UPDATES IN UROLOGY

President's Message,
Singapore Urological Association (SUA) aims to promote continuing medical education among professionals - specialists, general practitioners and family physicians. With the advancement in technology and innovation, there is a lot of new medical information. The Urology Updates series is a new initiative of SUA to provide practical and up to date information on common urological conditions for the medical professionals. The publication highlights the current trends in urology. The inaugural issue cover the topics on prostate cancer. Other urological conditions and issues will be covered in the upcoming series. We hope that our endeavor will improve your patient care and practice by keeping updated with the current treatments and latest surgical techniques in urology. Your suggestion and feedback is deeply appreciated.

Warm regards.

Dr Tan Yeh Hong
President, Singapore Urological Association

Dear colleagues,
It gives me immense pleasure to put this inaugural issue of the Urology focused newsletter in your hands. SUA is always at the forefront of organizing education activities and disseminating information through various forums. This newsletter is an initiative undertaken by the SUA to bring out the key insights, advances, developments and interesting updates from the field of Urology. We intend to make this publication a continuing affair. I sincerely hope you would find the information to be useful and applicable in your practice. We would be pleased to obtain your feedback and suggestions on the newsletter. I would also like to thank all the contributing Urologists for their researched and well-written articles.

Warm regards.

Dr. Ng Kok Kit
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PROSTATE CANCER SCREENING

IS IT STILL CONTROVERSIAL?

Serum prostate-specific antigen (PSA) screening was introduced to clinical medicine in the mid-1980s as a serum marker of prostate cancer and since then it has become the backbone of prostate cancer detection. There is convincing contemporary evidence that PSA-based screening programs result in the detection of many cases of asymptomatic prostate cancer and most recommendations for prostate cancer screening incorporate the measurement of PSA levels.
In 2012 the U.S. Preventive Services Task Force (USPSTF) released a recommendation against PSA–based screening for prostate cancer (grade D recommendation). The recommendation of the Task Force was based on the following assessments:

- The reduction in prostate cancer mortality 10 to 14 years after PSA-based screening is, at most, very small, even for men in the optimal age range of 55 to 69 years.
- PSA screening did not appear to reduce all-cause mortality. In contrast, the harms associated with the diagnosis and treatment of screen detected cancer are occur commonly, early, often persist, and may include a small but real risk of death.

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PROSTATE CANCER SCREENING

- In a substantial proportion of men who have asymptomatic cancer that were detected by PSA screening, the tumor will either not progress or progress so slowly that it would have remained asymptomatic during the man's lifetime, thus being often ascribed the terms “over-diagnosis” and “pseudo-disease”. Screening or treatment in such cases would have conferred no benefit, and would possibly result in overtreatment. Furthermore, there is a high propensity to treat most patients with screen-detected cancer, given the inability to distinguish tumors that would remain indolent from those destined to be lethal.
- It is suggested that many more men in a screened population may experience the harms of screening and treatment of screen-detected disease, than experience the benefit of early detection. In addition, false positive PSA test results have been closely linked to negative psychological effects, such as a persistent worry about prostate cancer.
- In a substantial proportion of men who have asymptomatic cancer that were detected by PSA screening, the tumor will either not progress or progress so slowly that it would have remained asymptomatic during the man's lifetime, thus being often ascribed the terms “over-diagnosis” and “pseudo-disease”. Screening or treatment in such cases would have conferred no benefit, and would possibly result in overtreatment. Furthermore, there is a high propensity to treat most patients with screen-detected cancer, given the inability to distinguish tumors that would remain indolent from those destined to be lethal.
- It is suggested that many more men in a screened population may experience the harms of screening and treatment of screen-detected disease, than experience the benefit of early detection. In addition, false positive PSA test results have been closely linked to negative psychological effects, such as a persistent worry about prostate cancer.

The Task Force thus concluded with moderate certainty that the benefits of PSA-based screening for prostate cancer do not outweigh the harms, given that a man's estimated lifetime risk of dying from prostate cancer is 2.8% and death would be extremely rare among men aged up to 60 years (as 70% deaths that were due to prostate cancer occur after age 75 years)

WHAT IS THE REFERENCE FOR THIS?

The USPSTF recommendation was based on two major trials of PSA screening: the U.S. PLCO (Prostate, Lung, Colorectal, and Ovarian) Cancer Screening Trial and the ERSPC (European Randomized Study of Screening for Prostate Cancer). The U.S. trial did not demonstrate any prostate cancer mortality reduction. The European trial found a reduction in prostate cancer deaths of approximately one death per 1,000 men screened in a subgroup of men 55 to 69 years of age.

However, weighing the relative potential benefits and harms of PSA-screening is difficult. The USPSTF’s recommendation came under criticism, due to the perceived “one-size-fits-all” approach to PSA testing, the possible overestimation of the harms and under-estimation of the benefits of PSA testing. A number of flaws in methodology and evaluation of results of the PLCO and ERSPC were the primary reasons for disagreement with the USPSTF's recommendation by a number of groups and associations. The major controversies surrounding USPSTF’s recommendation against screening are as follows:

PROSTATE CANCER SCREENING

A) PROSTATE, LUNG, COLORECTAL AND OVARIAN (PLCO) CANCER SCREENING TRIAL

The U.S. PLCO Cancer Screening Trial randomly assigned 76685 men aged 55 to 74 years to receive either annual screening for 6 years or “usual care” at 10 U.S. centers. Significant flaws in the PLCO are:

1) One of the most obvious problems identified by many in the PLCO trial is the extremely high contamination by screening of the so-called ‘control or usual care' group. It is estimated that the PLCO trial had ≥52% of men in their ‘control' arm who underwent screening as part of ‘usual care’ during the study. A fundamental requirement for a valid screening study is the absence or only minimal and well-documented contamination by screening in the control ‘unscreened' arm. With such a high rate of contamination, the PLCO study suffered from insufficient statistical power to detect a mortality difference. Computer simulation models indicate that contamination substantially limited the ability of the PLCO to identify a clinically significant screening benefit. As such, whilst the PLCO trial may show that annual screening does not reduce mortality relative to population screening, the substantial contamination would preclude it from concluding whether screening actually reduces mortality relative to no screening.

2) Pretrial PSA screening in ≥43% of the study cohort within 3 years of study entry would have eliminated many life-threatening prostate cancers from the study population..

3) PLCO's protocol did not include a biopsy recommendation for men with abnormal results, and about 60% of such men did not undergo biopsy within the first year, thus potentially compromising early detection and treatment. Also, PLCO enrolled men up to 74 years old who are less likely to have a screening benefit.

4) The 4-year interval between screenings in the PLCO study could have missed a significant proportion of detectable cancers. This was demonstrated by the observation that as many as 1755 cancers were diagnosed outside the screening protocol in the screening arm.

5) Furthermore, the compliance rate for men in the screening arm was only 85%.

PLCO reported higher but non-statistically significant prostate cancer mortality in its screening arm at 7 to 10 years follow-up, suggesting possible harm from screening. However, prostate cancer mortality was shown to be 25% lower amongst men who had undergone ≥2 PSA tests at baseline than in those who had not been tested. PLCO also reported a subset analysis in which subjects with minimal co-morbidity had 44% lower prostate cancer mortality with an NNT (number needed to treat) of 5. These were not considered by USPSTF in their recommendation.

The subsequent updated 13-year follow-up results showed a 9% higher prostate cancer mortality rate (but not statistically significant) in the screening arm, despite having proportionately less high-stage and high-grade disease. PLCO also re-examined the prostate cancer mortality rates by age, co-morbidity, and pretrial PSA testing. In their update, they changed the definition of co-morbidity to exclude many important conditions that could have affected clinical decisions and overall mortality. Using the new definition, no prostate cancer mortality benefit was reported in any of the subgroups. However, using a more complete definition of co-morbidity from their first subset analysis, there remained a statistically significant 27% lower prostate cancer mortality rate in subjects with minimal co-morbidity who underwent screening.

B) European Randomized Study of Screening for Prostate Cancer

The ERSPC (European Randomized Study of Screening for Prostate Cancer) randomly assigned 162,243 men aged 55 to 69 years from seven European countries to either PSA screening once every 4 years or an unscreened control group. ERSPC is suggested to be more informative than the PLCO, mainly because of the larger sample size and younger population studied. Also contributing to the strength of the study is the substantially lower rates of pre- and intra-trial screening of controls. In the ERSPC, very few men were screened prior to entry into the study and “contamination” of the control group was significantly lower at 15%. Compliance to biopsy recommendation was also much higher at 85%.

The main findings of the ERSPC at 9 years of follow-up were that the screening arm had a 71% higher detection rate of prostate cancer which also had a significantly lower proportion with high-risk tumors, a 41% lower rate of metastatic disease at diagnosis; and a statistically significant 20% reduction in the rate of prostate cancer death, which was observed largely in men younger than 70 years. However, when reviewing the ERSPC, the USPSTF included results from countries that enrolled men outside ERSPC's pre-specified age range and used the figures for calculation that statistically had negated the prostate cancer mortality benefit.

After a median 11 years of follow-up, the cumulative incidence of prostate cancer in the screened group and control group were 8.2% and 4.8% respectively. There was 21% reduction in prostate cancer mortality in the screened group compared with the control group and the reduction was more marked at 29% after adjusting for non-compliance. Furthermore, a secondary analysis of data from the Rotterdam site of the ERSPC showed that PSA screening reduced the risk of prostate cancer mortality by as much as 31%, after correcting for failure of subjects to have protocol-prescribed screening procedures and contamination. Despite these results, the USPSTF concluded that this reduced risk of dying from prostate cancer only amounted to few lives saved and did not outweigh the harms of screening, diagnosis, and the harms associated with treatment of screen-detected cancers.

C) Goteborg Trial

The USPSTF gave little weight to the Göteborg Randomized Population-Based Prostate-Cancer Screening Trial although it was considered to be a better conceived and executed randomized controlled trial (RCT). It had advantages of including younger men and longer follow-up. It also had a low contamination rate (pre- or intra-trial screening) of subjects at 3% and had low PSA cutoff values. Biopsy compliance for an abnormal screening test was 93% and 77% had 14 years of follow-up. The screening arm had 64% more prostate cancer cases diagnosed, and with fewer advanced cases, and 44% lower prostate cancer mortality rate. The number needed to treat to prevent one prostate cancer death (NNT) was 12, which was comparable with that of breast cancer screening. Although Goteborg is a stand-alone trial, designed and initiated before and independently of the ERSPC, the USPSTF discounted it as an independently confirmatory study because the Goteborg researchers contributed 60% of their subjects to ERSPC.

D) Emphasis on Epidemiologic Data

The USPSTF did not give weight to epidemiologic data that showed that since the widespread use of PSA testing began in the early 1990s, there has been a 40% decrease in prostate cancer deaths and a 75% decrease in presentation with advanced disease at initial diagnosis, which was attributed, in large part, to PSA screening. One of the reasons cited, was that it would have been impossible to reliably separate out the relative effects of screening from changes in diagnosis or treatment practices that could have occurred simultaneously during that time period. Another reason cited, was that data from randomized trials had suggested that potential mortality benefit from screening would not have occurred for at least 7 to 10 years, thus making it uncertain that the mortality rate decline seen in the USA, was really related to PSA screening.

E) Age

Another unaddressed issue is that the Task Force recommendation opposes PSA testing regardless of age. The expected life span for a man aged 75 years is approximately 10 years but reaches 30 years for men at age 45 to 50 years. It is plausible to expect that many men aged 75 years or older will die of other causes before developing metastatic prostate cancer, but the current recommendation, arguably to avoid adverse effects of screening, could result in delayed diagnosis of curable cancer in young men who may then present with advanced disease and illness and ultimately die of prostate cancer.

F) Other Limitations

- For men aged 50 to 60 years, who are likely to live much longer than 10 years, the results of the PRCO and ERSPC studies at 10-year median follow-up and may be too premature to conclude.

- The USPSTF analysis focused on mainly on mortality and did not consider the substantial illness associated with living with advanced cancer, such as painful bone metastases, pathologic fractures, and urinary tract obstruction.

- Furthermore, the USPSTF's recommendation lacks adequate consideration for high-risk populations, including men with a significant family history of prostate cancer and men of African descent, who have a higher risk of developing prostate cancer and a 2- to 3-times higher risk for dying from it compared with men of non-African descent.

PRACTICAL CONSIDERATIONS

Early detection of cancer has been a mainstay of modern medicine, and that although PSA testing is imperfect; its elimination would create a tremendous void in the early detection of prostate cancer. American Urologic Association (AUA) asserts that the PSA test "provides important information in the diagnosis, pre-treatment staging or risk assessment and monitoring of prostate cancer patients.

But not all prostate cancers are life threatening. The decision to proceed to active treatment or use surveillance for a patient's prostate cancer is one that men should discuss in detail with their urologists". The use of active surveillance has become much more common in recent years, in an attempt to treat only those cancers that are life threatening.

The American Society of Clinical Oncology (ASCO) has issued a provisional clinical opinion on the use of PSA testing to screen for prostate cancer in men with no symptoms of the disease:

- For men expected to live 10 years or less, general screening is not recommended because the risks appear to outweigh the benefits for most men.
- For men expected to live longer than 10 years, patients should talk about PSA testing with their doctors to find out if it is an appropriate test for them.

The current diversity of study methodology and available data allows for significant flexibility in their interpretation, which makes it difficult to use them to substantiate across-the-board recommendations. Rather, the decision of whether to screen or not to screen-using PSA testing and/or other means—is a decision best made between physicians and their individual patients.

MAN AND MACHINE

ROBOTIC PROSTATECTOMY

Radical prostatectomy (RP) is one treatment option available to men with clinically localized or selected locally advanced prostate cancer. Generally, the choice of treatment is dependent on the patients' cancer stage, age, comorbidities, potential complications and their personal preferences. Traditionally RP was performed via the open approach (ORP). Millin first carried out retropubic prostatectomy back in 1947, albeit with significant complications.[a] It was not until the 1970 and 1980s when Walsh reported his techniques of anatomical and physiological RRP that complication rates, especially those related to bleeding and sexual function, plummeted. This laid the foundation for ORP to eventually become the mainstay treatment for many years and the standard on which other surgical approaches are compared with. The first laparoscopic RP (LRP) was done in 1991, by Schuessler et al[1] and from then on it slowly gained acceptance.

However, the technical demands of the surgery and the protracted learning curve[2] prevented the widespread adoption of LRP by most urological surgeons. Specifically, the restricted ergonomics, two-dimensional vision, counter-intuitive hand-eye co-ordination between actual and intra-corporeal movements, and the reduced haptic sense are the main obstacles associated with a steep learning curve.[3]

The introduction of advanced robotic platforms such as the da Vinci Surgical System (Intuitive Surgical, Inc., Sunnyvale, CA, USA) into urological surgery armamentarium revolutionized the field of minimally invasive prostatectomy. The first robotic-assisted laproscopic surgery was performed in 2001 and since then techniques in RARP have continued to improve. There is currently little consensus among the urology community around the world with regards to the optimal surgical treatment of localized prostate cancer. This is largely attributed to the paucity of high-quality data showing relative superiority of one approach over the others. Indeed, major international urology guidelines do not recommend one surgical approach over the others because of the lack of compelling evidence in this aspect. However today, there is mounting evidence to suggest that RARP is associated with shorter OR time, decreased blood loss and transfusion rate, shorter LOS, less pain and promising continence, potency and oncological outcomes when compared to contemporary RRP and LRP series.

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ADVANTAGES OF ROBOTIC TECHNIQUES

- The da Vinci Surgical Platform automatically restores the optically correct hand-eye coordination between the camera and the robotic instruments, making surgery more intuitive. This is more difficult with laparoscopy, in which the camera is sometimes offset to the plane of dissection.
- The camera telescope in the da Vinci system is a combination of two optical channels (one for the right eye and one for the left eye), and these 2 images are displayed in the console to provide 3-dimensional (3-D) stereoscopic vision to the surgeon, providing depth perception lacking in conventional laparoscopy. The conventional laparoscopic technique does not provide a 3-D depth of view.

- The movements of the robotic system are intuitive (ie, a movement of the master control to the right causes the instrument to move to the right), as opposed to the counterintuitive movements in laparoscopy due to fulcrum movement effects (ie, movement of the laparoscopic instrument to the right by the surgeon causes the tip of the instrument to move to the left inside the patient's body).

- The robotic system provides increased precision by filtering hand tremors, providing magnification (up to 10-15 times) and providing scaling for the surgeon's movements (a 1:3 scaling means that a 3-inches movement of the master is translated into a 1-inches movement of the robotic instrument).

- The robotic instruments have articulated tips, which permit 7° of freedom in movements (ie, they mimic human wrist movements, including rotation), which is unlike conventional laparoscopy, with which only 4° of freedom are permitted.

INDICATIONS FOR RARP ACCORDING TO INTERNATIONAL GUIDELINES-

American Urological Association, 2007	European Association of Urology, 2011	National Comprehensive Cancer Network, 2011
Low-risk localized PCa	Low- and intermediate-risk localized PCa and a life expectancy >10 yr	Very low-risk cancer (T1c, GS ≤6, PSA <10, <3 positive prostate biopsy cores, ≤50% cancer in any core) and life expectancy >20 yr
Intermediate-risk localized PCa	Selected patients with low-volume high-risk localized PCa	Low- and intermediate-risk patients with life expectancy survival >10 yr
High-risk localized PCa	Highly selected patients with very high-risk localized PCa (cT3b–T4 N0 or any T N1) in the context of multimodal treatment	High-risk and very high-risk (T3b–4) patients

EVALUATION OF CLINICAL EVIDENCE ON RARP-

Traditionally, the “holy grail” of RRP is the trifecta outcomes - namely biochemical recurrence-free survival, urinary continence and potency.[2]

However, in the light of the increasing expectation of surgeons and patients, some authors have recently extended the trifecta to a pentafectac, with the addition of negative surgical margins and the absence of perioperative complications.

Although radical retropubic prostatectomy is the gold standard for the treatment of clinically localized prostate cancer, RALP has yielded comparable and promising outcomes in medium to long-term follow-up series.

ONCOLOGIC OUTCOMES

The ultimate aim of all radical prostatectomies of curative intent is to prevent clinical progression and death from prostate cancer. Treatment failure was historically defined as clinically evident local recurrence or development of distant metastasis. However, because of the protracted natural history of prostate cancer, clinical recurrence might take many years to manifest, thus biochemical (PSA) recurrence and positive surgical margins (PSM) are often taken as surrogate markers. However of note, not all PSM on histology or PSA recurrence will eventually lead to eventual clinical recurrence of cancer.

A recent meta-analysis of comparative trials of RARP versus ORP or LRP reported similar overall PSM rates (RARP vs ORP: odds ratio [OR]: 1.21; p = 0.19; RARP vs LRP: OR: 1.12; p = 0.47). Subset analysis of only pathologically localized prostate cancers (pT2), PSM rates (RARP vs ORP: OR: 1.25; p = 0.31; RARP vs LRP: OR: 0.99; p = 0.97), and BCR-free survival estimates (RARP vs ORP: hazard ratio [HR]: 0.9; p = 0.526; RARP vs LRP: HR: 0.5; p = 0.141), regardless of the surgical approach. This led to the authors to conclude that PSM rates are similar following RARP, ORP, and LRP. The few data available on PSA recurrence are promising, but definitive comparisons with RRP or LRP/ORP are not currently possible. Finally, significant data on cancer-specific mortality are not currently available.

FUNCTIONAL OUTCOMES

With long-term survival ensured for localized prostate cancer, functional outcomes (urinary continence and potency) have become the focus of prostatectomy. Analyzing functional outcome data is hampered by the lack of standardized criteria for assessment of continence and potency.

In general, just looking at high level evidence, recent meta-analyses of functional outcomes after prostatectomy seemed to favour RARP over LRP or ORP. With regards to 12-month continence rates, compared with ORP, RARP was associated with better continence in 2 of 2 recent meta-analyses.[e,f] Compared with laparoscopic approach, RARP was associated with better continence in 2 of 3 meta-analyses.[e,f,g]

With regards to 12-month potency rates, results tend to favour RARP over ORP. 2 recent meta-analyses reported RARP being associated with better potency rate at 12 months.[g,h] However, no significant differences in potency rates were found when compared with LRP.

PERIOPERATIVE OUTCOMES

Primum non nocere (First, do no harm) has always been the fundamental belief in the history of medicine. The epitome of oncological surgery is complete oncological clearance with no morbidities or complications. However, this is impossible to guarantee in most if not all surgeries. As such, perioperative and postoperative morbidities and complications are equally important considerations in patients' choice of therapy. Patients should never suffer more from their treatment than from their disease itself.

The main reasons for the introduction of MIS were smaller incisions, shorter hospital stays, and decreased convalescence with lesser complications. Not surprisingly, most studies analyzing perioperative outcomes favor RARP over ORP. In a paper that provides a contemporary snapshot of current

perioperative outcomes, Trinh et al[g] assessed the rate of RARP utilization and the differences in perioperative complication rates between RARP and ORP. Of 19,462 surgeries performed, 61.1% were RARPs, 38.0% were ORPs, and 0.9% were LRPs. Patients undergoing RARP were less likely to receive a blood transfusion (odds ratio [OR]: 0.34; 95% confidence interval [CI], 0.28–0.40), to experience an intraoperative complication (OR: 0.47; 95% CI, 0.31–0.71), to experience a postoperative complication (OR: 0.86; 95% CI, 0.77–0.96), or to have a prolonged length of stay (OR: 0.28; 95% CI, 0.26–0.30). Moreover, when individual postoperative complications were examined, cardiac, respiratory, and vascular complications were found to be less likely to occur in patients undergoing RARP than in patients undergoing ORP, indicating a beneficial effect of RARP on medical complications as well. Recent meta-analyses also echoed similar finding

CONCLUSION

RARP has allowed more surgeons to offer patients a minimally invasive approach. In terms of perioperative outcomes, there is clear evidence showing shorter hospital stays, less blood loss, lower complication rates, and shorter convalescence with RARP. With regard to functional and oncologic outcomes, there is a definite trend towards better results with RARP. Long-term studies and more uniform data reporting are needed to definitively answer the question of which approach is associated with better outcomes. However, in this face-off of man versus man and machine, Man and Machine might eventually prevail.

RADIOTHERAPY FOR PROSTATE CANCER

WHAT'S NEW?

Radiotherapy has been driven by constant technological advances since the discovery of X-rays in 1895 and remains a standard option for men with localized prostate cancer. Alone or in combination with androgen-deprivation therapy, it represents a curative treatment and has been shown to prolong survival in selected populations.Radiotherapy aims to sculpt the optimal isodose on the tumour volume while sparing normal tissues. The benefits are threefold: patient cure, organ preservation and cost-efficiency.

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Recent years have seen dramatic improvements in the treatment of prostate cancer with radiation. Advances related to treatment techniques, photon versus proton radiation, modification of treatment fractionation, and brachytherapy focus on better disease control and impact on morbidity.

Along with these advances, refinements in risk stratification of men with prostate cancer help in matching patients to appropriate treatments better than ever before and improve treatment options, in particular around the use and duration of concurrent hormonal therapy. For the 90% of men who have localized prostate cancer at diagnosis after PSA screening, the risk groups are commonly defined by the tumor (T)-classification, the Gleason score, and the PSA level at diagnosis. Classically, these were defined as low-risk (Gleason ≤6, and PSA <10 ng/mL, and T1-T2a), intermediate-risk (Gleason 7, or PSA 10-20 ng/mL, or T2b), and high-risk (Gleason 8-10, or PSA >20 ng/mL, or ≥T2c) disease, but refinements into 5 strata are now represented in the National Comprehensive Cancer Network (NCCN) guidelines –[6]

Risk Stratification	PSA	Gleason Score	Clinical Stage
Very Low Risk	< 10 ng/ml (and PSA density <0.15 ng/ml/g)	and ≤ 6 (and < 3 positive cores and ≤ 50% of any one core)	and T1-T2a
Low Risk	< 10 ng/ml	and ≤ 6	and T1-T2a
Intermediate Risk	10 - 20 ng/ml	or 7	or T2b - T2c
High Risk	> 20 ng/ml	or 8 - 10	or T3a
Very High Risk			T3b or T4

RADIOTHERAPY FOR PROSTATE CANCER

RISK STRATIFICATION AND RADIOTHERAPY– [7]

- For men with low-risk and favorable intermediate-risk prostate cancer who favor treatment over active surveillance and wish to receive radiation, both brachytherapy and external beam radiation are options. Decisions between the 2 should be made based on patient factors and the anticipated differences in short-term and long-term toxicities

- For men with unfavorable intermediate-risk prostate cancer who elect to have radiation, evidence suggests that 4 to 6 months of ADT should be added.

- For men with high-risk disease, the exact duration of ADT is not yet established but can range from 28 to 36 months and possibly can be as little as 18 months.

ADVANCES IN TREATMENT MODALITIES

A) External Beam Radiation (EBR)

Dose investigating randomized studies with EBR showed statistically significant improvements in disease control but without improvements in overall survival in the higher dose arms. Also, these improvements come at the cost of increased toxicity. This recognition of improved disease control at the cost of increased toxicity has been a driving force for technologic advances in improving the conformality of treatment in EBR for prostate cancer.

- ### Three-Dimensional Conformal Radiation to IMRT

In the previous standard 3-dimensional (3D) conformal radiation therapy (CRT), in which multiple shaped radiation beams were used to limit dose to structures other than the prostate. Although this approach allowed improved conformality, the use of more advanced imaging, and escalation of the radiation dose, there were limitations in its ability to constrain high doses of radiation to the immediately adjacent bladder and rectum. Intensity modulated radiation therapy (IMRT) evolved from 3DCRT but, rather than using fixed radiation portals, treatment planning takes place through an iterative, computer-based optimization to create dynamic fields that vary in intensity across their cross section. The result is a 3D dose volume that more closely conforms to the specific patient's anatomy with steep dose gradients between the target and nearby normal structures. As measured by the distribution of dose to the target and normal tissues, IMRT can improve target coverage and reduce the dose to organs at risk relative to 3DCRT.Furthermore with the advances in imaging and onboard verification systems as part of image guided radiotherapy (IGRT) the capabilities of IMRT enable an even more sophisticated dose distribution and are the reasons for further dose escalation and hypofractionated schemes.[14]

- ### Proton Radiation Therapy

Protons differ from the high-intensity x-rays typically used in radiation treatments in how they interact with tissue to deposit radiation dose. Although they are no more effective biologically than the x-rays used in typical external beam radiation, the physical properties of protons result in the ability to regulate the range they penetrate within the body. The resulting sparing of damage to tissue before and beyond the target is unattainable with traditional x-ray–based approaches and makes proton beam radiation appealing dosimetrically.

- ### Hypofracionated Radiation

Delivering radiation in small doses, or fractions, over several weeks is an established way of sparing normal tissue relative to tumor, thereby improving the therapeutic ratio. Hypofractionation is the delivery of fewer, larger fractions. The biologic underpinnings of the importance of fractionation relate to the relative DNA repair mechanisms to sublethal damage within different cell types. Summarized by the alpha-beta ratio (α/β), it has generally been believed that this sensitivity to fractionation is high for tumors and low for the late effects in normal tissues. The result is that, if a tumor has a lower α/β than the nearby normal tissue, then

RADIOTHERAPY FOR PROSTATE CANCER

hypofractionation may improve outcomes. There is a growing body of evidence suggesting that prostate cancer has a low α/β-level of 1.4 Gy and therefore lower than that of surrounding organs at risk, such as rectum or bladder. This poses a therapeutic rationale for hypofractionation with the possible result of a better tumor control at a lower toxicity rate. Vital for a safe application of hypofractionated schemes are IMRT and IGRT. These tools are the technical prerequisite for administering high single doses.[14]

B) Brachytherapy

Low-dose-rate brachytherapy with iodine or palladium remains the most common approach for prostate cancer, but high-dose-rate brachytherapy is increasingly used. This technique uses iridium-192 as a source and radiobiologically, this approach more closely corresponds to hypofractionated treatment. The latter approach allows for the treatment of higher risk features, such as extracapsular extension. Typically delivered over fewer than 10 fractions, several single-institutional series have demonstrated both excellent disease control and modest acute GU and GI side effects. 15 In this technique, catheters are placed transperineally into the prostate, and the radioactive source on a wire is sequentially threaded down each catheter and withdrawn at an appropriate rate to shape the radiation to the prostate; this procedure is repeated for each fraction.

Recent years have seen dramatic advances in the treatment of prostate cancer with radiation. The advantages of the modern approaches lie in their ability to escalate the tumor dose (thus enhancing disease control) while minimizing toxicity to normal tissue (thus improving patient compliance and satisfaction).

The coming years should bring results from hypofractionation trials to guide the widespread adoption of this potentially more convenient treatment approach. With the recently expanded availability of molecular and genetic tests of localized and resected prostate cancer, there should be further significant refinements in predicting the aggressiveness of disease in the near future.

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