Principles of Management of Localized Prostate Cancer

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Characteristics of Prostate Cancer

1. Age is the most important risk factor:

- Increasing prevalence attributed to increasing life expectancy
- More common in elderly patients
- Co-morbidities should always e considered
- Need not always be the cause of death
- Treatment is NOT always necessary

2. Long latent period:

- Up to 10 years
- Slow growing tumour, tumour doubling time of 3 to 4 months
- Amenable for screening

Characteristics of Prostate Cancer

3. Tumour marker:

- Sensitive and reproducible assay for PSA
- Not tumour specific, but organ specific
- Raised in non malignant prostatic conditions also
- Often combined with digital rectal examination for screening
- To increase specificity, other indicators like PSA density, PSA velocity, free / total PSA ratio, etc are used

PSA level (ng/mL)	Risk of PCa (%)
0.0-0.5	6.6
0.6-1.0	10.1
1.1-2.0	17.0
2.1-3.0	23.9
3.1-4.0	26.9

Characteristics of Prostate Cancer

4. Hormone dependent:

- Endocrine manipulation is an option
- Development of hormone resistance over time, due to selection of hormone independent clones has been observed
- Short tumour doubling times of < 1 month have been observed, as hormone resistance develops → rapid progression

5. PFS vs OS:

- Significant gap between PFS and OS curves
- Implies indolent disease, and salvageability of recurrences

AJCC Stage Grouping

Group	T	N	M	PSA	Gleason
I	T1a-c	N0	M0	PSA <10	Gleason ≤6
	T2a	N0	M0	PSA <10	Gleason ≤6
	T1-2a	N0	M0	PSA X	Gleason X
IIA	T1a-c	N0	M0	PSA <20	Gleason 7
	T1a-c	N0	M0	PSA ≥10 <20	Gleason ≤6
	T2a	N0	M0	PSA <20	Gleason ≤7
	T2b	N0	M0	PSA <20	Gleason ≤7
	T2b	N0	M0	PSA X	Gleason X
IIB	T2c	N0	M0	Any PSA	Any Gleason
	T1-2	N0	M0	PSA ≥20	Any Gleason
	T1-2	N0	M0	Any PSA	Gleason ≥8
III	T3a-b	N0	M0	Any PSA	Any Gleason
IV	T4	N0	M0	Any PSA	Any Gleason
	Any T	N1	M0	Any PSA	Any Gleason
	Any T	Any N	M1	Any PSA	Any Gleason

Localized Prostate Cancer??

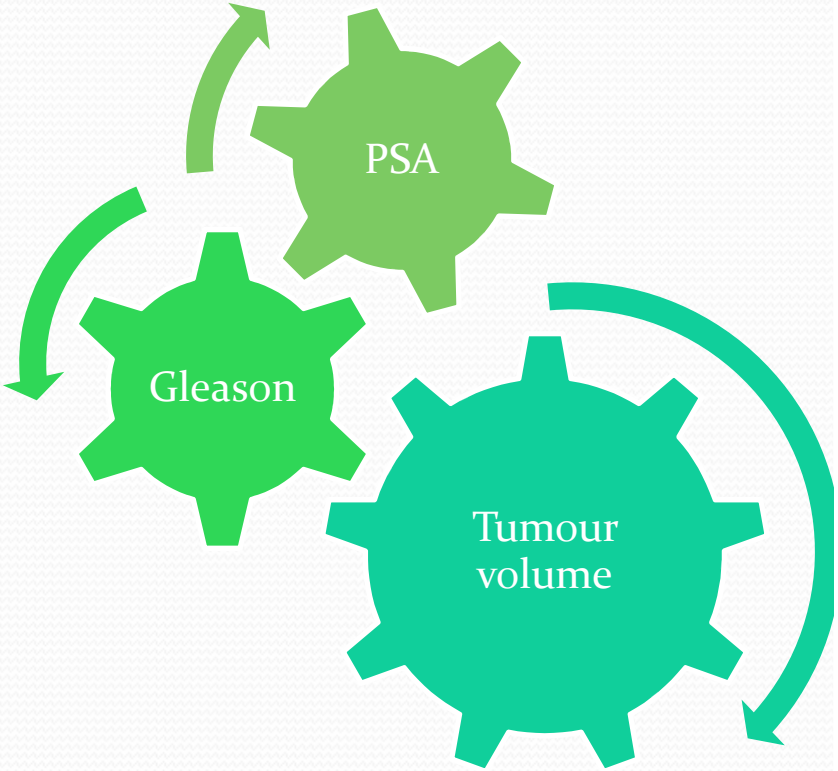
- Adapted from D'Amico's classification system
- TNM stage, serum PSA, and Gleason's score
- Risk groups based on biochemical recurrence free survival, when treated with surgery or radiotherapy

Table 4.1.2: EAU risk groups for biochemical recurrence of localised and locally advanced prostate cancer

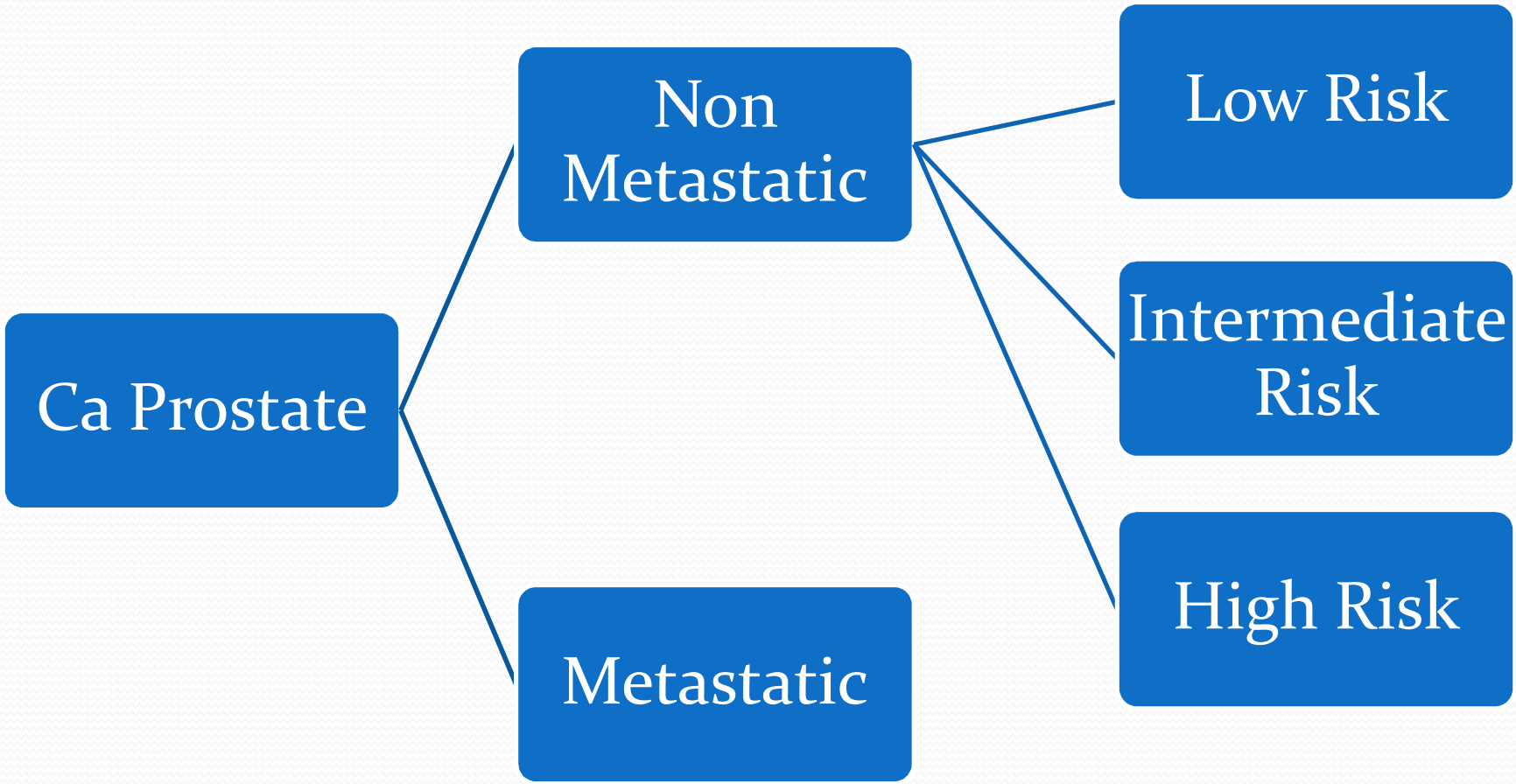
	Low-risk	Intermediate-risk	High-risk	
Definition	PSA < 10 ng / mL and GS < 7 and cT1-2a	PSA 10-20 ng /mL or GS 7 or cT2b	PSA > 20 ng / mL or GS > 7 or cT2c	any PSA any GS cT3-4 or cN+
	Localised			Locally advanced

Principles of Risk Stratification

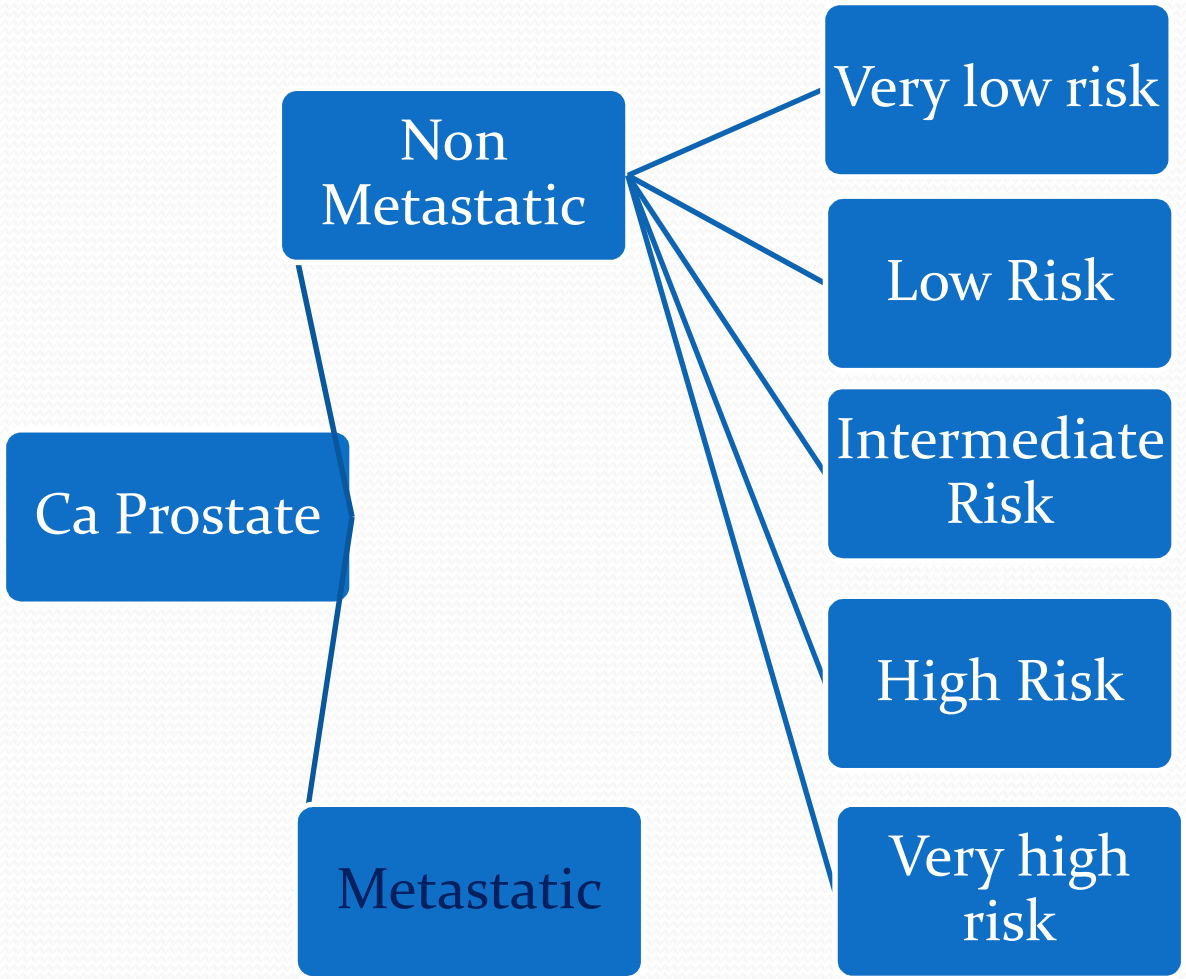
- Unlike other cancers, stage is not the only determinant of outcomes
- PSA levels, as well as the grade of the tumour (determined by the Gleason score) have important prognostic significance
- Moreover, these risk factors are interdependent
- Necessary to identify *RISK GROUPS instead of RISK FACTORS* for prognostification



Principles of Risk Stratification



Principles of Risk Stratification



Principles of Risk Stratification

Low:
- T1-T2a
- Gleason score ≤6
- PSA <10 ng/mL

High:[e]
- T3a or
- Gleason score 8–10 or
- PSA >20 ng/mL

Very Low:
- T1c
- Gleason score ≤6
- PSA <10 ng/mL
- Fewer than 3 prostate biopsy cores positive, ≤50% cancer in any core
- PSA density <0.15 ng/mL/g

Intermediate:[e]
- T2b-T2c or
- Gleason score 7 or
- PSA 10–20 ng/mL

Very High:
- T3b-T4
- Primary Gleason pattern 5 or
- >4 cores with Gleason score 8–10

Options Available

- Observation alone
- Active Surveillance
- Radiotherapy
- Surgery
- Androgen Deprivation Therapy

Principles of “Observation”

- Increasing screening lead to huge increase in the diagnosis of very early stages of prostate cancer in a large number of patients, especially the elderly
- Relative risk of dying due to malignancy in some of these cases is very less
- Treating or even actively following up all such patients will result in un necessary burden on the health care system, as well as creates un necessary toxicity
- A “very low risk group” has been separated from the low risk group

- Risk of cancer related death in a 20 year follow up period was less than 10% in these very low risk patients
- Hence, option of Treatment is offered ONLY if the life expectancy is more than 20 years
- Those with a life expectancy of 10 to 20 years, are best offered Active Surveillance
- Only “Observation” is offered for those with life expectancy less than 10 years

The 2014 NCCN Guidelines for Prostate Cancer distinguish between active surveillance and observation. Both involve no more often than every-6-month monitoring but active surveillance may involve surveillance prostate biopsies. Evidence of progression will prompt conversion to potentially curative treatment in active surveillance patients, whereas monitoring continues until symptoms develop or are eminent (ie, PSA >100 ng/mL) in observation patients, who will then begin palliative ADT.

Principles of “Active Surveillance”

- Different from “Observation”
- Active monitoring of disease
- Expectation to intervene with CURATIVE INTENT, when progression occurs, as compared to palliative intent in “observation”
- May include regular (6 monthly) PSA monitoring, Digital Rectal Examinations (yearly) or even Surveillance biopsies to see progression of Gleason scores
- Offered for those with a life expectancy of > 10 years

- Avoids possible side effects of treatment that may be unnecessary
- Reduced health care burden on patient as well as the system

- Inherent risk of a “missed opportunity for cure”
- Anxiety of receiving no treatment may impair the quality of life

Problems for Developing Countries

- Estimation of life expectancy
- Screening costs
- Burden on health care system to handle “very low risk and low risk” cases
- Compliance for follow up

Principles of Surgery

- Radical prostatectomy is the standard of care
- Nerve sparing can be done to preserve erectile function, in high volume tertiary centers
- Bladder neck preservation and sphincter preservation for maintenance of urinary continence
- Robotic assisted → Laparoscopic → Open RP have similar survival rates, with increasing complication rates
- Ro resection should be the aim

Principles of Surgery

- Previous concept: Pelvic LND should be done for all high risk cases
- Present concept: Using normograms, the risk of occult disease in the pelvic lymph nodes should be estimated, and PLND performed only in those with a risk >2%
- If PLND is performed, extended PLND yields better results compared to standard PLND

Principles of Radiotherapy

Tumour	Surrounding Normal Tissues
Moderately Radiosensitive	Radiosensitive
Low alpha/beta (lower than the normal tissues???)	Low alpha/beta
Minimal movement with respiration	Significant change in volume and position during between fractions
Small volume of treatment, with minimal volume changes during treatment	

- High doses to tumour are required for cure
- RT of fewer, larger fractions can be used for therapeutic efficiency
- Normal tissue toxicity is of great concern, and is volume dependent
- Rapid fall off of dose is desirable
- High precision during dose escalated radiotherapy is paramount

How to escalate the dose??

- High precision external beam radiotherapy
- Altered fractionation schedules
- Brachytherapy

Dose escalation using Precision radiotherapy

Evolution of EBRT techniques

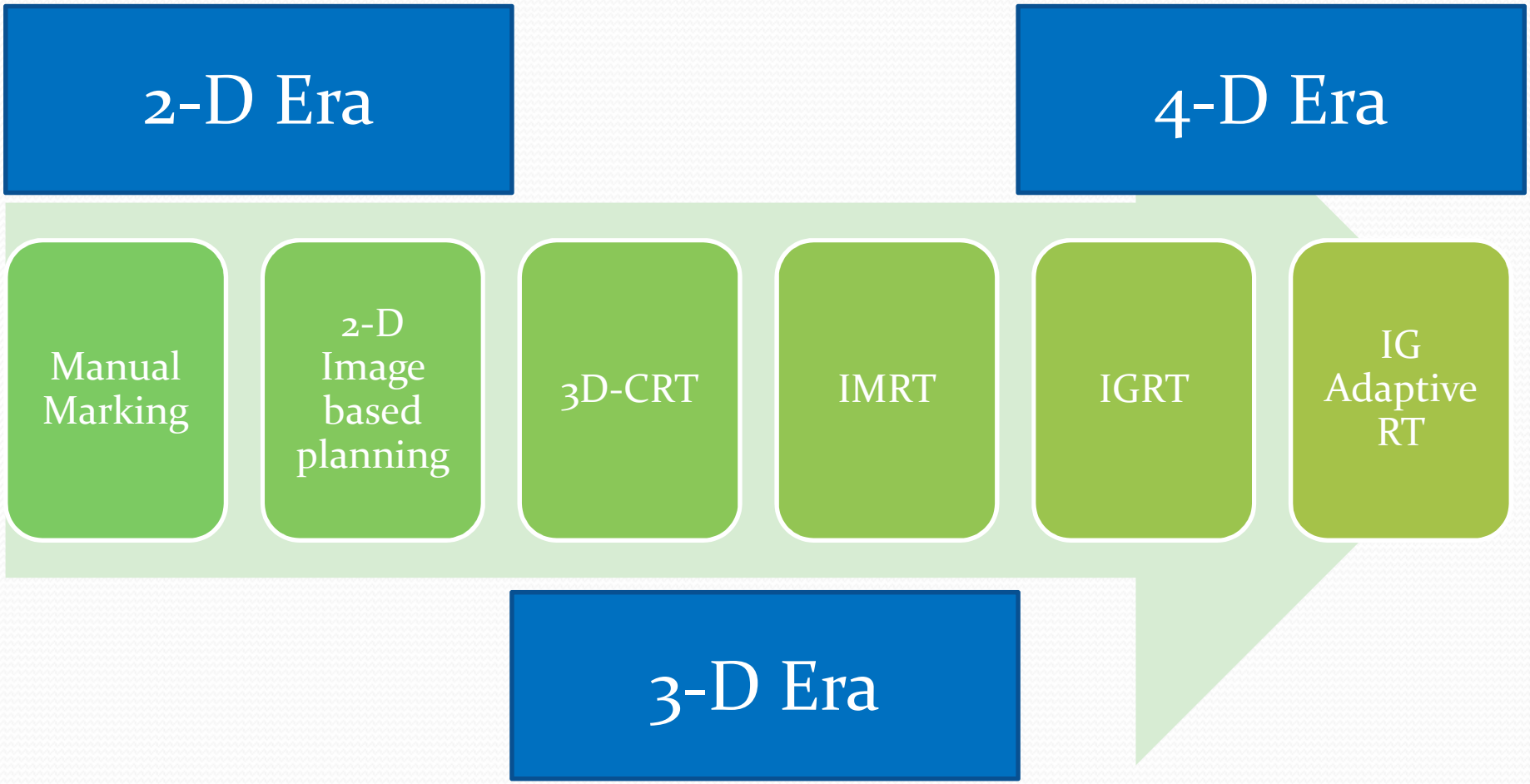


Image guidance techniques

2D on board imaging	EPID kV X rays	skeletal o precise
2D imaging plus Implanted fiducials	EPID kV X ra	on s a
3D on board imaging	CBCT USG	g n
3D imaging plus implanted fiducials	CBCT USG	ntage alone

75.6 Gy to 79.2 Gy for Low Risk cases

81 Gy to Intermediate and High Risk cases

Role of Whole Pelvic RT??

- No role of whole pelvic RT in cases of low risk and intermediate risk prostate cancer
- Based on the extrapolation from surgical series → omission of whole pelvic RT being considered, even for high risk cases
- Multiple studies → RTOG 9413, GET-TUG, RTOG 0924 → no significant difference
- In practice, similar to surgical approach, normograms can be used to predict the incidence of pelvic nodal metastases in clinically node negative cases, and treatment decisions made accordingly

Dose escalation using altered fractionation

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Indian J Urol. 2012 Jul-Sep; 28(3): 300–306.
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PMCID: PMC3507400

Dosimetric comparis… …nsional conformal radiothe… …dulated radiotherapy boo… …) with simultaneous in… …tment plan in patients

A. Bansal, R. Kapoor, …

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Original A…

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For identical PTV coverage, SIB-IMRT markedly reduced doses to critical structures

SIB-IMRT achieves lesser NTCP than sequential-IMRT

SIB can be considered as an alternative strategy for dose escalation

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Randomized Trial of a Hypofractionated Radiation Regimen for the Treatment of Localized Prostate Cancer

Charles N. Catton, Himu Lukka, Chu-Shu Gu, Jarad M. Martin, Stéphane Supiot, Peter W.M. Chung, Glenn S. Bauman, Jean-Paul Bahary, Shahida Ahmed, Patrick Cheung, Keen Hun Tai, Jackson S. Wu, Matthew B. Parliament, Theodoros Tsakiridis, Tom B. Corbett, Colin Tang, Ian S. Dayes, Padraig Warde, Tim K. Craig, Jim A. Julian, and Mark N. Levine

- March, 2017
- 60 Gy in 20 fractions, at 3 Gy per fraction
- IGRT was used
- Non inferior to conventionally fractionated regimes
- Additional benefit of short treatment duration

Dose escalation using Brachytherapy

Principles of Brachytherapy

As a Monotherapy:

- Ultra low dose rate brachytherapy is used
- Permanent implantation
- For Low Risk cases and limited volume Intermediate Risk cases
- Dose depends on the isotope used
- Iodine 125 (144 Gy); Pd 103 (125 GY)

Principles of Brachytherapy

As a Boost after EBRT:

- Permanent implant of Ultra low dose rate (ULDR) or temporary implant of high dose rate(HDR) isotopes can be used
- For Large volume Intermediate risk cases and High risk cases
- 45 Gy to 50.4 Gy of EBRT
- Boost dose depends on the dose rate and the isotope used
- ULDR: Iodine 125 (100 Gy to 110 Gy); Pd 103 (90 Gy to 100 GY)
- HDR: Iridium 192 (21 Gy in 2 fractions or 15 Gy in single fraction)

Principles and Indications of Androgen Deprivation Therapy

- Surgical castration → Bilateral Orchiectomy
- Medical castration → GnRH agonist/antagonist
- Equivalent outcomes with both modalities
- Medical castration is generally preferred for short term androgen deprivation therapy
- Combined Androgen Deprivation using androgen receptor antagonists → widely practised → additional benefit over ADT alone is being debated

- No definitive role in Very low and Low risk cases
- In those receiving radiation as treatment, use of ADT in adjuvant settings has been proven to be beneficial
- Given as short course adjuvant therapy (6 months) for Intermediate risk cases, and long course adjuvant therappy (2 to 3 years) for High risk cases
- In those undergoing surgical management, no evidence to support use of ADT in neo adjuvant or adjuvant setting, unless pathologically node positive
- ADT should never be used as monotherapy for localized prostate cancer

Very Low Risk

Life Expectancy	Options
< 10 years	Observation
10 to 20 years	Active Surveillance
> 20 years	Active Surveillance
	RT
	Surgery

Low Risk

Life Expectancy	Options
< 10 years	Observation
> 10 years	Active Surveillance
	RT
	Surgery

Intermediate Risk

Life Expectancy	Initial Therapy	Adjuvant Therapy
< 10 years	Observation	
	RT	ADT (short course)
> 10 years	RT	ADT (short course)
	Surgery	RT if adverse features ADT if LN positive

High Risk

Initial Therapy	Adjuvant Therapy
RT	ADT (long course)
Surgery	RT if adverse features ADT (long course) if LN positive

Very High Risk

Initial Therapy	Adjuvant Therapy
RT	ADT (long course)
Surgery	RT if adverse features ADT (long course) if LN positive
Treat like metastatic disease, with ADT alone (selected patients)	

Conclusion

- Ca Prostate is a slow growing malingnancy.
- Identification of various risk factors is important for tailoring the treatment in localized prostate cancer.
- It is of Paramount importance to have risk adopted treatment approach.
- Focus on preventing long term complications is important because of long term survivals.