Organ at risk
PAhs	: Polycyclic aromatic hydrocarbons
PFS	: Progression free survival
Ps	: Performance status
PTV	: Planning target volume
PUNLMP	: Papillary urothelial neoplasms of low malignant potential
RALC	: Robotic-assisted laparoscopic cystectomy
Rb	: Retinoblastoma gene
rP	: Radical prostatectomy
RTKs	: Receptor tyrosin e kinases
RTOG	: Radiation Therapy Oncology Group
SCCs	: Squamous cell carcinomas
SEER	: Surveillance, Epidemiology and End Results
SES	: Socioeconomic status
SWOG	: Southwest Oncology Group
TCC	: Transitional cell carcinoma
TKI	: Tyrosine receptor kinase inhibitors
TNM	: Tumor,node,metastasis
TUR	: Transureasal resction
TURBT	: Transurethral resection of bladder tumor
URCa	: Urothelial carcinoma
US	: Ultrasonography
VEGF	: Vascular endothelial growth factor
WHO	: World Health Organization
3-D	: three - Dimensional
4-ABP	: 4-aminobiphenyl
5-ALA	: 5-aminolevulinic acid
5-FU	: 5-fluorouracil

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Introduction

Bladder cancer is a common urologic cancer. In 2010, the urinary bladder was the fourth most common site of new cancer cases in the United States, with an estimated 70,530 new cases and 14,680 deaths More than 60,000 new cases of bladder cancer are diagnosed each year in united state. It is more common in men, with a male: female ratio of 4:1 ***(Jemal et al., 2010).***

Age appears to increase the risk; the median age upon presentation with bladder cancer is 72 years for men and 74 years for woman ***(Jacobs et al., 2010).***

In developed countries, 90% of bladder cancers are Transitional cell carcinoma (TCC). In developing countries—particularly in the Middle East and Africa—the majority of bladder cancers are squamous cell carcinomas (SCCs), and most of these cancers are secondary to Schistosoma haematobium infection ***(Steinberg, 2013).***

In Africa, the highest incidence of SCC has been seen in schistosomal-endemic areas, notably Sudan and Egypt. In recent years, a few studies from Egypt have shown a reversal of this trend due to the better control of schistosomiasis in the region, whereas in other parts of Africa the association is unchanged ***(Heyns et al., 2008).*** Increased smoking incidence is

believed to have contributed to the shift toward TCC in Egypt, which has a stronger smoking association ***(Steinberg, 2013)***.

A number of etiological factor are associated with the development of bladder cancer such as chronic urinary infection, pelvic Radiation, chemotherapy with cyclophosamide and occupational exposure to aromatic amines. However Cigarette smoking is the largest risk factor for bladder cancer ***(Jacobs et al., 2010).***

Clinically, Hematuria is the hallmark sign of bladder cancer, occurring in 85% of patients at presentation. Increased urinary frequency and dysuria may also be presenting symptom. More advanced disease may present with pelvic pain and all the symptoms of urinary obstruction ***(Stenzl et al., 2010).***

The American Joint Committee on Cancer TNM (primary tumor, regional lymph nodes, and distant metastasis) Staging System is used for staging bladder cancer. Correct staging can estimate the prognosis and risk of recurrence and is used to determine treatment strategies. Under staging, a common problem may result in incorrect treatment decisions ***(Kulkarni et al., 2010).*** There is a 10% chance that a high-grade Ta or T1 lesion is really muscle-invasive disease ***(Babjuk et al., 2010)***.

Muscle-invasive bladder cancer (clinical stage cT2-cT4a) is an aggressive epithelial tumor with a high rate of early

systemic dissemination and 5-year survival depending principally on pathologic stage and nodal status.Although only one-third of the newly diagnosed bladder cancers are advanced at presentation, another 15–30% of high-grade superficial tumors progress to muscle-invasive tumors, usually within 5 yr ***(Fabio and Cora, 2008).***

The gold standard for diagnosis is cystoscopy. Intraurethral lidocaine is used to perform this procedure, in which abnormal tissue is resected. This resection is called *transurethral resection of bladder tumor* (TURBT**)** ***(Babjuk et al., 2010).*** Urinary cytology is an important adjunct to cystoscopy and is helpful for identifying high-grade tumors, such as carcinoma in situ (CIS). The presence of exfoliated cancerous cells can indicate cancer anywhere along the urinary tract, and the absence of cancer cells does not rule out the presence of a low-grade lesion ***(Sexton et al., 2010).***

CT and MRI may be used to determine the stage of bladder cancer; however, they are unable to accurately detect early metastatic disease**.** Ultrasonography is being used more frequently and is advantageous because it does not require contrast agent ***(Babjuk et al., 2010).*** Another imaging modality is IV urography. If invasive disease is suspected, diagnostic imaging should be done prior to TURBT because inflammation from TURBT can be impossible to distinguish from tumor growth in the perivesical fat ***(Suzanne et al., 2011).***

Approximately one-third of patients diagnosed with muscle-invasive bladder cancer have metastatic disease at the time that the first tumor is treated ***(Stenzl et al., 2010).*** It is important to determine the presence of distant metastasis prior to treatment selection. The most common sites of metastasis are the lungs, bones, and liver ***(Jacobs et al., 2010).***

TURBT performed during cystoscopy is a treatment as well as diagnostic tool. All visible lesions should be removed, along with muscle tissue, to ensure complete resection and proper staging ***(Pharmd et al., 2011).*** For localized muscle-invasive disease, radical cystectomy is the standard treatment. Although it is desirable to preserve the bladder, delaying radical cystectomy is thought to increase the risk of lymph node metastasis by 26% **(*Mslis et al., 2011).***

Neoadjuvant therapy administering chemotherapy prior to radical cystectomy can help determine the sensitivity of the carcinoma to the selected chemotherapeutic agents. Other advantages include better patient tolerability to chemotherapy prior to radical cystectomy and delivery of therapy at the earliest time, when occurrence of micrometastatic disease is expected to be low. Among the disadvantages associated with the use of neoadjuvant are staging errors and overtreatment ***(Suzanne et al., 2010).*** Chemotherapy should include a cisplatin-containing regimen, either MVAC (methotrexate, vinblastine, doxorubicin, and cisplatin) or GC (gemcitabine and cisplatin). Neither

combination has been shown to be superior to the other; However, GC is less toxic ***(Sonpavde et al., 2010)***.

The use of adjuvant chemotherapy postoperatively has not been shown to have a benefit. Additionally, patients often cannot tolerate systemic chemotherapy after radical cystectomy. The European Association of Urology (EAU) guidelines recommend adjuvant therapy for clinical trials, but not for routine use ***(Cowan et al., 2010)***.

Bladder -preserving approaches are reasonable alternatives to cystectomy for patients who are medically unfit for surgery and those seeking an alternative ***(National Comprehensive Cancer Network (NCCN), 2013)***.

A trimodality treatment approach for muscle-invasive bladder cancer consists of transureasal resction (TUR)for the primary tumor followed by a combination of local radiation therapy and systemic chemotherapy ***(Weiss et al., 2006).***

Radiation alone is not considered standard treatment for patients with an invasive bladder tumor. Because the initial complete response and long-term bladder preservation rates are higher with chemotherapy combined with radiotherapy ***(Gospodarowicz, 2000).***

Antiangiogenic therapy is under investigation as second-line therapy ***(Bellmunt et al., 2010).*** Vascular endothelial growth factor (VEGF) is the most important stimulator of