Active Surveillance in Prostate Cancer

BCG Failure – Options In Management

Neoadjuvant Treatment For Carcinoma Bladder

Management of Inguinal Nodes in Carcinoma Penis

Management of High Risk Prostate Cancer
Urological malignancies require comprehensive multimodality treatment.

Amrita provides it

- Multimodality approach
- Dedicated Uro oncology OPD
- Regular Tumour Board meetings for decision making. Team include
  - Uro Oncology Surgeon
  - Medical oncologist
  - Radiation oncologist
  - Psycho oncologist
  - Medical social worker
  - Uro pathologist
  - Molecular scientist
- Full spectrum of diagnostic service
  - PET CT scan
  - Nuclear scans
  - MDCT

- MRI
- Dedicated uro pathology
- Cytopathology
- Molecular biology

- High volume of complex surgeries
  - Laparoscopic radical prostatectomy
  - Radical nephrectomy with IVC thrombus
  - Lap radical nephrectomy
  - Lap nephroureterectomy
  - Post chemotherapy RPLND
  - Radical Cystectomy and Orthotopic Neobladder

- Advanced radiotherapy facilities
  - IMRT
  - IGRT
  - HDR
  - Therapeutic nuclear medicine services

- Advanced Chemotherapy
  - Adequate back up of blood bank, hematology
  - BMT (in near future)

- Robotic surgery in near future

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Uro-oncology is one of the most dynamic fields in Urology. The last three decades saw a quantum leap in the management strategies of urological malignancies. Introduction of PSA in mid eighties was only a beginning. It has not only improved the management of carcinoma of prostate, but also added controversies regarding the mode and need of treatment of the Tumor. Use of laparoscopy and robotics in surgery, the advances in radiation technologies and new medicines like TKIs etc have changed the entire scenario. Better understanding of the tumor biology was translated successfully into the management of these tumors.

Advances in the diagnostic techniques helped us to diagnose more and more diseases in its early asymptomatic stage. Development in surgical and radiation techniques and introduction of new medicines have provided scope for more discussion regarding how we can reduce the morbidity without compromising the outcome of the disease. Now more and more partial nephrectomies are done than earlier. Carcinoma of prostate is the best example to show the importance of efforts to maintain the quality of life without compromising the cure-rate of the disease. We are trying to improve the QOL of the bladder cancer patients by introducing neobladders and bladder preservation techniques (trimodality treatments). Chemotherapy has changed the treatment and outlook of testicular cancers in the last three decades. It has become more and more convincing that the treatment of urological cancer is the combined responsibility of the urologist, radiation oncologist, medical oncologist and the paramedical staff including the onco-psychologist, medical social worker, pain and palliative care personnels supported by the labarotary, radiology and nuclear medicine departments. Treatment decision has to be taken in tumour boards which comprises not only the treating doctors but also the representatives of pathology, cytogenetics and molecular biology.

The field of uro-oncology has changed a lot in the last few decades by the the thrust of research. The general practitioners should also be aware of these developments so that the best care can be given to your patients. I hope the articles we selected in this journal issue are the relevant and useful in your practice.
Endless remain the efforts to find answers to some of the eternal questions.

Why were you born in to this world ? Where were you before ? Where will you go when you die ? What is the purpose served by this life? Who will remember you when you are gone ? Is it necessary that someone should remember you when you have already left this world ? What do you gain by such remembrance ? The existential enigma can never end. But you want to give some meaning to your life. It is not for just living at basic biological level.

You are not satisfied, just by eating, mating, evacuating and sleeping. Your life is lived at different plane. It has an emotional plane. It has an intellectual plane. It has a spiritual plane in addition to these and the biological levels. The happiness you derive by helping others, by being able to lessen the pains and burdens of at least one person to some extent comes out of a longing for identity with the rest of the universe. This is because in essence you are spiritual, a soul with a body rather than a body with a soul. The time to seek satisfaction of biological longings is over and it is now time to seek satisfaction of intellectual and spiritual cravings. Even emotions have evened out. No strong likes or dislikes. No strong attachments. Not elated by praise or depressed by blame.

This is the state of mind you wanted. Equanimity! Ever present peacefulness.

A state of pristine purity and happiness. Let this be your blessings. What more do you want? What more can you expect?

Many existential dilemmas disturb the mind occasionally. Yet a certain amount of peace and tranquility prevails also. The major existential dilemma is the purpose of life. Is it necessary to have a purpose in life ? Do every being that is born in to this world live with a purpose of which it is aware ? Don’t they just continue to live just the way they are after being born till they meet their death ? Do they bother about the purpose of life ? What is it that makes you worry about the meaning and purpose of life ? What makes us human is the ability for self awareness and the quest to understand the meaning of life. That may be in the natural process of evolution. Scriptures say that the purpose of human life is to find final liberation- Moksha- the eternal freedom. That is where you transcend the limitations imposed by nature. You pass beyond the qualities of good and evil.

Where no laws bind you because you live in tune with the highest laws of the universe. When you become Law abiding, you lose the fear of consequences of your actions. You become liberated from all anxieties. You see the Law maker’s face through the Laws which you obey. That is probably what is meant by Mukti. Mukti is not an escape from this world. It lies in living in tune with the world, working for its good, unconcerned about personal problems. The Universal law of eternal goodness ensures that it takes care of the welfare of those who take care of the welfare of the world and their fellow beings. They will be amply provided and adequately protected. When Self awareness grows you can manage to live your life without basing your happiness on other people’s interactions with you. Interacting or alone, you always remain happy. Shun none. Unnecessarily do not go after anyone. Less of dependency and more of independence will make you liberated. Dependency is only on God’s laws. Do everything according to the divine laws and feel free in your heart.
In humans, the only cancer which can be cured and yet need not be cured is prostate cancer. Prostate cancer (PCa) typically begins in the third or fourth decade of life. For the next 20 years, there occurs a period of slow subclinical tumor progression. This may be followed by a period of clinical progression for about 15 years. This is because the doubling time of prostate cancer is generally about 2 to 4 years. Hence, the majority of PCa may not become symptomatic. PCa is a highly heterogeneous disease, the natural history and the biological potential of which is difficult to predict. It has been reported that >50% of males above 50 years have prostate cancer. A unique feature of PCa is that patients with similar serum PSA levels, histological features on prostate biopsy and digital rectal examination may have markedly different outcome. Not all men with favorable features do well nor do all men with unfavorable features do poorly.

Screening for PCa, a lower threshold of serum PSA for prostate biopsy and the trend towards extensive sampling of prostate during biopsy (≥12 cores) have lead to increased detection rate of PCa. One estimate is that approximately 23-42% of these are over diagnosed and would not have been detected but for the screening. These are considered as ‘insignificant cancers’ a word coined by Epstein in 1994. Because, a significant majority of these patients are having low risk PCa, it would be prudent to avoid any radical modalities of treatment with their attendant morbidity. Active surveillance (AS) is a solution available for these patients with low risk PCa.

AS consists of monitoring the patients with low risk PCa periodically with multiple parameters to identify development of high risk factors so that curative treatment can be offered promptly with equally good outcome compared to those who underwent active treatment in the beginning itself. The concept of AS was formally introduced by Choo et al in 2001. Data from CaPSURE has shown that in 2001 only 6.2% patients opted for AS whereas in 2006, this was 10.2%. This is because of the fact that majority of patients are reluctant to avoid any form of treatment due to the fear of progression of the PCa while on AS thereby losing the opportunity of a cure. Hence the AS as a treatment option is likely to be under used. The aim of AS is to individualize the treatment for early PCa patients by selecting those patients with significant cancers for curative therapy. AS may spare two third of men with early PCa the side effects of radical treatment without compromising the survival.

**Definition of AS (active surveillance with selective delayed intervention):**

AS refers to a systematic program wherein men diagnosed with early prostate cancer with low risk are periodically monitored so as to detect predictors of progression promptly and timely curative treatment is offered.

**Criteria for patient selection for AS**

The most critical aspect of a successful AS program is patient selection. Which patients are the best candidates for AS? Most of the selection criteria are based on Epstein’s definition of clinically insignificant prostate cancer which includes no Gleason grade 4 or 5 in the biopsy specimen and one of the following: i) PSA density of ≤0.1 ng/mL/gm with fewer than 3 biopsy cores positive for cancer (minimum of 6 cores obtained) and no core >50% involvement. ii) PSA density of ≤0.15ng/mL/gm and only one of 6 or more biopsy cores with cancer smaller than 3mm. At present 5 different classification systems are used to define favorable clinical prostate cancer. These include Hardie et al, Roemeling et al, Choo et al, Klotz et al and D’Amico and Coleman criteria. The last scheme is commonly used in patient selection. This includes clinical stage of T1c-T2a, serum PSA of < 10ng/ml and biopsy Gleason score of ≤6 (no pattern of 4 or 5). Other characters that are included by some protocols include PSA density <0.15, < 50% of any core involved by cancer and stable PSA kinetics.

Of late, the most stringent criteria for AS has been defined which includes cT1c, PSA ≤4ng/mL and Gleason score ≤6. However, the use of this will limit the number of patients offered AS. Some series describe surveying...
men with Gleason score 3+4. Most centers do not consider age as a criterion and older men with higher risk features have been offered AS. It has been reported that initial misclassification at the entry criteria may occur in about 22-33% of men. This has been thought to be due to limited sampling during initial biopsy.

Based on various schemes for selection of patients, 6.9% to 88.2% (most stringent to most liberal) qualify for AS. When the D’Amico and the Klotz criteria were used, which are considered the “strict criteria” the characteristic of selected cohort were more favorable to that compared to Hardie et al or Roemeling criteria. The misclassification with D’Amico was only 15.4% whereas it was 26.7% with Hardie et criteria.

Partin table, Kattan indolent cancer nomogram and CAPRA score are some of the useful tables and nomograms available for selecting patients for AS. The literature available about their utility is limited. Various imaging modalities especially MRI/MRSI has been found to be useful when they are considered along with other clinical criteria.

Monitoring during AS

The recommended surveillance schedule according to Dall’Era et al is
1. PSA: every 3-4 months
2. DRE: every 3-6 months
3. TRUS: every 9-12 months
4. Prostate biopsy: after 1 year, then every 1-2 years as indicated by PSA or examination trends.

This may vary from center to center.

Predictors of progression:

The most critical aspect of AS is to identify the predictors of progression so that timely active treatment can be offered and the patients cured. There is still no consensus on which parameters, how frequently and at which point of time to intervene. However the following parameters when determined serially are found to be useful.

The most important and useful predictor of progression is upgrading in biopsy Gleason score. Different schedules have been described for repeat biopsy. One school of thought is that the upgrading is actually an initial misclassification because of limitations of sampling. If initial biopsy was sufficiently extensive (more than 12 Core) then repeat biopsy need not be so frequent. The university of Toronto protocol is to repeat the biopsy at one year whereas Patel and associates perform it at 6 months. Interestingly, in the series reported by Patel, 61% had no cancer on repeat biopsy. Absence of cancer on repeat biopsy is strong indicator of non progression of cancer.

Gerber et al reported on the changes in the serum PSA level and found that serial estimation of serum PSA is not useful as PSA levels are highly variable in men with untreated prostate gland. The estimation of PSADT as predictor of progression has been ascertained by several reports. Choo et al suggested a PSADT of less than two years as a predictor of progression and as a trigger for active treatment. Later they increased this PSADT to less than three years. Even though PSA kinetics may be useful in predicting cancer progression, the exact trigger point at which to recommend treatment is unclear. By the time PSADT or PSA velocity are rapid, the window of curative treatment may be lost for some patients.

The significance of DRE as an independent predictor of progression is questionable. At this early stage the subtle changes in consistency may be difficult to appreciate. More over DRE is subjective and inter-examiner variation is significant. Serial TRUS, CT, MRI and bone scan examination is also of limited value.

There is still no consensus on the criteria used to define disease progression that trigger active treatment.

Outcomes of AS:

The disease specific and all cause survival over the short term is high among patients in AS. Up to one third of patients received further treatment after a median of 2.5 years of AS. Even though the concept of AS was formally described in 2001, a study from Royal Marsden group was reported in 2003. This included 80 patients with early prostate cancer put on AS between 1993 and 2001. In this group, 10 patients received radical treatment, 3 patients died from unrelated causes and 67 continued on AS! No patients developed metastatic disease or died of PCa. The median PSADT in this group was up to 14 years which suggested an indolent course of disease in most patients.

A study from the university of Toronto which included a cohort of 331 patients with favorable risk factors (including expanded criteria like Gleason score 3+4 and PSA of 15 ng/mL) was reported with a median follow up period of 72 months. In this group 34% of the patients received radical treatment. Of this, 15 % had a PSADT of < 3 years, 7% had histological or clinical progression and 12% did not have any feature of disease progression. Overall survival was 85% and disease specific and metastasis free survival was 99% at 8 years! Carter et al reported a group of 417 men on AS. Of this 239 (59%) remained on AS, 103(25%) received active treatment with a median of 2 years (range 0.96-7.39 years). Of the 103 men who underwent active treatment 53 (51%) had radical prostatectomy of which 20% had advanced disease (locally advanced). All these studies suggest
that carefully selected patients with proper monitoring can be offered AS a rational alternative to immediate radical treatment.

**Drawbacks of AS**

Active surveillance as an option in the management of early PCa takes into consideration several assumptions:

1. The cancer which is diagnosed is clinically insignificant and indolent,
2. The progression of the cancer can be reliably monitored,
3. If the cancer progresses it still can be cured,
4. Treatment can be delayed with out effecting survival,
5. The outcome for delayed treatment and the treatment at the beginning is the same, and active treatment is invariably associated with significant morbidity.

Many of these assumptions are questionable.

Repeated biopsy may lead to difficulty in Prostatectomy. It may also lead to significant risk of erectile dysfunction in the future.

**The future of AS**

The results of prospective randomized clinical trials like START (standard treatment against restricted treatment), PRIAS (prostate cancer research international active surveillance), Protec-T(prostate testing for cancer and treatment and PASS(prostate cancer active surveillance study) may help in finally determining standard of care for early prostate cancer. With the discovery of novel markers of high risk disease like TMPRSS2:ERG gene fusion, genomic alterations like 11q13.1 and 8p23.2 etc monitoring of patients would be easier and hence active treatment may be offered earlier.

**Conclusion:**

Active surveillance for favorable risk localized prostate cancer may reduce the risk of over treatment while retaining the option of active intervention when progression occurs during follow up. Studies suggest that less than half of patients on AS have progression while on long term follow up and treatment appears be effective with equally good out come compared to patients having active treatment at diagnosis. Major areas of future studies should include research in identification of markers of high risk disease and better imaging tools for patient selection as well as follow up. With appropriate selection of patients, close follow up and selective use of local therapies in those with local cancer progression AS is an acceptable alternative for the management of selected patients with low risk early stage PCa. The decision between active surveillance and surgery should be shared between patient and physician.

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**Active Surveillance in Prostate Cancer**


BCG Failure – Options In Management

Felix Cardoza

ABSTRACT

Adjuvant intravesical Bacillus Calmette-Guerin (BCG) is currently the recommended first-line treatment for high-risk non-muscle-invasive bladder cancer. However, the treatment fails in 30%–40% of patients. BCG failure is a heterogeneous term that encompasses a number of differing clinical scenarios. The management of patients who do not respond to BCG treatment is controversial.

1. Introduction

The association between tuberculosis and cancer, and the demonstration that bacillus Calmette-Guerin invoked immunological reactivity, inhibiting tumor growth in experimental animal models, led to clinical trials showing that intravesical bacillus Calmette-Guerin eradicated and prevented recurrence of superficial bladder tumors. For the last 3 decades bacillus Calmette-Guerin therapy has remained the most effective local therapy for superficial bladder cancer, an outstanding example of successful translational medicine in urology.

Adjuvant intravesical Bacillus Calmette-Guerin (BCG) is currently the recommended first-line treatment for high-risk non-muscle-invasive bladder cancer. However, the treatment fails in 30%–40% of patients, and 30%–40% of those who initially respond relapse.

The management of patients who do not respond to BCG treatment is controversial.

2. When do we say a patient has failed BCG therapy?

BCG failure is a heterogeneous term that encompasses a number of differing clinical scenarios. The International Bladder Cancer Group has defined four subcategories of BCG failure:

BCG refractory: Failure to achieve a disease-free state by 6 months after initial BCG therapy with either maintenance or re-treatment at 3 months due to either persistent or rapidly recurrent disease. Also includes any progression in stage, grade, or disease extent by 3 months after first cycle of BCG, i.e., non-improving or worsening disease despite BCG.

BCG resistant: Recurrence or persistence of disease at 3 months after induction cycle but of lesser degree, stage or grade which subsequently is no longer present at 6 months from BCG re-treatment with or without Trans Urethral Resection (TUR), i.e., disease improves then resolves with further BCG.

BCG relapsing: Recurrence of disease after achieving a disease-free status by 6 months, i.e., disease resolves after BCG therapy then returns. Relapse is further defined by time of recurrence: early (within 12 months); intermediate (12–24 months); late (> 24 months).

BCG intolerant: Disease recurrence after a less than adequate course of therapy is applied due to a serious adverse event or symptomatic intolerance that mandates discontinuation of further BCG, i.e., recurrent disease in setting of inadequate BCG treatment from drug toxicity.

Recently The European Association of Urology in their 2011 update on the Guidelines on Non–Muscle-Invasive Urothelial Carcinoma of the Bladder have considered treatment with BCG to have failed in the following situations:

(1) Where muscle-invasive tumour is detected during follow-up

(2) When high-grade non–muscle-invasive tumour is present at both 3 and 6 months.

(3) Any deterioration of the disease under BCG treatment, such as a higher number of recurrences, higher T stage or higher grade, or the appearance of CIS, despite an initial response.

The current definitions of BCG failure do take into account the timing of failure but do not reflect the type of BCG schedule administered (Induction vs. Maintenance schedule) or the primary indication for BCG (High grade Non muscle invasive bladder cancer or Carcinoma in situ vs Refractory Low grade disease).

3. Can We Predict BCG failure?

With complex interactions between mycobacteria, a host and a tumour, it is unlikely that one single parameter could be predictive for all patients, regardless of their immunological and tumour background.

Currently, there are no accurate biological or pathological markers capable of predicting the response to intravesical BCG, and only the clinical response observed can provide a guide as to whether conservative
or radical treatment is most appropriate.

The clinicopathologic variables thought to increase the risk of failure include female sex, older age, multifocality, recurrent tumours, associated CIS (particularly in the prostatic urethra), lymphovascular invasion, detectable disease at 3-mo check-up cystoscopy, depth (and multifocality) of lamina propria invasion, timing of failure (early vs. late), and two or more prior courses of BCG.

4. What options can we give patients who have failed BCG therapy?

A patient who has failed BCG therapy has two options –

A. To proceed with Immediate Radical Cystectomy or
B. Further Bladder Preservation strategies.

All conservative treatments for BCG failure patients must be considered oncologically inferior and Radical Cystectomy remains the standard of care. It is paramount to inform patients about this prior to opting a treatment strategy. However, some patients are not candidates for radical surgery due to comorbid medical illness and others refuse to consider the change in their lifestyle that the surgery entails despite being counselled about the risks.

4.1. Radical Cystectomy for BCG Failure.

The American Urological Association’s Bladder Cancer Clinical Guidelines Panel recommends Radical cystectomy as the treatment of choice for CIS failing adequate BCG and as an option in other high-risk tumours. The same opinion has been echoed by The EAU in their 2011 update. The advantage of Cystectomy in superficial tumours that failed BCG treatment is obvious. Tumour-specific survival is between 80% and 90% at 5 years, and thereby approaches the 5-year tumour-specific survival of patients with superficial bladder cancer. There is evidence that Immediate Radical Cystectomy in this setting improves disease-specific survival, life expectancy, and quality of life-years and decreases overall cost of treatment.

Patients progressing to invasive disease after BCG have a poorer prognosis compared with stage-matched primary muscle-invasive disease with three year Cancer specific survival of 37 % and 67 % respectively.

However, cystectomy for high-risk superficial disease is an invasive procedure with significant morbidity and mortality. This must be considered when deciding treatment for a disease that usually involves patients with advanced age and multiple comorbidities. In the elderly population undergoing radical cystectomy, one can expect a complication rate of 24–60% and a 90 day mortality rate of 10%.

4.2. Bladder preservation strategies for BCG failure.

Several bladder preservation strategies are now available that can be categorised as immunotherapy, intravesical chemotherapy, device-assisted therapy, radiochemotherapy and combination therapy.

4.2.1. Immunotherapy

4.2.1.1. Further BCG

In patients who have persistent disease at 3 months, a further course of BCG is reported to be able to provoke a complete response in more than 50% of cases, both in patients with papillary tumours and carcinoma-in-situ. However, further courses of BCG (beyond two) are not recommended because of the reduced likelihood of tumour progression.

4.2.1.2. Interferon Alpha (IFN-α)

Interferon Alpha is a naturally occurring cell-signalling cytokine that is produced by the immune system in response to insults such as tumour cell growth. The long-term success rate of IFN α monotherapy of BCG failure patients is generally under 15%. Furthermore, in a study of IFN α monotherapy for primary stage T1 disease, IFN α monotherapy was found to be no better than water placebo at 43 months’ follow-up, suggesting it has no role for recurrent stage T1 disease.

Joudi et al. Reported the results of a national multicentre randomised trial, involving 1007 patients, comparing the effect of IFN α 50 million Units plus reduced-dose BCG in BCG-failure patients to a cohort of BCG-naive patients who received the same IFN α dose but with a standard-dose BCG protocol. Fifty-nine percent of the BCG-naive cohort remained disease free, with a 24-month median follow-up compared with 45% of the previous BCG failure group. Furthermore the same group subsequently reported that if BCG failure occurred >1 year after BCG treatment, then combination IFN α + BCG is a reasonable salvage option compared with BCG failure occurring <1 year after starting BCG or after two or more BCG failures, when Radical Cystectomy should be offered in preference to IFN α + BCG.

4.2.2. Intravesical Chemotherapy

4.2.2.1. Gemcitabine (GC)

Gemcitabine is now a standard first-line systemic chemotherapeutic agent used in the neoadjuvant, adjuvant and palliative treatment of urothelial carcinoma. It is a nucleoside analogue that causes defective DNA replication, leading to apoptosis of tumour cells.

Dalbagni et al. conducted a phase 2 study of 30 patients with NMIBC who were deemed ‘BCG failures’. The patients received two courses of intravesical gemcitabine twice weekly at a dose of 2000 mg/100 mL for three consecutive weeks. The median follow-up was 19 months. The complete response rate was 50% and the
Bartoletti et al. reported the results of a phase 2 prospective multicentre study of intravesical gemcitabine following transurethral resection. A total of 116 patients with intermediate and high-risk bladder cancer were treated with one cycle (once a week for 6 weeks) of GC 2000 mg. It was well tolerated, with 81% reporting no side-effects. In the BCG-refractory intermediate-risk group, after 12-mo follow-up, recurrence developed in only 25%. However 56% in the corresponding high-risk group developed recurrence.

In a study conducted at Salfdarjang Hospital, New Delhi, Mohanty et al. evaluated 35 BCG-failure patients who were given intravesical gemcitabine 2 weeks following TUR for 6 weeks and followed for a mean of 18 months. Twenty-one (60%) patients showed no recurrence and three (8.75%) progressed, with an average time to recurrence and progression of 12 months and 16 months, respectively. Adverse effects were mild and well tolerated.

In a multicentre prospective randomised phase 2 trial of maintenance GC versus BCG, Di Lorenzo et al. reported on 80 high risk NMIBC patients that failed one course of BCG therapy. These patients were subsequently randomised between gemcitabine (2000 mg in 50 ml) versus BCG Connaught strain (81 mg). The authors reported that gemcitabine reduces incidence of recurrence (87.5% vs 52.5%) and improves 2-year recurrence-free survival (19% vs 3%). There was no effect on progression or time to first recurrence.

A 2012 cochrane review on Intravesical gemcitabine therapy for non-muscle invasive bladder cancer concluded “The available evidence suggests that intravesical gemcitabine may have a role in the management of intermediate-risk patients, as an alternate choice to MMC in previously treated patients with recurrent disease and in high-risk, BCG-refractory patients with NMIBC. Although at present It is unclear how effective intravesical gemcitabine is in preventing or delaying disease progression and ultimately overall survival.”

4.2.2.2. Docetaxel

Docetaxel is a microtubule depolymerisation inhibitor that belongs to the taxane group of chemotherapy agents.

McKiernan et al. first reported a phase 1 trial of intravesical docetaxel in 18 patients with NMIBC refractory to ‘standard intravesical therapy’. Docetaxel was administered as six weekly instillations. Ten (56%) patients were disease-free on completing the trial at 12 weeks. Subsequently the same group reported their experience in a specific BCG-refractory population (13 patients) who were given a further 6-week 75 mg induction dose and then single-dose monthly maintenance therapy for 9 months if there was a complete response. With a median follow-up of 13 months, 10 of the 13 patients had a CR after induction and six were disease free during the follow-up. 44% of the patients reported mild to moderate adverse effects – primarily dysuria.

Attempts to promote drug delivery and increase concentration of chemotherapeutic agents in the urothelium have been investigated by binding standard chemotherapy agents to mucoadhesive nanoparticles. Mugabe et al. In in vivo evaluations have shown that mucoadhesive nanoparticulate docetaxel is superior to standard docetaxel for intravesical treatment of NMIBC due to an increased inhibitory effect on UC cell proliferation.

4.2.2.3. Valrubucin

Valrubucin is a semisynthetic derivative of the anthracycline antibiotic doxorubicin, and it has been shown to benefit patients with BCG refractory carcinoma in situ of the bladder.

Steinberg et al. gave six weekly instillations of 800 mg intravesical valrubucin to 90 patients with recurrent CIS after BCG; 21% had a Complete Response with a median follow-up of 30 months, but only seven (8%) remained disease-free at the end of the study. In all, 56% had a Radical Cystectomy, including 15% with ≥ T3 disease.

4.2.2.4. Mitomycin C (MMC)

Only a few attempts have been made to treat ‘BCG failure’ with subsequent intravesical mitomycin C chemotherapy. The most notable observation comes from the Swedish- Norwegian bladder cancer group, who compared BCG and MMC in patients with NMIBC. In that study crossover was permitted for treatment failure. Overall, 21 patients crossed over to receive MMC when BCG failed, but only four remained disease-free with a median follow-up of 64 months.

4.2.3. Device assisted therapy

4.2.3.1. Thermochemotherapy (TC)

The combination of intravesical MMC and bladder wall hyperthermia is termed TC, and is also referred to as the Synergo system. Heating of the bladder wall to temperatures of ≥ 42 degree Celsius using a thermo-couple-monitored catheter and microwave equipment with sequential administration of intravesical MMC was shown to be superior to conventional MMC alone.

Witjes et al. recently reported the results of the European Synergo working party, for CIS. Fifty-one patients, including 34 in whom BCG had previously failed, underwent outpatient TC, weekly for 6–8 weeks, followed by four to six sessions every 6–8 weeks. The
initial complete response rate was 92%, which remains at about half after 2 years. Nativ et al. published their experience with TC in 111 patients who had BCG-refractory high-risk bladder cancer. Their protocol was similar to the European Synergo group. The estimated disease-free survival was 85% and 56% after 1 yr and 2 yr, respectively. Lack of a maintenance regimen led to an increased recurrence rate at 2 yr (61% vs. 39%), and the overall progression rate was 3%. Halachmi et al. analysed 56 patients with high grade T1 disease 33.9% of which had failed BCG. Overall recurrence was 33% with median time to recurrence of 9 months. For those who failed prior BCG, there was a 50.7% estimated recurrence rate at 2 yr. Progression occurred in just 7.9% with a quoted bladder preservation rate of 88%. In a systematic review of TC, it was reported that TC offered a 59% relative reduction in NMIBC recurrence compared with MMC alone, with a bladder preservation rate of 87.6%

4.2.3.2. Photodynamic therapy (PDT)

Photodynamic therapy works on the principle of exciting photosensitized bladder tumour cells with a specific wavelength of intravesical light, leading to their destruction.

Waidelich et al. administered oral 5-aminolaevulinic acid to patients with rapidly recurring, multifocal BCG-refractory high-risk NMIBC. At a median follow-up of 36 months, seven of 24 (29%) patients were recurrence free, four (17%) progressed and three (13%) had RC. A similar high recurrence rate was reported by Berger et al. In a small group with BCG failure (10 patients) and after a mean follow-up of 23.7 months, six had a recurrence. These studies involved small numbers of patients, with less than encouraging results, so PDT is not a realistic option for BCG-failure patients currently. In both the above studies the authors commented on the high occurrence of haemodynamic instability after oral 5-aminolaevulinic acid administration in patients with pre-existing cardiovascular comorbidity.

4.2.3.3. Electromotive drug administration (EMDA)

It is possible to enhance transmembrane transport of intravesical chemotherapy agents by applying a current gradient between the drug and the bladder wall, and this technique, termed electromotive drug administration (EMDA), has been proven superior to passive MMC transport.

Di Stasi et al. reported a randomized prospective study of EMDA-MMC vs. passive MMC vs. standard BCG in 108 BCG-naïve patients with high-risk NMIBC. The CR for EMDA-MMC, passive MMC and BCG at 3 months was 53%, 28% and 56% and at 6 months was 58%, 31% and 64%. The respective median time to recurrence was 35, 19.5 and 26 months. Peak plasma concentrations of MMC were 5.5 times higher in patients who received EMDA than by passive diffusion. EMDA-MMC is equal to BCG in terms of recurrence rate in BCG-naïve high-risk NMIBC and significantly better than passive standard MMC.

There are no studies of EMDA in patients specifically with ‘BCG failure’.

4.2.4. Radiochemotherapy

No evidence shows that radiotherapy (RT) is better than conservative therapy for pT1G3 bladder cancer, and currently no data are available for the use of radiochemotherapy in patients with high-risk NMIBC who have failed prior intravesical BCG.

External beam radiation therapy with or without systemic chemotherapy is rarely appropriate for the treatment of superficial bladder cancer because it may cause significant morbidity while displaying limited efficacy. CIS is particularly resistant and low-grade disease responds more poorly than higher-grade disease. Weiss et al. evaluated 84 patients with high-risk T1 disease, who were treated with platinum-based RT after TUR. Tumour progression at 5 yr and 10 yr was 13% and 29%, respectively. DSS rates were 80% and 71% at 5 yr and 10 yr, respectively, with a >80% bladder preservation rate.

4.2.5. Combination / Sequential Therapy

4.2.5.1. MMC and BCG:

This combination has been prospectively investigated, including a study by the European Organisation for Research and Treatment of Cancer, and there is no clear advantage to be gained with the combination of immuno- and chemotherapy.

4.2.5.2. BCG and EMDA-MMC:

Sequential BCG and EMDA MMC, compared with BCG alone, appears to generate a superior response, as it is postulated the BCG-induced inflammation may increase the permeability of the bladder urothelium to MMC delivered via EMDA.

Di Stasi et al. evaluated 212 patients who were randomised to the two arms. Notably there were no patients with previous BCG failure. After a median follow-up of 88 mo, those who received sequential BCG and EMDA MMC had a higher disease-free interval (69 vs 21 months), lower recurrence (42% vs 58%), lower progression (9.3% vs 22%), lower disease-specific mortality (5.6% vs 16.2%), and lower overall mortality (21.5% vs
32.4%) than those assigned BCG alone.\textsuperscript{16}

### 4.2.5.3. MMC and Gemcitabine:

Breyer et al. reported their experience with the combination of intravesical MMC and gemcitabine in ten BCG-refractory patients who received 1000 mg gemcitabine followed by a 40-mg MMC 6-week induction course, which was followed by a maintenance regimen of the same dosage once a month for 12 months. At a median follow-up of 26.5 months six patients (60%) were recurrence-free.\textsuperscript{37}

### 4.2.5.4. PDT and BCG:

In an article from China, Pan et al. hypothesized that after PDT destroyed targeted tumor cells on a large scale, Intravesical BCG could elicit and amplify the immune responses, which would directly form an in situ autovaccine in vivo against the primary tumor and metastases at distant sites. BCG would elicit and amplify the immunological response, which would lead to the formation of an in-situ auto vaccine against urothelial tumour cells, whether local or systemic.\textsuperscript{38}

### 5. Conclusion

Radical Cystectomy should be the default position on failing BCG. When faced with the clinical scenario of a patient with high-risk NMIBC, who has ‘failed’ intravesical BCG but is not a candidate for a recommended radical cystectomy, there are now several new alternative intravesical salvage options including gemcitabine, docetaxel, electromotive drug administration, thermochemotherapy and sequential combinations of these novel techniques with traditional intravesical agents, e.g. BCG and MMC. However, the current data are still inadequate to formulate definitive recommendations, and data from further high-quality studies are needed.

### Reference


Introduction

Bladder is the 9th most common cancer worldwide accounting for 2% of all cancer deaths. In India, the incidence is 1.7/100,000/year. Majority of patients present above the age of 60 years and the median age at diagnosis is around 65 years. Naturally, it follows that medical co-morbidities are frequent complicating problems in the management of bladder cancer. The usual method of diagnosis of carcinoma of the bladder is by transurethral resection of bladder tumour (TURBT). Pre-cystectomy ‘T’ staging depends on the extent of bladder wall invasion in the biopsy specimen. Transitional cell carcinoma (TCC) is the most common histological subtype, accounting for more than 90% of the cases. Superficial bladder tumours account for 65-70% of the presentation, and are mostly managed conservatively, whereas muscle invasive bladder tumours (MIBC) are managed more aggressively. The standard of care for MIBC in the US, for a long time, was radical cystectomy with pelvic lymph node dissection, whereas in Europe it was radical radiotherapy. As a single modality, radical cystectomy always had a better survival than radical radiotherapy. Hence, tri-modality treatment, with maximal TURBT, radiation therapy, and concurrent chemotherapy has been tried, and this has shown to produce 5 year and 10 year overall survival rates comparable to radical cystectomy. There are no randomized phase III clinical trial data directly comparing radical cystectomy versus radiotherapy or concurrent chemo radiotherapy (chemo RT) in MIBC. Current dogma states that radiotherapy based protocols are inferior to cystectomy, in the absence of careful patient selection for radiotherapy. Now in the US, tri-modality treatment is being increasingly tried in selected cases and in the UK, the practice has moved away from radical radiotherapy alone, towards tri-modality approach or cystectomy for selected patients. This article is an attempt to review the evidence for tri-modality treatment in MIBC with details regarding patient selection, bladder preservation rate, survival outcome, toxicities and impact on quality of life.

Treatment of MIBC – Surgical approach

Radical cystectomy with pelvic lymph node dissection is the gold standard treatment for MIBC and all modalities of treatment have to be compared with this for assessing efficacy, survival and quality of life. More recently, extended lymph node dissection has also shown some survival advantage. The probability of survival following cystectomy is determined by the pathologic stage of the disease.

<table>
<thead>
<tr>
<th>Stage</th>
<th>10Yr DFS</th>
<th>10Yr OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>PT2N0</td>
<td>73%</td>
<td>49%</td>
</tr>
<tr>
<td>PT1-T4a or N1-N2</td>
<td>33%</td>
<td>23%</td>
</tr>
</tbody>
</table>

DFS: disease free survival, OS: overall survival.
Chemotherapy, especially neo-adjuvant to surgery, has been recommended by National Cancer Comprehensive Network 2012, in locally advanced cases, for a 5yr survival advantage of 5% as evidenced by the meta analysis of neo adjuvant trials. A major deciding factor in selection of patients for radical surgery, are the comorbidities and issues with urinary diversion. Furthermore, early and late morbidity after radical cystectomy can be problematic and can include risks of hemorrhage, infection, urinary leaks, pelvic lymphoceles. Even the construction of a neo-bladder can not be a substitute for a person's original bladder and is also associated with both acute and long term metabolic and neuro-mechanical complications. There are also a few retrospective reports of increased sexual dysfunction in radical cystectomy series compared to radical radiotherapy. Partial cystectomy as a bladder preserving approach is seldom tried, because it is possible only in a highly select group with small unifocal tumour well away from ureteric orifice and bladder neck with random bladder biopsies negative for multifocality and Carcinoma in situ (Cis).

Radical cystectomy with pelvic node dissection is the gold standard treatment for MIBC and all modalities of treatment have to be compared with this for assessing efficacy, survival and quality of life. More recently, extended lymph node dissection has also shown some survival advantage. The probability of survival following cystectomy is determined by the pathologic stage of the disease.

**Tri-modality approach in MIBC.**

Over the past 50 years, the field of oncology has embraced organ preserving therapies in malignancies of breast, anal, head and neck, gynecologic and prostate with success rates equivalent to radical surgery. Organ preservation approaches in MIBC, were initially with radiation alone, with inferior results, and subsequently with tri-modality approach (maximal TURBT, radiation and chemotherapy) which showed equivalence in properly selected patient subgroups. This approach requires close coordination among all disciplines involved (urologists, radiation and medical oncologists). Tri-modality treatment has been shown to produce 5-year and 10-year overall survival (OS) rates comparable to those of radical cystectomy. The current 5-year OS rates, that range from 50-67% with this approach, and 75% of surviving patients preserve their bladder. After tri-modality approach, a complete response (CR) is obtained in more than 70% of patients.

In Europe, from the 1950s to the 1980s, radiotherapy was extensively used and local control was found to be inferior to radical cystectomy, with multiple studies having documented local control rates of 30-40%. Shelley et al, in a meta analysis of three randomized trials examined the efficacy of pre-operative radiotherapy followed by surgery, versus radiation therapy in 439 patients, 221 of whom were randomized to surgery and 218 to radical radiotherapy, showed 36% 5-year survival for surgery versus 20% 5-year survival for radiation alone.

Bladder preservation approaches became increasingly favored, and became successful, essentially after the emergence of concurrent chemo-radiation protocols with cisplatin. The National Bladder Cancer Group first demonstrated the safety and efficacy of cisplatin, as a radiation sensitizer, in patients with MIBC who were unsuitable for cystectomy. The National Cancer Institute, Canada randomized trial, was instrumental in proving the survival benefit of cisplatin in the concurrent setting. In addition several single institution studies also showed improvement with combined modality approach with TURBT and concurrent chemo-radiation. These encouraging results led RTOG to develop protocols for bladder preservation with maximal TURBT followed by concurrent chemo radiation (CTRT). The careful selection of complete responders, for bladder preservation after neo-adjuvant CTRT is the key to the success of such programmes.

Centers like Massachusetts General Hospital (MGH), the University of Erlangen and the University of Paris have considerable experience in bladder preservation strategies with the tri-modality approach. Published data from such institutions indicate that, a complete response to an initial treatment consisting of TURBT followed by chemo radiation, selects patients whose tumour is likely to be controlled by a bladder sparing approach. If interval cystoscopy after 4-6 weeks shows evidence of residual disease, the intent of bladder preservation is aborted and only complete responders is considered for consolidation chemo radiation.

**Table 2: Organ preservation in MIBC**

<table>
<thead>
<tr>
<th>Center</th>
<th>No. of patients</th>
<th>T-stage</th>
<th>Protocol</th>
<th>DSS with bladder</th>
</tr>
</thead>
<tbody>
<tr>
<td>MGH (Shipley et al)</td>
<td>190</td>
<td>T2-T4a</td>
<td>TURBT + CTRT(Cisplatin)</td>
<td>45% at 10yrs</td>
</tr>
<tr>
<td>University Erlangen</td>
<td>415 (1982-2000)</td>
<td>T1-T4</td>
<td>TURBT + CTRT(Cisplatin)</td>
<td>42% at 5 yrs</td>
</tr>
<tr>
<td>(Rodel et al)</td>
<td>RT = 126</td>
<td>(T1 = 89)</td>
<td>or carboplatin or cisplatin,</td>
<td></td>
</tr>
<tr>
<td></td>
<td>chemoRT = 289</td>
<td>5FU</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

DSS: Disease specific survival.
In the Erlangen series, interval cystoscopy was not done and reassessment was done at the completion of concurrent chemo radiotherapy with restaging TURBT. Complete responders were kept on follow up and patients with persistent or recurrent disease went for re-TURBT + intravesical treatment, or cystectomy depending on depth of invasion. The investigators concluded that chemo radiation was more effective than radiotherapy alone, in terms of complete response (CR) and overall survival (OS). Salvage cystectomy for failure was associated with 45% 10yr DFS, with 80% bladder preservation in survivors. Multivariate analysis of prognostic factors revealed that T stage and a completeness of TURBT were the strongest predictors of OS24. The data also suggested that adjuvant radiotherapy is of benefit even among selected patients who had complete TURBT. In this latter group, the incidence of bladder preservation was 85%, compared with 75% reported by Herr 26 for highly selected patients with muscle-invasive tumors treated with TURBT alone.

Radiation Therapy Oncology Group (RTOG) has just as well extensively investigated bladder preservation protocols in MIBC. During the years 1985-2001 the RTOG conducted 6 trials, of which 5 were phase I and II and the 6th a phase III trial, which tested the role of adjuvant chemotherapy with tri-modality treatment. A total of 415 patients were enrolled in these trials. The five year OS was approximately 50%, with 75% of surviving patients retaining a functionally preserved bladder27.

The tri-modality approach, used in all of these RTOG protocols, is more effective compared to radiation monotherapy used in the 1950s.

The primary objective of RTOG has been to improve cure rates, with a secondary objective to improve bladder preservation rates and an additional objective was to evaluate the tolerance and advantage of newer chemotherapeutic agents. Results of these trials are summarized in Table 3.

### Table 3: Tri-modality Treatment in Muscle Invasive Bladder Cancer - What is the current status?

<table>
<thead>
<tr>
<th>Study</th>
<th>Number (N)</th>
<th>Stage</th>
<th>Neo adj</th>
<th>CTRT</th>
<th>CR %</th>
<th>Consolidation in CR</th>
<th>5yr OS %</th>
<th>Intact bladder %</th>
</tr>
</thead>
<tbody>
<tr>
<td>85-1228</td>
<td>42</td>
<td>T2-T4a</td>
<td>TURBT</td>
<td>40Gy CDDP</td>
<td>66</td>
<td>24Gy CDDP</td>
<td>52</td>
<td>42(5yrs)</td>
</tr>
<tr>
<td>88-0229</td>
<td>91</td>
<td>T2-T4a</td>
<td>TURBT +2 cycles MCV</td>
<td>39Gy CDDP</td>
<td>75</td>
<td>25.2Gy CDDP</td>
<td>62(4yrs)</td>
<td>44(4yrs)</td>
</tr>
<tr>
<td>89-0330</td>
<td>123</td>
<td>T2-T4a</td>
<td>TURBT +2 cycles MCV vs no chemo</td>
<td>39.6Gy CDDP</td>
<td>61.55</td>
<td>25.2Gy CDDP</td>
<td>49vs48</td>
<td>36vs40 (5yrs)</td>
</tr>
<tr>
<td>95-0631</td>
<td>34</td>
<td>T2-T4a</td>
<td>TURBT</td>
<td>24Gy,5FU, CDDP</td>
<td>67</td>
<td>20Gy CDDP,5 FU</td>
<td>83(3yrs)</td>
<td>66(3yrs)</td>
</tr>
<tr>
<td>97-0632</td>
<td>47</td>
<td>T2-T4a</td>
<td>TURBT</td>
<td>40.8Gy CDDP</td>
<td>74</td>
<td>24Gy CDDP,3 Adj MCV</td>
<td>61(3yrs)</td>
<td>48(3yrs)</td>
</tr>
<tr>
<td>99-0633</td>
<td>73</td>
<td>TURBT</td>
<td>Acc RT+TAX,CDP</td>
<td>81%</td>
<td></td>
<td>RT+adj Gem,CDDP</td>
<td>56%</td>
<td>NA</td>
</tr>
</tbody>
</table>

MCV: methotrexate, Cisplatin, vinblastine, TAX: taxol, OS: overall survival, CR: complete response.
RTOG 97-06, phase III trial with adjuvant chemotherapy failed to show the survival benefit of neo adjuvant chemotherapy with tri-modality. This trial stopped accrual prior to the planned 174 patients because of the poor tolerance of MCV regimen and 3 treatment related deaths. Trials using neo-adjuvant or adjuvant chemotherapy, showed more grade 3-4 acute toxicities but late effects were similar. It seems reasonable to conclude from the RTOG data that, tri-modality treatment is an effective bladder preservation approach in a highly select group of patients with MIBC, with the understanding that radical cystectomy is an available option for those who fail combined modality, with no decrease in survival due to delay in cystectomy.

RTOG 0233, examined the role of accelerated twice-daily radiation therapy in combination with either paclitaxel/cisplatin or 5-FU/cisplatin. Both cohorts also received four cycles of adjuvant gemcitabine/paclitaxel/cisplatin chemotherapy. Both regimens had high rates of response, completion and bladder preservation. 73% and 69% of patients had their bladder preserved at 4 years.

A diverse approach tried by Memorial Sloan -Kettering in MIBC is radical TURBT alone for a select group of patients who have no residual tumour on a repeat resection. But whether the good results with this approach can be reproduced is a question, and the answer to which will be clear only after multi institutional studies.

Newer chemotherapeutic agents tried in Concurrent setting

After RTOG 85-12 and NCIC trials the efficacy and safety of cisplatin in CTRT bladder was proved. Newer agents and combination regimens with taxanes, gemcitabine and platinum is being increasingly used in neo adjuvant, concurrent and adjuvant settings with some increase in response rates compared with platinum monotherapy. But as of now, there are no definite recommendations for any particular combination chemotherapy in tri-modality setting. RTOG 0524 is ongoing and will evaluate the role of concurrent trastuzumab/paclitaxel in patients with human epidermal growth factor receptor 2 (her2)/neu over expression.

Prognostic factors for bladder preservation

From the available data a few prognostic factors can be identified for bladder preservation. Tumor stage, as expected, affects both local control and survival. Other factors associated with increased preservation rates are complete TURBT, a complete response (CR) to chemoradiation, solitary tumour without carcinoma in situ, and absence of hydronephrosis and nodal disease. On multivariate analysis of Erlangen series completeness of TURBT was found to be one of the strongest predictors of OS. Anemia has been shown to produce reduced local control and increase in distant metastasis. In addition to T stage, actual T size also is an important predictor of disease recurrence. The Boston experience shows that in the presence of hydronephrosis CR rate was 37 % as compared with 68% in the absence of hydronephrosis, which led to hydronephrosis being an exclusion criterion for their bladder preservation protocols. Presence of Tis has also shown aggressive behavior with increased local recurrence as well as metastasis. Chung et al showed that even in a subset of T2N0M0 patients, those with a T size of less than 2 cm had lesser chance of local failure indicating that not only the T stage, but even the actual size of the tumor was important.

So patient selection criteria helpful for selection of patients for successful bladder preservation include T size < 2cm, T2-T3 disease, a visibly or microscopically negative TURBT, absence of hydronephrosis and pelvic node metastases, absence of Tis, good renal function and performance status. They should also undergo a good TURBT, examination under anaesthesia and metastatic work up.

Recent studies have identified EGFR over expression as a prognostic factor but data regarding this is conflicting with EGFR expression associated with better outcome and Her2neu over expression associated with reduced complete response with tri-modality treatment.

Morbidity of tri-modality treatment.

Tri-modality treatment is well tolerated in patients with good performance status and is associated with slightly increased acute toxicities when compared to RT alone. These acute toxicities are usually self limiting or can be managed with symptomatic measures. Another concern is the increase in peri-operative morbidity for non responders going for radical cystectomy after tri-modality treatment. Early reported series in the 1960s and 70s had shown an increase in mortality and significant peri-operative morbidity with urinary leak and intestinal complications, but recent series failed to demonstrate this increase probably due to better radiation and surgical techniques. A recent retrospective comparison from Japan in 192 patients (treated between 1989-2010) revealed a slight increase in anastomotic leak, in the post chemo-RT cystectomy arm compared to radical cystectomy arm (11% vs 2%), but no significant increase in severe complications or mortality. Christie hospital also had analyzed their morbidity and mortality in cystectomy patients with or without pre-op chemo - RT in 420 primary and 426 salvage cystectomy cases, treated between 1970 and 2005. They also reported no significant increase in peri-operative mortality or medical or surgical morbidity between the two groups except anastomotic site stenosis which was slightly higher in the RT group. So their conclusion was that 40-45 Gy pelvic irradiation is safe as far as salvage cystectomy is concerned.
Quality of life (QOL) after tri-modality treatment.

One of the frequent arguments against tri-modality approach is the lack of prospective QOL data. Recently, the Study Group on Genito-Urinary Tumours (GETUG97-015) study provided results of a prospective evaluation both by investigators and patients on quality of bladder preservation. This study reported 67% bladder preservation rate with good quality of bladder function and data was in concordance with the retrospective bladder quality data from MGH and Erlangen series and the retrospective QOL comparison data of Hennigsohn et al. According to GETUG97-015, sexual function was also preserved in 79% of the patients at 18 months. Urodynamic study in preserved bladder by Zietman et al also showed good bladder function (75%) after trimodality treatment.


The RTOG and other tri-modality protocols, have shown that, the most effective way of bladder preservation without compromising survival seems to be interval cystoscopy evaluation and early cystectomy in non-responders.

Figure: Schema for tri-modality treatment

Radiation Treatment.

Conventional fractionation treatment with a whole pelvis dose of 40-45 Gy, followed by reassessment and boost to the entire bladder or bladder tumour with margin, to a dose of 20-24 Gy is the most common regimen used in tri-modality treatment. Altered fractionation regimens have been evaluated in trial setting with slightly increased acute toxicity rates, with similar or moderate increase in response rates. With improvements in radiation techniques tolerance of radiation with
concurrent chemotherapy has increased and now image guided and adaptive radiotherapy is being increasingly used in bladder tumour radiotherapy with a hope to decrease the morbidity further.

Advancements in radiotherapy, with techniques like intensity modulated radiotherapy and adaptive radiotherapy with implanted fiducials, offers the interesting prospect of increasing the radiation dose favoring better tumor control with lesser normal tissue morbidity.\(^7\)

**Conclusion**

Data from various randomized and single institution studies appear to indicate that bladder preservation strategies with tri-modality approaches in bladder cancer has come of age and should be considered as an alternative first line treatment to radical surgery in selected group of patients with MIBC. Five year survival rates of 50% are achievable, with 70-75% of long term survivors having a native and normal functioning bladder. Many newer chemotherapy agents are making their way to the therapeutic arena, hitherto ruled by platinum agents and the taxanes. Gemcitabine is a promising agent, with good tolerance and bladder preservation rates in studies. Proper patient selection, patient education regarding realistic goals in bladder preservation and multidisciplinary coordination and cooperation are all vital in producing the best possible outcome and survival. Translational research would help to identify molecular predictors of poor response to chemo-radiation facilitating tailor made treatment for bladder cancer patients.

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Neoadjuvant Treatment For Carcinoma Bladder

M. Wesley Jose, K. Pavithran

ABSTRACT

Neoadjuvant chemotherapy is the application of cytotoxic treatment prior to a definitive surgery or radiation with intent to cytoreduce the tumor bulk making it amenable for a complete resection or definitive radiation. Neoadjuvant chemotherapy has a role in the treatment of stage II and III urinary bladder cancer. The current standard for muscle-invasive bladder cancer patients is cisplatin-based neoadjuvant chemotherapy followed by radical cystectomy and pelvic lymph-node dissection.

BACKGROUND

Among the genitourinary cancers, urinary bladder remains a predominant site of malignant growth and accounts for majority of morbidity and mortality. Ninety percent of urothelial malignancy originates in the urinary bladder followed by renal pelvis and ureter (8%) and urethra (2%). The incidence is higher among males. In the 1984-93 data from RCC Thiruvanathapuram, the male to female ratio for urinary bladder cancer was 7:1 and fifty-one percent of patients with malignancy presented with regional (locally advanced) disease.

Urinary bladder carcinoma is uncommon in younger age group and is more prevalent in the elderly population (60 years and above). This aggravates the clinical problem in form of late identification of disease leading to advanced stage at diagnosis and presence of other co-morbidities interfering with treatment of these individuals.

Major prognostic factors in bladder carcinoma are the depth of invasion into the wall and the degree of differentiation of the tumor. The deeply invasive bladder malignancy is commonly less well (poorly) differentiated compared to the superficial tumors and therefore have a higher risk of recurrence and dissemination. Even in a stage II bladder cancer (T2a-bN0) after a radical cystectomy, a 50% risk of recurrence exists for patients with muscle-invasive disease.

A phase three trial done two decades ago by Smith et al comparing preoperative radiation therapy followed by cystectomy against cystectomy alone found that there was absolutely no survival advantage and majority of the failures were distant suggesting poorer results were secondary to systemic disease1. This incited the use systemic therapy upfront instead of local radiation with the aim to improve survival outcomes.

Neoadjuvant chemotherapy may have varied responses ranging from partial improvement to occasionally complete clinical and pathological remission2. The clinical end points of any treatment in oncology relates to better progression free and longer overall survival. The initial studies in bladder cancers in the neoadjuvant setting were done with single agents, which did not project an improvement in the survival benefits. This then lead to trials involving polychemotherapy which has now become a standard of care.

PRESENT SCENARIO AND STANDARD OF CARE

The Medical Research Council and European Organization for Research and Treatment of Cancer (MRC-EORTC) conducted a collaborative trial (BA06 30894) with 976 patients of T2 (grade 3), T3-4a stage, evaluating three cycles of neoadjuvant Cisplatin, Methotrexate and Vinblastine (CMV) followed by either cystectomy or radiation therapy. The absolute survival benefit of 5.5 percent among the groups (50% in no
neoadjuvant group compared with 55.5% in the neoadjuvant group) was not statistically significant (P = .075) probably because the study was originally powered to detect a 10% absolute difference in survival. A Radiation Therapy Oncology Group (RTOG) trial by Shipley and colleagues of neoadjuvant CMV plus chemoradiation versus chemoradiation alone showed no difference in survival.4 This may have been because of the use of chemoradiation in both arms. The phase III study by RTOG to evaluate the potential benefit of adding two cycles of neoadjuvant CMV prior to concurrent chemoradiation with cisplatin was associated with increased hematologic toxic effects and yielded no improvement in response rate, freedom from distant metastases, or overall survival (OS) compared with chemoradiation therapy alone. Both these trials showed no clear evidence of improved survival.

However the updated long-term results of the BA06 30894 international phase III trial concluded that neoadjuvant CMV resulted in a 16% reduction in the risk of death (hazard ratio: 0.84; 95% confidence interval: 0.72-0.99; P = .037), which translated to an increase in the 10-year survival rate (from 30% to 36%).

The use of neoadjuvant polychemotherapy was further investigated by Southwest Oncology Group (SWOG).6 In 317 patients with stage T2 - T4a bladder cancer three cycles of neoadjuvant Methotrexate, Vinblastine, Adriamycin (Doxorubicin) and Cisplatin (MVAC) prior to cystectomy was compared with cystectomy alone. The results revealed a 5-year survival of 57% in neoadjuvant chemotherapy group compared to 43% in the cystectomy alone group however this difference was of only borderline statistical significance (P = .06). The interesting feature however was that no deaths or postoperative complications were reported with neoadjuvant chemotherapy, 38% of patients with neoadjuvant chemotherapy had a complete pathologic response at surgery, and 85% with complete pathologic complete response were alive at 5 years.

The Nordic Cooperative Bladder Cancer Study Group conducted a randomized phase III study to assess the possible benefit of neoadjuvant chemotherapy with two cycles of Doxorubicin and Cisplatin (DC) in patients with bladder cancer undergoing radical cystectomy after short-term radiotherapy.7 They concluded that neoadjuvant chemotherapy seemed to improve long-term survival after cystectomy in patients with stages T3 to T4a bladder carcinoma, while no survival benefit was found for stages T1 to T2 disease.

Advanced Bladder Cancer Meta-analysis Collaboration did a meta-analysis of 11 randomized trials of neoadjuvant chemotherapy covering updated data for 3005 individual patients. It showed that platinum-based combination chemotherapy was associated with a 14% relative reduction in the risk of death and resulted in an improvement in 5-year survival from 45% to 50% (P = .02). However use of single-agent cisplatin in the neoadjuvant setting did not translate into any survival benefit.

Based on the above mentioned results, a reasonable case exists in favor of neoadjuvant, platinum-based combination chemotherapy prior to cystectomy in patients with muscle-invasive bladder cancer. The two regimens of MVAC and CMV have shown the strongest evidence of benefit.

Whether the newer regimens of gemcitabine and cisplatin or high-dose MVAC would have a similar or superior clinical effectiveness to MVAC or CMV is not yet proven in large randomized trials.

GEMCITABINE AND CISPLATIN BASED CHEMOTHERAPY

Use of Gemcitabine and cisplatin based chemotherapy has been studied in seven small series (including from 16 to 68 patients).

A recent pooled analysis of clinical outcomes with neoadjuvant Gemcitabine and Cisplatin (GC) chemotherapy for muscle invasive bladder cancer from seven studies encompassing 164 patients published between 2007 and 2012 by Yuh BE et al concluded that neoadjuvant cisplatin and gemcitabine yield appreciable pathological response rates in patients with muscle invasive bladder cancer. Pathological down staging to pT0 and less than pT2 occurred in 25.6% and 46.5% patients, respectively. Since pathological response is implicated as a potential surrogate for survival in muscle invasive bladder cancer, neoadjuvant cisplatin and gemcitabine may warrant further prospective assessment.

As these studies do present major limitations regarding size and design, it is impossible to conclude that GC could be a safe alternative to MVAC as NAC.

CARBOPLATIN BASED CHEMOTHERAPY

Owing to the toxicities related to Cisplatin administration, researchers have tried to use the combinations with Carboplatin which is comparatively less toxic among the two platinum agents. A recent retrospective analysis by the Japanese group from Iwate reported on sixty-eight patients with locally advanced bladder cancer who either received the standard neoadjuvant chemotherapy with MVAC (n = 34) or gemcitabine and carboplatin (n = 34) followed by cystectomy. They concluded that neoadjuvant chemotherapy with MVAC (n = 34) or gemcitabine and carboplatin (n = 34) followed by cystectomy led to a 30% improvement in overall survival compared to the carboplatin group. Another retrospective analysis from University of South California reviewing the data of 116 patients who had received neoadjuvant chemotherapy (GC: n = 58; M-VAC: n = 58) found that pathologic and survival outcomes did not differ in patients who received GC.
and M-VAC as neoadjuvant chemotherapy\textsuperscript{11}.

A single institution retrospective analysis from Netherlands identified 167 patients with non-organ confined urothelial carcinoma between 1990 and 2010, who received induction cisplatin based combination chemotherapy (n=126) or gemcitabine and carboplatin (n=41). Complete clinical response rates, disease specific survival were statistically not different in either group\textsuperscript{12}.

Most of the studies addressing the use of Gemcitabine and Carboplatin are of retrospective nature and therefore has gross limitations in allowing a recommendatory status for the regimen. The 11th annual meeting of the Society of Urologic Oncology aptly concluded that there are no data for the administration of non-cisplatin-based neoadjuvant chemotherapy, such as carboplatin-combinations. Cisplatin-ineligible patients should proceed directly to surgical extirpation. These patients may have adjuvant cisplatin-based chemotherapy based on pathologic findings however, the data for adjuvant chemotherapy is less compelling\textsuperscript{13}.

**AGGRESSIVE INDUCTION CHEMOTHERAPY - TRIPLE COMBINATIONS**

Smith et al conducted a small phase II neoadjuvant study of nab-paclitaxel plus carboplatin-gemcitabine in T2-4N0M0 or TanyN1-2M0 bladder cancer.\textsuperscript{14} Twenty five of twenty-seven patients received 3 cycles of chemotherapy followed by radical cystectomy. Six patients (27\%) achieved pathologic complete response. Five patients had only carcinoma in situ present in their surgical specimen, and 1 patient had persistent T1 tumor present. Fifty-four percent of the patients had no muscle invasive cancer present at surgery. All patients experienced grade 3-4 neutropenia however only 2 episodes of febrile neutropenia were reported.

It is too early to make recommendations on such an aggressive stance of neoadjuvant chemotherapy in the absence of larger randomized trials.

**FUTURE DIRECTION**

A phase II trials is on to understand if standard chemotherapy (gemcitabine and cisplatin) given on a dose-dense (DD) treatment schedule (with less time between treatments) can help shrink the tumor better than standard chemotherapy given on a standard treatment schedule before the patient undergoes surgery for bladder cancer [Protocol IDs: 12-071, NCT01589094].

Another single arm Phase II study is studying neoadjuvant DD GC in patients with muscle invasive urothelial carcinoma of the bladder who will be undergoing cystectomy with goal of cure [Protocol IDs: ERP-GU-052, NCI-2012-00906, IRB#12-015, NCT01611662].

A phase III randomized, head to head trial comparing the present standard of care schedule of MVAC or CMV with newer more tolerable agents like Gemcitabine would be required to assess if these could replace the more toxic treatment presently in use.

Predictive biomarkers are urgently needed in order

<table>
<thead>
<tr>
<th>Trial Group / Author</th>
<th>Number of patients</th>
<th>Stage</th>
<th>Neoadjuvant chemotherapy regimen</th>
<th>Definitive treatment modality</th>
<th>Pathological CR (%)</th>
<th>Chemotherapy mortality</th>
<th>Median OS with/ without NACT</th>
<th>5 year OS with/ without NACT</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRC-EORTC\textsuperscript{3}</td>
<td>976</td>
<td>T2 G3, T3, T4a, N0- NX</td>
<td>CMV – 3 cycles (n=491)</td>
<td>Cystectomy or RT</td>
<td>32.5%</td>
<td>1%</td>
<td>44 months vs 37.5 months</td>
<td>55.5% vs. 50% (P=0.075) At 3 years</td>
</tr>
<tr>
<td>RTOG\textsuperscript{4}</td>
<td>123</td>
<td>T2-4aNXM0</td>
<td>CMV – 2 cycles (n=61)</td>
<td>CTRT + Cystectomy if less than a CR</td>
<td>NA</td>
<td>NA</td>
<td>36 months vs 36 months</td>
<td>48% vs. 49%</td>
</tr>
<tr>
<td>Intergroup\textsuperscript{5}</td>
<td>317</td>
<td>T2-4aN0M0</td>
<td>MVAC – 3 cycles (n=153)</td>
<td>Cystectomy</td>
<td>38%</td>
<td>0%</td>
<td>77 months vs 46 months (P=0.06)</td>
<td>57%/43% (P=0.06)</td>
</tr>
<tr>
<td>NORDIC\textsuperscript{7}</td>
<td>325</td>
<td>T1 G3, T2-4a, NXM0</td>
<td>DC – 2 cycles (n=153)</td>
<td>Cystectomy</td>
<td>NA</td>
<td>NA</td>
<td>Not reached vs.72 months</td>
<td>59%/51% (P=0.1)</td>
</tr>
</tbody>
</table>
to determine which patients are more likely to benefit from neoadjuvant chemotherapy.15

CONCLUSIONS

Neoadjuvant chemotherapy has a role in the treatment of stage II and III urinary bladder cancer. The current standard for muscle-invasive bladder cancer patients is cisplatin-based neoadjuvant chemotherapy followed by radical cystectomy and pelvic lymph-node dissection. MVAC and CMV are the present recommended schedules for use in neoadjuvant settings.

A change to gemcitabine based treatment at present needs randomized trial to prove its mettle, however it is common practice to use gemcitabine and cisplatin combinations in neoadjuvant settings among the clinicians and this is based on extrapolated information from trial done on metastatic and advanced urinary bladder malignancy.

REFERENCES


Management of Inguinal Nodes in Carcinoma Penis: Current concepts

T.B. Yuvaraja, Harshvardhan

ABSTRACT
The presence and the extent of inguinal lymph node metastasis are the most important factors for the prognosis of the patient with penile cancer. Squamous carcinomas exhibit a prolonged locoregional phase before metastasising and therefore regional lymphadenectomy must be performed. The real challenge, however, lies in managing patients with clinically normal nodes. An early inguinal lymphadenectomy is indicated especially in patients with a high occult nodal micrometastases risk (G3 and pT2-4).

Introduction
The presence and the extent of inguinal lymph node metastasis are the most important factors for the prognosis of the patient with penile cancer. Regional lymphatic spread of penile cancer generally signifies a worse prognosis, whereby pelvic nodal involvement is more menacing than inguinal node involvement. Squamous carcinomas exhibit a prolonged locoregional phase before metastasising and therefore regional lymphadenectomy must be performed. The real challenge, however, lies in managing patients with clinically normal nodes.

Clinical Situations
1. Patients with palpable lymph nodes at the time of presentation
2. Clinically node negative disease at the time of presentation
3. Patients presenting with lymph nodes sometime after the treatment of the primary lesion
4. Patients with Bulky Adenopathy and Fixed Nodal Metastasis

Patients with palpable nodes
Current studies indicate 43% positivity for malignancy in nodes which are palpable, 2-5 making a 4 to 6 week waiting period an unnecessary delay. Thus, this practice is no longer advocated as a tool to select patients who either should or should not undergo lymphadenectomy. Fine Needle Aspiration Cytology (FNAC) is employed to achieve a diagnosis with a positive value of about 70-80%.

In patients with cytologically or histologically proven inguinal node metastases which are considered to be surgically resectable, a complete (radical) inguinal node dissection should be performed ipsilaterally, because this may be curative (Grade B).

Pelvic (iliac) lymphadenectomy is recommended if there are 2 or more inguinal nodes with proven metastases, or grade 3 tumour in the nodes, or extracapsular extension of inguinal node metastases, or large (2-4 cm) inguinal nodes, or if the most proximal femoral (Cloquet’s) node is involved (Grade B).

It is not recommended to perform a pelvic (iliac) node dissection before proceeding with ILND, but histopathological staging of the inguinal nodes is recommended before deciding on the need for pelvic node dissection (Grade B).

Patients with clinically non-palpable nodes
Fine needle aspiration cytology (FNAC) should be performed in all patients with palpable nodes, and under ultrasound guidance in those with nonpalpable nodes, because if it is positive, therapeutic rather than diagnostic lymphadenectomy can be performed (Grade B).

Although early lymphadenectomy improves survival in patients with inguinal metastases, the challenge remains to identify those patients who are truly lymph node negative to avoid the morbidity of traditional lymphadenectomy. Data gained from analysis of a variety of histopathologic variables within the primary penile tumour allow the classification of patients into risk groups for lymph node metastasis:

- Low risk group – Carcinoma in situ (Tis), verrucous carcinoma (Ta), Stage T1 Grade 1
- Intermediate risk group – Stage T1 Grade 2
- High risk group - presence of venous, perineural or lymphatic invasion and pathologic invasion of the corpus spongiosum or urethra, Stage T1 Grade 3 onwards

The statistical probability of inguinal micrometastases can be estimated using risk group stratification or a risk calculation nomogram, provided histopathological assessment of the complete primary lesion is available, not just a biopsy specimen (Grade B).
Surveillance of the inguinal regions is recommended if the probability of positive nodes on the nomogram is less than 0.1 (10%), alternatively if the primary lesion is G1, pTis, pTa (verrucous carcinoma) or pT1 and cN0 with no lymphovascular invasion, provided the patient is willing to comply with regular followup, and provided obesity, prior inguinal surgery or radiotherapy do not prevent clinical assessment of the groins (Grade B).

In socio-economic circumstances which may seriously impede regular surveillance, prophylactic inguinal lymph node dissection (ILND) may be a preferable option, despite the level of morbidity (Grade C).

In the intermediate risk group (nomogram probability 0.1 to 0.5 (10% to 50%) or primary tumour G1-2, T1-2, cN0, no lymphovascular invasion), surveillance is an acceptable management option, provided the patient is fully informed of all the risks, and is willing and able to comply with strict surveillance (Grade B). If not, sentinel node biopsy (conventional or dynamic) or limited (modified) ILND should be performed (Grade B).

In the high risk group (nomogram probability more than 0.5 (50%) or primary tumour G3 or T2-4 or cN1-2, or with lymphovascular invasion), complete (radical) ILND should be performed bilaterally, because early ILND (at initial presentation) leads to higher survival rates compared with delayed ILND when groin metastases become palpable during followup (Grade B).

**Options for detecting positive nodes in clinically node negative patients**

1. **Fine Needle Aspiration Cytology (FNAC)**
2. **Lymph Node Biopsy**
3. **Dynamic Sentinel Node Biopsy (DSNB)** The goal of DSNB is to define where in the inguinal lymph node field the sentinel lymph node resides utilizing a combination of visual (vital blue dyes) or gamma emission (hand-held gamma probe) techniques at the time of surgery. Some false negative rates still remain though.
4. **Modified or traditional Inguinal Lymphadenectomy with Frozen Section studies**

Both superficial inguinal and modified complete dissections have been proposed as staging tools for the patient without palpable inguinal lymphadenopathy. 14-16 Superficial node dissection involves removal of those nodes superficial to the fascia lata. A complete ilioinguinal lymphadenectomy (removal of those nodes deep to the fascia lata contained within the femoral triangle as well as the pelvic nodes) is then performed if the superficial nodes are positive at surgery by frozen-section analysis.

**Limited dissections have the following advantages:**

- more information is provided than by biopsy of a single node or group of nodes
- the possibility of not identifying the sentinel node is limited by removal of all potential first-echelon nodes
- morbidity is minimal compared with standard lymphadenectomy
- the dissection is readily performed by any surgeon experienced in inguinal surgery without the need for specialized equipment

**Recommendations for patients presenting with lymph nodes sometime after the treatment of the primary lesion**

- Unilateral disease: dissection of the same side only with either modified or standard technique.17
- Bilateral disease: bilateral inguinal node dissection18

**Recommendations for Patients with Bulky Adenopathy and Fixed Nodal Metastasis**

Survival in this cohort of patients is related to complete eradication of extensive disease. This task is difficult to achieve with surgery, chemotherapy, or radiation therapy alone. The combination of surgery and chemotherapy has shown some benefit in advanced penile carcinoma. The optimal integration and timing of such therapy are unknown. A reasonable approach in this cohort of patients is to use neoadjuvant chemotherapy followed by an aggressive surgical resection for patients demonstrating either response to therapy or stable disease.19-22

**Radiotherapy and chemotherapy**

Radiotherapy to the inguinal areas in patients without cytologically or histologically proven lymph node metastases (prophylactic RT) is not recommended, because it is not guaranteed to eradicate occult metastases, it may make surveillance more difficult, and may increase the morbidity and decrease the cure rate of surgery if there is inguinal recurrence (Grade B, LE 3).

Radiotherapy to the inguinal areas in patients with lymph node metastases proven on FNAC or sentinel node biopsy (therapeutic RT) is not recommended, for the same reasons as above (Grade B).

Adjunctive radiotherapy after complete ILND can be considered in patients with multiple or large inguinal node metastases or extranodal extension of malignancy, although there are no data comparing adjuvant radiotherapy and chemotherapy with regard to risks and benefits in this setting (Grade C).

Adjunctive chemotherapy after complete ILND can be used instead of radiotherapy in patients with inguinal node metastases that are multiple (more than 2), large or with extranodal extension, or if there is pelvic nodal
metastasis, although there are no studies comparing it with adjuvant radiotherapy (Grade C).

Follow up should be individualized, with the intervals and duration of visits determined by the histopathological features and initial management chosen for the primary tumour and inguinal nodes (Grade C).

REFERENCES


Surveillance as an Option for the Treatment of Small Renal Masses

R. Kannan Nair, Appu Thomas

ABSTRACT
Small renal masses (SRMs) are frequently encountered due to the widespread use of abdominal cross-sectional imaging. Data suggest that a substantial proportion of SRMs are benign and that a significant proportion demonstrate indolent clinical behavior, leading to increased implementation of active surveillance strategies. Active surveillance is a reasonable initial strategy in most patients with SRMs, particularly those with limited life-expectancy and increased perioperative risk. Intervention should be considered for growth greater than 3–4 cm or increase in size greater than 0.4–0.5 cm/year while on active surveillance.

Small Renal Mass (SRM) corresponds to the American Joint Committee on Cancer clinical stage T1a renal tumor and is generally defined as a contrast-enhancing mass within the kidney with a maximal dimension of 4 cm. Due to technological advancements and increased availability of radiography, including computed tomography (CT) and MRI, the presentation of renal cell carcinoma has changed dramatically over the last decade. Hence, renal masses are being identified at much earlier stages before symptoms suggest locally advanced or metastatic disease. Incidentally discovered renal masses currently comprise 48–66% of tumors as compared with 3–13% in the 1970s.

This downward stage migration, together with an increasing number of treatment choices, can present the practicing urologist with a number of dilemmas when considering the most appropriate management of these tumors.

Treatment option in small renal tumors
First, on the basis of the small size and often benign behavior of the tumors, some of these tumors need not be treated, at least initially. Second, for those patients selecting treatment, a decision between performing radical nephrectomy and nephron-sparing procedure must be made. Although localized kidney cancer is primarily a surgically managed disease, with radical nephrectomy considered the historical treatment of choice, clinical guidelines currently recommend nephron sparing approaches for cT1 renal tumors, if technologically feasible based on tumor location and complexity. Changes to the clinical guidelines in the surgical management of SRM were based on the increasing number of observational studies suggesting that nephron sparing approaches were associated with a lower risk of chronic kidney disease (CKD) and improved overall survival in comparison to radical nephrectomy without compromising oncologic outcome.

Primary objective of all nephron sparing approaches are to preserve as much renal function as possible. It can be done in different methods:
1. open / laproscopy / robotic partial nephrectomy.
2. energy ablation
3. active surveillance

What is the expected biologic behavior of SRM?
In SRM less than 3 cm, on average, 20% are benign, 60% are indolent cancers, and 20% are potentially aggressive cancers, making active surveillance a reasonable option for many patients. Most SRMs grow slowly, 0.3 cm/year on average, and therefore can be followed with serial imaging to assess for growth in diameter or volume. Between 20 and 33% exhibit zero net growth, with no reported metastases in this subset; metastasis is also rare with SRMs less than 3 cm in size, but there is 10% chance that they become pT3a, 4 to 7% chance of being grade 3 or 4 and the risk of metastasis of SRM under surveillance is 1 to 2%. The Growth kinetics does not predict any malignant potential since the growth rate of benign lesions are not known.

Rationale of AS in SRM
Majority of Small Renal Mass (SRM) are noted in old age people with multiple co morbidities which make them high risk candidates for renal ablative surgeries, 25% of these patients have impaired renal function. Many of the SRM are not RCC even if they found to be malignant they are found to be of low grade.

The cancer specific mortality is stable or increasing despite increase in early detection and treatment for RCC, the down staging of the RCC in fact does not manifest in decrease in cancer specific/non cancer specific mortality. Treatment outcome is excellent even
in T1a tumor with margin positivity.\footnote{1}

What are the selection criteria for active surveillance in SRM?

Active surveillance has traditionally been reserved for the treatment of SRMs in elderly patients with multiple co-morbidities or in those who decline surgery. Patients with limited life-expectancy, as their risk of death from competing causes far exceeds the risk of cancer-specific mortality for a clinical T1 RCC. Patients with familial RCC are often treated with active surveillance until tumor(s) exceed 3 cm (the ‘3-cm rule’), because the risk of metastasis is negligible for SRMs less than this size. It has not been proposed as the treatment of choice in young fit patients because of the small but real risk of developing incurable metastatic disease while on surveillance.

Possible inclusion and exclusion criteria for active surveillance of SRM.

Inclusion:

1. Benign lesion on renal tumor biopsy
2. Aged and infirm patient
3. Tumor size <3 cm on cross-sectional imaging
4. Chromophobe RCC, low-grade, on renal tumor biopsy
5. Chromophobe-oncocytic hybrid tumor on renal tumor biopsy
6. Willingness of the patient to undergo regular CT or MRI scans and repeated biopsies (good compliance)

Exclusion:

1. Young and healthy patient
2. Sarcomatoid features
3. Collecting duct or unclassified RCC
4. Evidence of ≥T3a disease on cross-sectional imaging
5. High grade
6. Symptomatic lesions

Unclear:

1. Low grade clear-cell RCC
2. Low-grade papillary RCC
3. Multifocal RCC
4. Hereditary RCC

What are the criteria for definitive treatment in patients in whom active surveillance is initiated?

Criteria for intervention for patients on an AS protocol are yet to be clearly defined in the management of SRMs. At present, rapid tumor growth and progression beyond a maximal size are the most commonly used triggers for intervention. The aim is to distinguish between high-risk tumors and low-risk SRMs. The identification of rapid growth rates in an active surveillance protocol for SRMs may act as a marker of aggressive disease.

Criteria for for intervention:\footnote{9,10}

1. An increase in tumor size more than 4cm, 3cm in VHL.
2. An increase a linear growth rate of >0.5 cm/year.
3. Tumor doubling time less than 12 months.
4. New onset symptoms and metastasis.

What is the benefit of pretreatment evaluation in SRM? (Normograms, Imaging and Renal Mass Biopsy)

It would be ideal to predict the probability of cancer specific mortality and mortality due to unrelated causes to counsel the patient before incorporation to AS, but majority of of the normograms are preoperative normograms with tumor histology as a variable.

The overall clinical ability of preoperative nomograms incorporating primarily patient characteristics (age, gender, smoking history, symptom classification, and tumor size) to predict malignant potential in SRMs is quite limited. Lane et al.\footnote{4} incorporated the aforementioned factors into nomograms and found only 55.6 – 58% accuracy, implying that tumors would be misclassified in over 40% of patients, which is clearly clinically inadequate. The main drawback majority of all proposed normograms was the incorporation of tumor histology as a variable.

Kutikov et al. performed a sophisticated analysis of over 30000 patients treated for kidney cancer and assessed outcomes in terms of kidney cancer death, non-cancer death, and other cancer death. Age was strongly predictive of nonkidney cancer death. The authors constructed a very useful yet simple to use preoperative nomogram that allows the physician to estimate 5-year probability of kidney cancer-specific mortality, noncancer mortality, and other cancer mortality.\footnote{14} This nomogram, incorporating only four variables (age, race, sex, and tumor size) can easily be used particularly when counseling elder patients.

At present no preoperative or postoperative predictive models are validated for Active surveillance.

Time interval and most appropriate imaging modality for SRM in AS in yet to be defined. CT and MRI are found to be more appropriate to note the size variation of SRM in AS though its superiority over Contrast US is not proven. Substantial efforts to correlate radiographic characteristics with cancer behavior have been made. Differential degrees of contrast enhancement because of variable vascularity are associated with histological
subtypes of RCC, which are known to have varying degrees of malignant potential. Alshumrani et al\textsuperscript{11}. assessed contrast enhancement on the CT scan in patients with T1 renal tumors. Median absolute nephrographic phase enhancement (nephrographic minus unenhanced phase) was clear cell RCCs 65 HU, oncocytomas 80 HU, and papillary RCCs 16 HU. In this analysis, absolute nephrographic phase enhancement of 32 HU or less distinguished papillary RCCs from clear cell RCCs and oncocytomas. Again, these studies are helpful but not sufficient to make a standalone clinical decision as not all papillary tumors are without malignant potential; further, benign (oncocytoma) from malignant (clear cell) cannot be reliably confirmed. Tumor morphology and anatomy also provide prognostic information regarding disorder and clinical behavior. Generally, small, well marginated, and homogeneous tumors have lower nuclear grade, whereas more aggressive grade III lesions displayed irregular margins and greater inhomogeneity distinguished. Kutikov et al\textsuperscript{14} recently used the R.E.N.A.L nephrometry scoring system to evaluate whether radiographic features correlated with histology and high-grade disease. The R.E.N.A.L. score was initially developed to standardize radiographic tumor reporting for assessment of operative complications and partial nephrectomy utilization rates. These authors found that nephrometry score correlated with both histology (P < 0.0001) and grade (P < 0.0001).

New technologies in their investigational phases are also being assessed. Iodine-124-labelled antibody chimeric G250 (124I-cG250) positron emission tomography reliably predicts clear cell renal carcinoma from other histologies. Another early experience with arterial spin labeling (ASL) MRI in showed a significant correlation between an increase in blood flow to the renal mass on ASL and its potential of being malignant or metastasize in the future. Again, radiographic findings and their incorporation into nomograms have clear limitations with respect to predicting histology, grade, and clinical outcomes and should be utilized with this in mind. These limitations have led to a renaissance of a percutaneous renal mass biopsy, which provides tissue-confirmed pathological diagnosis in 70 – 85% of patients\textsuperscript{8}.

The number of studies regarding the value of the biopsy in the SRMs is still scarce, an accurate diagnostic biopsy may have prognostic implications and definitely lead to changes in the management depending on age and comorbidity. Fine-needle aspiration (FNA) of the kidney may be an excellent diagnostic tool when used in the appropriate setting. It has been advocated that FNA is easier to perform, has lower morbidity and may result in higher accuracy than percutaneous needle biopsy. FNA is usually performed under radiological guidance and its accuracy in distinguishing benign from malignant lesions ranges from 73 to 94% \textsuperscript{11}. The controversy on the value of FNA is not yet solved and justifies why at the present time, if biopsy is indicated, 90% of the urologists prefer histology core biopsy over cytological biopsy. Core tissue biopsy, with co axial needle under image guidance is the preferred mode of tissue sampling in SRM but there are no recommendations on the number of biopsies. Percutaneous renal biopsies are with self limiting complications, chance of seedling is only anecdotal only 6 cases are reported so far with last one in 1994.

Most important limitation in biopsy is sampling error. Sampling error is more common in smaller lesion but also seen in larger lesions because of necrosis, chance of sampling error is 30% in index and subsequent biopsy, so if, the reported the first biopsy fails second biopsy is indicated. Biopsy is contraindicated in cystic lesions because of high chance of seedling and in large lesions with necrosis due to increase chance in sampling error.

There are two main sources of non diagnostic biopsies for both, core biopsy or fine-needle aspiration cytopology (FNAC)\textsuperscript{12}.

1. Failed biopsy: insufficient cellular material to make a diagnosis.
2. Inconclusive biopsy or indeterminate disorder: when the pathologist cannot make a biological diagnosis, including those cases in which the available material is not sufficient for immunohistochemistry.

Whether failed or indeterminate a biopsy should be considered non diagnostic when:

1. There is insufficient material for analysis.
2. Sample contains only normal renal parenchyma.
3. Sample contains only fat or fibrofatty connective tissue.
4. Sample contains only necrotic tissue or a blood clot.
5. Sample contains only inflammatory or fibrotic tissue.

Subtype determination is possible in those SRM biopsies in up to 93% of the malignant masses, although immunohistochemistry may be necessary in a considerable number of cases for a correct identification of the different RCCs. Assuming sufficient material is obtained in biopsy of SRM the sensitivity is 70 to 100%, specificity is 100%. Accuracy 90% is and false positive rate is 0.45%, yield of second core tissue biopsy is also same as index biopsy which is around 70%.

In the future, we are hopeful that molecular imaging, such as PET-CT with 124I-anti-CA-IX antibody (girentuximab), will be able to provide a similar degree of information without the risks of a percutaneous biopsy. Carbonic anhydrase IX (CA-IX) is a member of a family of enzymes that convert carbon dioxide to bicarbonate and protons in response to hypoxia. The expression
of CA-IX is very limited in normal tissue, but is highly expressed by greater than 90% of clear cell RCC and by type 2 papillary RCC.15

In summary, ‘enhanced’ renal mass biopsy and advanced imaging studies are not a requirement for initiation of active surveillance, but can provide information regarding the predicted behavior of a given SRM.

**What is the surveillance protocol for SRM?**

A definite protocol for ‘active’ surveillance of SRMs has yet to be defined. On the basis of their prospective trial experience, Jewett et al. have recommended imaging with MDCT/MRI at every 3 months for 1 year, every 6 months for the second year, and annually thereafter if there is no progression of the disease; with initial and yearly chest X-rays, as a compromise between oncological safety and risk of radiation due to imaging and renal compromise due to contrast administration.9

**ACTIVE TREATMENT OPTIONS**

In the majority of the patients, nephron-sparing surgery remains the gold standard treatment because it is a safe and effective procedure and even very small lesions may progress to metastatic disease. For frail patients who are not fit for open or laparoscopic nephron-sparing surgery, treatment option by minimally invasive techniques, such as radio frequency ablation and cryoablation under ultrasound or CT guidance, might be a middle way between aggressive treatment and active surveillance.

**Conclusions**

AS is a good option if tumor growth rate and metastasis rate can be predicted, but currently no imaging technique, nomograms or histology can predict the outcome of SRM. AS for small renal masses should only be considered in elderly and/or infirm patients with competing health risks, in those with limited life expectancy, and in those for whom surgery is not an option. In the majority of the patients, nephron-sparing surgery remains the gold standard treatment.

**REFERENCES**

Role of Radiation after Radical Prostatectomy –
Review of Literature

S.K. Raghunath, N. Srivatsa

ABSTRACT
Biochemical relapse after radical prostatectomy occurs in approximately 15–40% of patients within 5 years. Postoperative radiotherapy is the only curative treatment for these patients. The current standard of care has been to offer salvage radiotherapy (SRT) with biochemical failure. A different strategy fast evolving is adjuvant radiotherapy (ART). ART is defined as treatment given directly after surgery in the presence of unfavorable risk factors (R1 resection, pT3) before biochemical relapse occurs. It consists of 60–64 Gy and was shown to increase biochemical relapse-free survival in three randomized controlled trials and to increase overall survival after a median follow-up of 12.7 years in one of these trials. SRT, on the other hand, is given upon biochemical relapse and is currently the preferred option, by many centers as it does not include patients who might be cured by surgery alone. As described in only retrospective studies the dose for SRT ranges from 64 to 72 Gy and is usually dependent on the absence or presence of macroscopic recurrence. Available literature has while proven intermediate benefit of ART in reducing cancer progression rates, no added impact of adjuvant radiation has been seen in cancer specific survival rates. Further, the impact on Quality of Life (QoL) in men receiving ART in comparison to those patients with unfavorable risk factors cured with prostatectomy alone is not known as yet. Furthermore, there is compelling evidence of occurrence of secondary malignancies of higher grade by as early as 7 years following radiation of prostate cancer with curative intent. Adding unnecessary radiation, in the backdrop of these factors needs substantial evidence in its favor. Randomized trials are currently investigating the role of ART and SRT. Patients with biochemical relapse after prostatectomy should at the earliest sign of relapse be referred to salvage radiotherapy and those with unfavorable risk factors should preferably be treated within a clinical trial.

1. Introduction
Radical prostatectomy (RP) provides excellent cancer control in patients with localized prostate cancer. However, half of all patients present with one or more risk factors for recurrent disease including higher Gleason Score, extracapsular extension (TNM tumor classification pT3a), invasion of the seminal vesicles (pT3b), or positive resection margins (R1). As a result, the risk of biochemical relapse is approximately 15–40%, 5 years after RP, and further increases thereafter.¹ In addition, patients with a higher preoperative PSA, and a subsequent postoperative rapid PSA doubling time of less than 12 months have shown to have earlier disease progression and low metastasis free survival rates of around 20% at the end of 5 years.

Postoperative radiotherapy (RT) can be performed directly after RP based on risk factors (ART), or it is performed in case of biochemical relapse after RP or in patients who have persistently detectable PSA levels postoperatively (SRT). Three randomized controlled trials investigating the role of adjuvant RT demonstrated improved biochemical control rates, whereas metastasis-free survival and overall survival were improved in only one trial after 12.7 years of follow-up.² In contrast, to date, improved biochemical control for salvage RT has been shown only in retrospective studies.

Despite the lower level of evidence, salvage RT in patients with biochemical recurrence as compared to adjuvant RT in all high-risk patients may avoid side effects in at least a subgroup of patients being already cured by surgery alone and is therefore the preferred postoperative treatment option in many centers. Five years after RP approximately 45–54% of patients with risk factors remain without evidence of disease without adjuvant RT. This can be estimated from the control arms of the three randomized adjuvant RT trials.

2. Materials and Methods
Data for this paper were identified by searches of MEDLINE, Current Contents, PubMed, and references from relevant articles using medical subject headings including prostate cancer, postoperative, radiotherapy, adjuvant, and salvage.

3. Results and Discussion
3.1. Adjuvant Radiotherapy
Three randomized phase III trials have addressed the benefit of adjuvant RT to the prostatic bed in an immediate postoperative period [6-8]. The studies are summarized in Tables 1 and 2. Two trials have been initiated 3 decades ago, using old 2 D radiation techniques, and none of these trials provided details of the performed lymph node dissection. While the EORTC 22911 & SWOG 8794 trials included many patients with PSA > 0.2 ng/mL, the ARO 96-02 trial included men only with adverse prognostic factors & with PSA

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values less than 0.2 ng/mL. Hence, two out of three trials allowed the inclusion of patients with postoperatively elevated PSA values which currently defines PSA recurrence and therefore represents early salvage RT as compared to adjuvant RT. Therefore, data and discussion of these trials have to be interpreted carefully, and can only be transferred into modern radiation oncology with caution.

### Table 1: Characteristics of randomized trials on immediate adjuvant RT.

<table>
<thead>
<tr>
<th>Trial</th>
<th>SWOG 8794</th>
<th>EORTC 22911</th>
<th>ARO 96-02</th>
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</thead>
<tbody>
<tr>
<td>Year of initiation</td>
<td>1988</td>
<td>1992</td>
<td>1996</td>
</tr>
<tr>
<td>Pat.</td>
<td></td>
<td></td>
<td>307 from 385 selected</td>
</tr>
<tr>
<td>Randomized Eligible Patients</td>
<td>431</td>
<td>1005</td>
<td>266</td>
</tr>
<tr>
<td>Percent</td>
<td>98.6%</td>
<td>96.3%</td>
<td>87.3%</td>
</tr>
<tr>
<td>Median age</td>
<td>64.5 years</td>
<td>65 years</td>
<td>64 years</td>
</tr>
<tr>
<td>Inclusion criteria</td>
<td>cT1-2, post-RP: Extraprostatic extension and/or seminal vesicle invasion and/or positive resection margins pT3 and/or R1, c/p N0 (97% pelvic LN-dissection) cM0</td>
<td>Extraprostatic extension and/or seminal vesicle invasion and/or positive resection margins pT2 R1 or pT3 R0-1, c/p N0 (99% pN0) cM0</td>
<td>cT1-3, post-RP: Extraprostatic extension and/or seminal vesicle invasion pT3-4 R0-1 pN0 cM0</td>
</tr>
<tr>
<td>Age not reported</td>
<td></td>
<td>WHO PS 0-1</td>
<td>WHO PS 0-1</td>
</tr>
<tr>
<td>Postop. PSA</td>
<td>&lt;0.2 ng/mL: 66.2%</td>
<td>≤0.2 ng/mL: 88.7%</td>
<td>&lt;0.1 ng/mL: 100%</td>
</tr>
<tr>
<td></td>
<td>≥0.2 ng/mL: 33.8%</td>
<td>&gt;0.2 ng/mL: 10.7%</td>
<td></td>
</tr>
<tr>
<td>stratification</td>
<td>Positive margins or capsule invasion versus invasion of seminal vesicles versus positive margins and capsule invasion; HT</td>
<td>Institution; capsule invasion; positive margins; invasion of the seminal vesicles</td>
<td>Gleason Score; resection margins; neoadjuvant HT; tumor stage</td>
</tr>
<tr>
<td>Hormonal therapy</td>
<td>8.5%</td>
<td>10.0%</td>
<td>11.5%</td>
</tr>
<tr>
<td>Adjuvant RT</td>
<td>30–32 × 2.0 Gy</td>
<td>30 × 2.0 Gy (n 90.8%)</td>
<td>30 × 2.0 Gy (n 82%)</td>
</tr>
<tr>
<td>Time from RP to RT</td>
<td>&lt;18 weeks</td>
<td>&lt;16 weeks</td>
<td>10–30 weeks</td>
</tr>
<tr>
<td>Treatment in observation arm</td>
<td>RT: 33.2%</td>
<td>RT: 22.5%</td>
<td>HT: 9.1%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Other: 1%</td>
</tr>
<tr>
<td>Median followup</td>
<td>12.6 years</td>
<td>5 years</td>
<td>4.5 years</td>
</tr>
<tr>
<td>Primary endpoint</td>
<td>Metastasis-free survival (bone, visceral, extrapelvic lymph nodes)</td>
<td>Biochemical progression-free survival</td>
<td>Progression-free survival</td>
</tr>
<tr>
<td>Definition of bNED</td>
<td>ng/mL for postop. PSA</td>
<td>ng/mL above lowest postop. PSA</td>
<td>2 increasing PSA values</td>
</tr>
</tbody>
</table>

bNED: biological no evidence of disease; RP: radical prostatectomy; RT: radiotherapy; HT: hormonal therapy; PS: performance status.
### Table 2: Results of randomized trials on immediate adjuvant RT.

<table>
<thead>
<tr>
<th>Trial</th>
<th>SWOG 8794</th>
<th>EORTC 22911</th>
<th>ARO 96-02</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall survival</td>
<td>HR: 0.72 (95% CI 0.55–0.96), P = 0.023</td>
<td>HR: 1.09 (98% CI 0.67–1.79), P = 0.68</td>
<td>Not reported</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>bNED</td>
<td>HR: 0.43 (95% CI 0.31–0.58), P &lt; 0.001</td>
<td>HR: 0.48 (98% CI 0.37–0.62), P &lt; 0.001</td>
<td>HR: 0.53 (95% CI 0.37–0.79), P = 0.0015</td>
</tr>
<tr>
<td>Metastasis-free survival</td>
<td>HR: 0.71 (95% CI 0.54–0.94), P = 0.016</td>
<td>Not reported</td>
<td>98% versus 95.1% (n.s.)</td>
</tr>
<tr>
<td>Clinical progression-free</td>
<td>HR: 0.62 (95% CI 0.46–0.82), P = 0.001</td>
<td>HR: 0.61 (98% CI 0.43–0.87), P = 0.009</td>
<td>Not reported</td>
</tr>
<tr>
<td>survival</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time to initiation of hormonal therapy</td>
<td>HR: 0.45 (95% CI 0.29–0.68), P = 0.001</td>
<td>Not reported</td>
<td>Not reported</td>
</tr>
<tr>
<td>Overall toxicity</td>
<td>23.8% versus 11.9%, P = 0.002</td>
<td>4.2% versus 2.6% (Grade 3; P = 0.07)</td>
<td>21.9% versus 3.7%, P &lt; 0.0001</td>
</tr>
<tr>
<td>Rectal toxicity</td>
<td>3.3% versus 0%, P = 0.02</td>
<td>Not reported</td>
<td>1.4% versus 0%</td>
</tr>
<tr>
<td>Urinary stricture</td>
<td>17.8% versus 9.5%, P = 0.02</td>
<td>Not reported</td>
<td>Not reported</td>
</tr>
<tr>
<td>Total urinary incontinence</td>
<td>6.5% versus 2.8%, P = 0.11</td>
<td>Not reported</td>
<td>Not reported</td>
</tr>
</tbody>
</table>

HR: hazard ratio; CI: confidence interval; n.s.: not significant.

### 3.2. Salvage Radiotherapy

Whereas an increase of PSA after RP of a nonorgan confined cancer can be seen in approximately 15–40%, a pure local recurrence is predominant with a slow slope of PSA (> 1 year after resection; PSA doubling time > 12 months; PSA increase within 12 months < 0.75 ng/mL), a better differentiated cancer, positive margins, and negative pelvic lymph nodes6,12. The observation from large retrospective trials as well as from the randomized trials of SWOG and EORTC suggests the need to start salvage RT at the earliest sign of biochemical failure, with PSA value being between 0.2 and 0.5 ng/mL14,16. The threshold for metastatic potential of a recurrent disease has been identified to be 0.5ng/mL and hence the development of a measurable local recurrence should be avoided6,14,16. Unfortunately, there are only retrospective studies available addressing the benefit of salvage RT (Table 3). A large multi-institutional retrospective study by Stephenson et al. analyzing 1540 patients and Trock et al. who analyzed 635 patients undergoing RP who experienced biochemical and/or local recurrence and received either no salvage treatment were analyzed. After a median follow-up of 6 years, salvage RT alone was associated with a 3-fold increase in prostate-cancer-specific survival compared to those with no salvage treatment. The increase in prostate cancer-specific survival associated with salvage RT was most marked in men with a PSA doubling time of less than 6 months and in patients with a Gleason Score of 8–10. This is an important finding as it suggests that patients with prostate cancer and adverse risk factors profit most from salvage RT.
3.3. Effect of Dose Escalation

Advent of Intensity-modulated RT & Image-guided RT has allowed presumed safer dose escalations to the prostate bed-up to 75 Gy. Large scale trials have reported reasonable safety in those doses. Though 30% late grade 2 genitourinary toxicity was reported in most series, no higher grade toxicities were reported\(^\text{16}\).

Also, it was observed that each Gy increase in total dose between 64 and 70 Gy may improve the biochemical tumor control by more than 3% per additional Gy delivered.

Therefore, a total dose towards 70 Gy might be considered in salvage situation, when the risk of severe toxicity can be minimized by using modern radiation techniques. Long term toxicity effects of these newer manipulations are still awaited.

3.4. Adjuvant versus Salvage Radiotherapy

The advantages of immediate adjuvant RT are not very obvious from three randomised trials, as more than 25% of the included patients had a PSA of more than 0.2 ng/mL at the initiation of RT which corresponds to a “salvage-like” situation\(^\text{5,6}\). Importantly, the alterna-

<table>
<thead>
<tr>
<th>First author</th>
<th>Year</th>
<th>No. Pat.</th>
<th>Median pre-RT-PSA (ng/mL)</th>
<th>HT (%)</th>
<th>Med. RT-dose (Gy)</th>
<th>RT technique</th>
<th>Followup (months)</th>
<th>bNED (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anscher et al.</td>
<td>2000</td>
<td>89</td>
<td>1.4</td>
<td>9</td>
<td>66.0</td>
<td>2 D/3 D</td>
<td>48</td>
<td>50 (4 y.)</td>
</tr>
<tr>
<td>Bernard et al.</td>
<td>2010</td>
<td>364</td>
<td>0.6</td>
<td>0</td>
<td>64.8</td>
<td>2 D/3 D</td>
<td>72</td>
<td>50 (5 y.)</td>
</tr>
<tr>
<td>De Meerleer et al.</td>
<td>2008</td>
<td>87</td>
<td>0.7</td>
<td>56</td>
<td>75.0</td>
<td>IMRT</td>
<td>30</td>
<td>67 (5 y.)</td>
</tr>
<tr>
<td>Do et al.</td>
<td>2002</td>
<td>73</td>
<td>2.8</td>
<td>9</td>
<td>64.8</td>
<td>2 D</td>
<td>42</td>
<td>45 (10 y.)</td>
</tr>
<tr>
<td>King and Spiotto</td>
<td>2008</td>
<td>84</td>
<td>0.45</td>
<td>57</td>
<td>70.0</td>
<td>2 D/3 D/IMRT</td>
<td>&gt;60</td>
<td>58 (5 y.)</td>
</tr>
<tr>
<td>Loeb et al.</td>
<td>2008</td>
<td>107</td>
<td>~0.7</td>
<td>0</td>
<td>63.0</td>
<td>IMRT</td>
<td>53</td>
<td>55 (7 y.)</td>
</tr>
<tr>
<td>MacDonald et al.</td>
<td>2004</td>
<td>102</td>
<td>1.1</td>
<td>0</td>
<td>65.8</td>
<td>n.r.</td>
<td>50</td>
<td>38 (5 y.)</td>
</tr>
<tr>
<td>Neuhof et al.</td>
<td>2007</td>
<td>171</td>
<td>1.1</td>
<td>29</td>
<td>60–66</td>
<td>3 D</td>
<td>39</td>
<td>35 (5 y.)</td>
</tr>
<tr>
<td>Pazona et al.</td>
<td>2005</td>
<td>223</td>
<td>0.8</td>
<td>4.5</td>
<td>63</td>
<td>3 D</td>
<td>56</td>
<td>40 (5 y.)</td>
</tr>
<tr>
<td>Pisansky et al.</td>
<td>2000</td>
<td>166</td>
<td>0.9</td>
<td>4</td>
<td>64.0</td>
<td>2 D/3 D</td>
<td>52</td>
<td>46 (5 y.)</td>
</tr>
<tr>
<td>Stephenson et al.</td>
<td>2004</td>
<td>501</td>
<td>0.7</td>
<td>17</td>
<td>64.8</td>
<td>2 D/3 D/IMRT</td>
<td>45</td>
<td>45 (4 y.)</td>
</tr>
<tr>
<td>Stephenson et al.</td>
<td>2007</td>
<td>1540</td>
<td>1.1</td>
<td>14</td>
<td>64.8</td>
<td>2 D/3 D/IMRT</td>
<td>53</td>
<td>32 (6 y.)</td>
</tr>
<tr>
<td>Trock et al.</td>
<td>2008</td>
<td>160</td>
<td>0.7</td>
<td>0</td>
<td>66.5</td>
<td>2 D/3 D</td>
<td>72</td>
<td>89 (10 y. OS)</td>
</tr>
<tr>
<td>Van Der Poel et al.</td>
<td>2008</td>
<td>41</td>
<td>2.15</td>
<td>7</td>
<td>60–70</td>
<td>n.r.</td>
<td>73</td>
<td>44 (10 y.)</td>
</tr>
<tr>
<td>Wiegels et al.</td>
<td>2009</td>
<td>162</td>
<td>0.33</td>
<td>0</td>
<td>66.0</td>
<td>3 D</td>
<td>41</td>
<td>54 (3.5 y.)</td>
</tr>
</tbody>
</table>

RT: radiotherapy; HT: hormonal therapy; Med. RT dose: median total dose of radiation therapy; bNED: biochemical no evidence of disease; n.r.: not reported; 2 D: 2-dimensional treatment planning; 3D: 3-dimensional treatment planning; IMRT: intensity-modulated radiation therapy; OS: overall survival.
tive concept of salvage RT avoids treatment of patients without tumor progression after RP despite having risk factors such as R1 or pT3b. The toxicity and morbidity of urethral stenosis and incontinence can be avoided by starting RT years after full recovery from RP.

More multiple prospective randomized clinical trials are on the offing using newer radiation delivery techniques and until results are obtained, it seems prudent to hold radiation till demonstrable biochemical failure is noted.

A score algorithm or nomograms may help in decision making using risk factors for recurrence as seminal vesicle infiltration, Gleason Score, and pre-RT PSA-value and these are being analyzed in the prospective studies.

3.5. Hormonal Manipulation with Radiation Therapy

Scores of clinical trials have failed to prove benefits of either neo-adjuvant or adjuvant hormonal therapy in these settings with no difference in overall survival.

Outside of clinical trials, a precipitated start of hormonal therapy can be avoided at least for patients carrying all favorable risk factors (ng/mL, Gleason Score 4–7, positive resection margins, PSA doubling time >12 months). Thereby, the distinction of local versus systemic tumor progression is not compromised, and additional side effects can be avoided. The recent EORTC trial (NCT00949962) on adjuvant RT in stage I–III prostate cancer, randomizing 6 months of hormonal therapy in addition to adjuvant RT to analyze its impact on bPFS has not considered overall survival as its end-point. In principle, by irradiation, the PSA can by decreased to non-measurable values in up to 50% of the cases at 5-year follow-up and hormonal manipulation should be reserved to the subset showing relapse.

3.6. Second malignancies after Radiation Therapy

Petros Sountoulides et al, in their meta-analysis utilizing data from the Surveillance, Epidemiology and End Results(SEER)Medicare Program, in 269,069 men with prostate cancer, noted heterochronous secondary cancers in 9.9% patients who received sole RT with curative intention with a mean follow up of 7 years. The secondary tumors were predominantly in the bladder and secondly in rectum. They also observed that these malignancies were consistently of higher grade necessitating aggressive therapy. Surgical outcomes in these patients with irradiated pelvis have not been analyzed but by default appear poorer. The effects of advanced radiation delivery techniques and irradiation with lesser doses in either SRT/ART are yet to be ascertained but prudence dictates avoiding unnecessary radiation till availability of strong evidence.

4. Conclusions

The natural course and life expectancy of men besides prostate cancer have to be considered, with its enormous global inequality. With a realistic life expectancy of less than 5 years, further treatment should not be offered in the adjuvant situation. It needs about 8 years from biochemical recurrence to the development of a clinically measurable progression and even with a life expectancy of up to 8 years, salvage RT seems to be appropriate.

Patients can be treated with salvage RT in the event of biochemical relapse, especially when they are carrying less dominant risk factors for tumor recurrence. It is recommended that such salvage RT should be performed as early as possible, preferably with PSA values below 0.5 ng/mL, and although it was shown to be most effective in patients with adverse risk factors, it should not be withheld from any definite subgroup of patients with biochemical recurrent disease. The optimal dose and timing of postoperative RT is subject of phase III trials. Outside of clinical trials, 60–64 Gy should be used in the immediate postoperative setting and 64–72 Gy in the salvage setting, dependent on the absence or presence of macroscopic recurrence.

The use of adjuvant RT after RP in patients with adverse risk factors has demonstrated improved biochemical control but has not translated into improved overall survival. There is also a relevant risk of overtreatment as patients might be included who are cured by surgery alone. ART can currently be considered to patients with R1 resection and pT3 disease and to also those with preoperative PSA values of more than 10 ng/mL and a preoperative PSA velocity of >2 ng/mL per year as additional risk factors for tumor recurrence.

Patients with biochemical relapse after RP should ideally be treated within clinical trials to answer open questions on dose and timing as soon as possible. Keeping these patients in trials will also enable answers to questions on relevance of hormonal therapy, possibility of second malignancies and quality of life issues.

REFERENCES.


Role of Neoadjuvant chemotherapy and regional lymphadenectomy for upper tract urothelial carcinoma

T. A. Kishore

ABSTRACT

Neoadjuvant chemotherapy was shown to be associated with significant rates of complete response and tumor downstaging in patients with UTCC. Lymphatic metastases is a common phenomenon in UTCC with an incidence of 30–40%. Nephroureterectomy with lymph node dissection (LND) is considered the standard surgical procedure.

Introduction

Upper urinary tract urothelial carcinomas (UTCC) are especially rare, accounting for only 5%-7% of all urinary tract tumors. The imaging, staging, and treatment paradigms for UTCC have been much more limited and challenging than for bladder cancer, and evidence has shown that survival has not improved for these patients in the contemporary era.

Role of Neoadjuvant chemotherapy for upper tract urothelial carcinoma

The rationale to pursue neoadjuvant, as opposed to adjuvant, chemotherapy for patients with high-risk UTCC is based on several important observations. First, data from the treatment of high-risk bladder cancer indicate favorable survival in patients who receive neoadjuvant chemotherapy. Second, most patients with high-risk UTCC suffer from underlying renal insufficiency and significant loss of renal reserve occurs after nephrectomy. This loss precludes effective dosing of chemotherapy in the adjuvant setting, providing one of the most compelling reasons for pursuing the neoadjuvant approach. Third, data indicate that the survival rates of patients with UTCC have not improved in the past two decades, during a time when initial nephroureterectomy was considered the standard of care and advances in imaging and endoscopy presumably may have allowed earlier detection of disease.

Neoadjuvant chemotherapy was recently shown to be associated with significant rates of complete response and tumor downstaging in patients with UTCC. Limitations of the neoadjuvant approach include the probability that some patients may not tolerate both chemotherapy and surgery. Another obvious limitation of the neoadjuvant approach is the limited means of preoperative risk stratification and the possibility of over treatment in some patients. The results of study have shown that the surgical outcomes of patients who have undergone radical nephroureterectomy and regional lymphadenectomy after neoadjuvant chemotherapy are not significantly different from those of patients who have not undergone neoadjuvant chemotherapy. Inability to properly stage the disease by imaging methods and ureteroscopy also pose a challenge for the selection of patients for neoadjuvant chemotherapy. While survival data need to mature and longer follow-up is awaited, current preliminary data provide justification for the sustained support of trials using this strategy in UTCC.

Role of lymphadenectomy for upper tract Transitional cell carcinoma

Lymphatic metastases is a common phenomenon in UTCC with an incidence of 30–40%. The lymphatic mapping studies have demonstrated that tumors of the renal pelvis and upper ureter was primarily to the para-aortic and para-caval nodes, and that from the distal ureter, spread was to the pelvic nodes. So nephroureterectomy with lymph node dissection (LND) is considered the standard surgical procedure. The TNM classification states that the regional lymph nodes (LN) for UTCC as the hilar, abdominal para-aortic and para-caval nodes, and for the ureter, the intrapelvic nodes. Recent studies conducted has proposed that nodal sites where the incidence of metastasis was 30% or more shoule be considered as the regional lymph nodes. Some authors advocate the removal of interaortocaval nodes for the tumours of right renal pelvis and presacral nodes for those of lower ureters.

Several studies also showed that LND could provide a staging benefit for patients by classifying the patients according to the prognosis. Two large multi-institutional studies and one single center study showed that the patients with no metastases to LN (pN0) confirmed by LND showed a better survival than pNx. In contrast, the results from two population-based studies and one multi institutional study demonstrated that pN+ showed worse survival than pNx. Identifying the patients with pathological lymphatic metastases might enable to consider adjuvant chemotherapy for patients with poor prognosis.

In contrast to the role of LND in accurate staging, its role in the therapeutic benefit has not been well determined. Few authors have shown that LND was an independent factor to improving patient survival. Contrary to this, the results of two population-based studies showed no therapeutic benefit from LND in
which the survival of the patients with pN0 did not differ from those with pNx. Thus, the therapeutic benefit of LND was controversial, although some studies favored the benefit of LND in improving the oncological outcome of UTCC as it is in bladder cancer. There may be subsets of patients that benefit from LND (pT2–pT4, pN0). Unfortunately, these subsets appear to only be identified pathologically, and current clinical staging precludes definitive identification of the cohorts that may benefit from LND. The current EAU guideline states the following, “However, these data are retrospective; it is not possible to standardize either indication or the extent of LND”.

An increase in the ratio of positive nodes to nodes removed among patients undergoing nephroureterectomy was associated with a decreased overall survival whereas the number of positive nodes and the total number of nodes removed did not predict survival. The ratio of the number of LN positive for metastasis to the total number of nodes removed (lymph node density) lower than 20% is likely to predict better survival of patients with bladder cancer who had lymph node involvement. Bolenz et al. showed that the patients with lymph node density of 30% or more were at greater risk of disease recurrence and cancer-specific mortality.

By performing LND for UTCC may not lead to increased blood loss, and is unlikely to give rise to major complications. But there are virtually no data regarding the complications, costs, and extra time added by including LND. Although majority of the studies support the benefit of extended lymphadenectomy, the level of evidence in the guideline is still low.

REFERENCES

Management of High Risk Prostate Cancer

P. Kanagarajah, M. Manoharan

ABSTRACT

High risk prostate cancer accounts for <15% of new cases and patients are at higher risk of suffering from systemic disease at the time of diagnosis and prostate cancer related deaths. Early identification of these patients and prompt counseling regarding treatment options carries great impetus prior to instituting treatment. With the change in trends and better understanding of the nature of the disease, a multimodal approach is recommended to successfully treat this patient population. In this review, we aim to provide a comprehensive overview on the diagnosis and treatment options available for high risk prostate cancer patients.

Introduction

Prostate cancer continues to be the most commonly diagnosed cancer in men in the United States, with 241,740 newly diagnosed cases and 28,170 deaths for the year 2012. This number has progressively increased following the routine use of prostate specific antigen (PSA) for the screening of prostate cancer in the late 1980’s. Risk stratification for prostate cancer has carried great impetus. Though low risk patients are often well served with active surveillance, high risk patients are acknowledged to be at higher risk for prostate cancer related deaths. Pre-operative PSA, clinical stage and biopsy Gleason score (GS) were combined to stratify risk groups for prostate cancer.

High risk patients are at increased risk to develop biochemical/disease recurrence after primary treatment for clinically localized prostate cancer. Thus identifying these patients prior to commencing therapy allows to plan appropriate treatment. D’Amico et al. and the AUA consider patients with PSA ≥ 20 ng/ml, GS 8-10 or clinical stage ≥ T2c as high risk patients. However, the EUA and the National Comprehensive Cancer Network (NCCN) adopted PSA ≥ 20 ng/ml, GS 8-10 or clinical stage ≥ T3 as criteria to define high risk group. The role of clinical staging in this stratification remains controversial due to significant inter-observer variability.

The Cancer of the prostate Risk Assessment score (CAPRA) by Cooperberg et al. combines age, PSA, clinical stage, biopsy GS, and percentage of positive biopsy cores. A score of 6-10 represents high risk disease [3]. Results from pooled analysis confirm the ability of the CAPRA score to correctly predict biochemical-recurrence-free survival at 3 years after radical prostatectomy across all three strata of risk. However, it under-predicts recurrence-free survival 5 years after radical prostatectomy across all three strata of risk.

Various other factors are also associated with high risk prostate cancer progression. Pre diagnosis PSA of > 2 ng/ml/year has shown to increase the likelihood of death from prostate cancer after radical prostatectomy and external beam radiation. PSA doubling time, volume of cancer at initial diagnosis has been associated with recurrence after primary treatment. Additionally, a tertiary Gleason pattern of 5 is a significantly adverse prognostic factor in patients with a GS of 7. Further factors include seminal vesicle invasion, margin status and extra prostatic extension. These factors are not universally adopted as a gold standard. However, they aim to predict high risk disease along with clinical and pathological stage.

Risk Stratification and Diagnosing High Risk Patients

High risk patients are at increased risk to develop...
RP is a viable treatment for select patients with cT3a, GS 8-10 or PSA > 20 ng/ml. It is recommended that patients with adverse tumor characteristics may benefit from extended pelvic lymphadenectomy as lymph node involvement is often found in these patients.

Eastham and Scardino et al. evaluated outcomes of 4700 high risk men undergoing RP. They reported that high risk patients have an increased probability of seminal vesical invasion (10-33%), extra-capsular extension (35-71%) and lymph node metastasis (7-23%). Interestingly, a third of these men had organ confined disease and approximately 50% remained without progression for 10 years with RP alone. In patients who relapsed, 26-39% had a doubling time greater than 10 months and 25% did not progress until 2 years following surgery. Patients with prolonged doubling time and disease free intervals as mentioned above were noted to be at low risk for metastatic disease and had reduced cancer related mortality. Studies have shown 5 year PSA free survival is approximately 50% for high risk patients undergoing RP alone. Table-1 illustrates the biochemical recurrence rates in high risk patients post radical prostatectomy. Recent reports have documented that robotic prostatectomy in high risk patients yield similar results to open prostatectomy. Silberstein et al. reported outcomes upon evaluation of 1454 patients. 961 (66%) and 493 (34%) underwent open and robotic prostatectomy respectively. 15% positive margin rate was reported in both arms and there were no significant differences in the biochemical recurrence rates in both treatment arms.

Extended pelvic lymph node dissection should be performed in patients undergoing radical prostatectomy for high risk disease. However, even in experienced hands, complication rates after extended lymph node dissection is reported to be high. Studies report pelvic lymph node dissection for high risk patients should include not only the external and obturator nodes but should also include internal iliac and common iliac nodes up to the ureteric crossing. This approach is projected to remove about 75% of all involved nodes. In patients with positive nodes time to progression directly correlates with the number of diseased nodes. Recent studies have shown that both the diameter of any individual lymph node metastasis and its extranodal extension have significant prognostic impact. Number of positive nodes and nodal density are also of important significance. In patients with positive lymph nodes, Engel et al. found that the 5-year and 10 year overall survival was 84% and 64% respectively in patients with completed radical prostatectomy compared to 60% and 28% respectively in patients where prostatectomy was aborted. These results suggest that radical prostatectomy may offer a survival benefit in patients with lymph node positivity.

Adjuvant and Salvage Radiotherapy after Radical Prostatectomy

The Southwest Oncology group (SWOG) and the European Organization for Research and Treatment of Cancer (EORTC) are randomized trials that compared outcomes after radical prostatectomy plus adjuvant radiation with prostatectomy alone. Both studies showed significant difference in biochemical failure rates at 5 years between patients who received adjuvant radiation compared to those who did not. The SWOG study showed significant increase in the metastatic disease free survival in the radiotherapy group. Despite the evidence, adjuvant radiotherapy is not accepted standard of care in all patients after radical prostatectomy. Many regard adjuvant radiotherapy to be an overkill owing to the fact that as many as 50% of high risk patients will be cured with radical prostatectomy alone. Hence, it is not uncommon for physicians to wait for biochemical/disease recurrence prior to initiating adjuvant radiotherapy in high risk patients post radical prostatectomy.

Salvage radiotherapy showed a strong PSA survival advantage when initiated at a PSA of <0.2 ng/ml compared to commencing therapy when the PSA has reached a level of 1 ng/ml. Reported 5 year survival was 98% for patients who received salvage radiotherapy upon a PSA relapse of 0.2 ng/ml.

Adjuvant Androgen Deprivation Therapy (ADT) after Radical Prostatectomy

Many high risk patients progress following radical prostatectomy (RP). This is due to the fact that patients are confined to a single form of primary treatment and are not managed with a multimodal approach. Recent Cochrane database meta-analysis showed that neo-adjuvant ADT significantly improves tumor stage and margin status but does not improve overall survival. Thus neoadjuvant ADT is not recommended in the RP setting per the EUA or the AUA guidelines. However, ADT given in the adjuvant setting has shown to improve biochemical and progression free survival. Its effect on overall survival is unclear. Studies have shown that immediate ADT in node positive patients after RP significantly decreases risk of biochemical and local recurrence. However, the side effects of ADT should be weighed against the benefits prior to instituting therapy.

Adjuvant and Neo-adjuvant Chemotherapy after Radical Prostatectomy

Studies have showed that neoadjuvant docetaxel and estramustine in high risk localized prostate cancer patients is safe and it offered a 2 year progression free survival of 45% following local treatment. However, its advantage over ADT and in an adjuvant setting remains controversial and mandates large phase 3 clinical trials.
Role of Radiotherapy

External Beam Radiation Therapy

Based on published literature, in men with high risk prostate cancer, radiation therapy in combination with adjuvant hormonal therapy has shown to provide an increased survival advantage. Monotherapy with radiation alone is not recommended. Unlike radical prostatectomy, which provides early undetectable PSA following surgery, it is tough to define cure and the timing of PSA nadir in patient post radiation therapy.

Five year survival of 79% was noted compared to 62% in a study with 401 men randomized to hormonal therapy 4 weeks prior to radiation and radiation therapy alone respectively. Disease free status was reported to be 85% in the combination group compared to 48% in those who received radiation alone. Similar results were reported by Granfors et al. comparing orchiectomy and radiation versus radiation alone in men with high risk localized prostate cancer (61% vs 38%)\(^2\). Benefits from androgen deprivation was even greater in those with lymph node metastasis.

Dose escalation studies combined with improved radiation delivery techniques have increased the 5 year biochemical recurrence free survival rates in a monotherapy setting. MD Anderson trial and a Dutch multi-center trial found a radiation dose of 78 Gy to be superior to the conventional 70 Gy.

In men with high risk localized prostate cancer choosing radiation therapy over surgery, combination hormonal therapy and administration of high radiation dose levels has become standard of care. There is no consensus on the timing and the duration of hormonal therapy. However, many propose 6 months of ADT for intermediate and 2 years for high risk patients\(^5\).

Brachytherapy

The addition of Brachytherapy to ADT and external beam radiation was found to improve prostate cancer specific outcome in high risk patients. Studying a population of 1342 prostate cancer patients with PSA >20 ng/ml, \(\geq cT3\) or biopsy GS 8-10 treated with brachytherapy alone or with supplemental ADT and external beam radiation, there was significant reduction in the prostate cancer specific mortality in the men treated with brachytherapy and both ADT and external beam radiation. Similar results were reported by Dattoli et al. showing a biochemical recurrence free survival of 74% at 16 years\(^2\).

Proton Beam Therapy

The use of proton beams to treat prostate cancer allows the entire dose to be directly delivered to the prostate limiting its penetration to surrounding organs like bladder and rectum and thereby reducing side effects. At the present time there is paucity of data validating its use. However, based on the dose delivered, PSA responses to nadir and the degree of damage to adjacent organs, proton therapy does not result in better cancer control outcomes compared to brachytherapy.

Role of Chemotherapy in High Risk Prostate Cancer

Owing to the sensitivity of prostate cancer to hormonal therapy, the negative impact on quality of life associated with chemotherapy and the relatively long natural history of prostate cancer in comparison to other solid organ cancers, chemotherapy has not gained popularity and is not considered standard of care for the initial treatment of prostate cancer, even those with high risk disease.

The role of chemotherapy is primarily in the setting of hormone refractory prostate cancer. Based on the SWOG 9916 and the TAX 327 studies, both docetaxel and mitoxantrone resulted in similar increases in overall survival, time to disease progression, pain control and PSA response\(^12,13\). However, it was later reported that docetaxel had a 2.9 months survival difference over mitoxantrone.

While, neoadjuvant hormonal or radiation therapy may help reduce positive surgical margins rate, chemotherapy with taxanes may treat distant micrometastasis. The rate of organ confined disease was noted to be high in patients with locally advanced cT3 disease after receiving LHRH followed by combination of estramustine and docetaxel. The 5 year disease specific survival was 85%\(^14\). However, the routine use of taxanes in a neoadjuvant setting prior to RP is not routinely practiced as studies have been underpowered and none have shown any evidence to reliably eradicate disease.

Conclusions

The best treatment for high risk prostate cancer is to incorporate a multimodal treatment strategy and match it to the level of disease aggressiveness. Change in trends has shown that radical prostatectomy is a viable treatment option alone or in combination with androgen deprivation therapy or radiation therapy. Radiation therapy is best served when given in conjunction with hormonal therapy. Neoadjuvant chemotherapy remains in its early stages and requires further studies to validate its routine use. Currently it is restricted only to research studies and in hormone refractory prostate cancer patients.
Management of High Risk Prostate Cancer

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REFERENCES


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