Systemic Treatment Options in Urological Malignancy

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Scope of Presentation

- Prostate cancer
- Urothelial cancer
- Kidney cancer

Systemic Treatment Options

- Cytotoxic chemotherapy
- Hormonally directed therapy (anti-androgen)
- Monoclonal antibody/Immune therapy
- Small molecule tyrosine kinase inhibitors (TKIs)

Prostate Cancer

- Prostate cancer is among the most common cancers in men worldwide, with an estimated 1,600,000 cases and 366,000 deaths annually. In the United States, 11 percent of men are diagnosed with prostate cancer over their lifetime, with the incidence generally rising with age. There are an estimated 165,000 cases and 29,000 deaths annually. The overall five-year survival rate is over 98 percent.

Prostate cancer: Risk stratification and choice of initial treatment

- Anatomic extent of disease (Tumor, Node, Metastasis [TNM] stage)
- Histologic grade (Gleason score/grade group) and molecular characteristics of the tumor
- Serum PSA level
- Estimated outcome with different treatment options
- Potential complications with each treatment approach
- The patient's general medical condition, age, and comorbidity, as well as individual preferences

Initial Screening

- PSA measurement
- DRE
- CT/WBBS/MRI pelvis +/- PSMA PET scan
- Biopsy (transrectal or transperineal)
- Gleason grade and % of cores involved used in risk stratification

Prostate cancer TNM staging AJCC UICC 8th edition

Primary tumor (T)

Clinical T (cT)

T category	T criteria
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Clinically inapparent tumor that is not palpable
T1a	Tumor incidental histologic finding in 5% or less of tissue resected
T1b	Tumor incidental histologic finding in more than 5% of tissue resected
T1c	Tumor identified by needle biopsy found in one or both sides, but not palpable
T2	Tumor is palpable and confined within prostate
T2a	Tumor involves one-half of one side or less
T2b	Tumor involves more than one-half of one side but not both sides
T2c	Tumor involves both sides
T3	Extraprostatic tumor that is not fixed or does not invade adjacent structures
T3a	Extraprostatic extension (unilateral or bilateral)
T3b	Tumor invades seminal vesicle(s)
T4	Tumor is fixed or invades adjacent structures other than seminal vesicles such as external sphincter, rectum, bladder, levator muscles, and/or pelvic wall

Pathological T (pT)

T category	T criteria
T2	Organ confined
T3	Extraprostatic extension
T3a	Extraprostatic extension (unilateral or bilateral) or microscopic invasion of bladder neck
T3b	Tumor invades seminal vesicle(s)
T4	Tumor is fixed or invades adjacent structures other than seminal vesicles such as external sphincter, rectum, bladder, levator muscles, and/or pelvic wall

NOTE: There is no pathological T1 classification.
NOTE: Positive surgical margin should be indicated by an R1 descriptor, indicating residual microscopic disease.

Regional lymph nodes (N)

N category	N criteria
NX	Regional nodes were not assessed
N0	No positive regional nodes
N1	Metastases in regional node(s)

Distant metastasis (M)

M category	M criteria
M0	No distant metastasis
M1	Distant metastasis
M1a	Nonregional lymph node(s)
M1b	Bone(s)
M1c	Other site(s) with or without bone disease

NOTE: When more than one site of metastasis is present, the most advanced category is used. M1c is most advanced.

Prostate-specific antigen (PSA)

PSA values are used to assign this category.

PSA values
<10
≥10 <20
<20
≥20
Any value

Histologic grade group (G)

Recently, the Gleason system has been compressed into so-called Grade Groups.

Grade Group	Gleason score	Gleason pattern
1	≤6	≤3+3
2	7	3+4
3	7	4+3
4	8	4+4, 3+5, or 5+3
5	9 or 10	4+5, 5+4, or 5+5

TNM: tumor, node, metastasis; AJCC: American Joint Committee on Cancer; UICC: Union for International Cancer Control.

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Prostate cancer TNM prognostic stage groups AJCC UICC 8th edition

When T is...	And N is...	And M is...	And PSA is...	And Grade Group is...	Then the stage group is...
cT1a-c, cT2a	N0	M0	<10	1	I
pT2	N0	M0	<10	1	I
cT1a-c, cT2a, pT2	N0	M0	≥10 <20	1	IIA
cT2b-c	N0	M0	<20	1	IIA
T1-2	N0	M0	<20	2	IIB
T1-2	N0	M0	<20	3	IIC
T1-2	N0	M0	<20	4	IIC
T1-2	N0	M0	≥20	1-4	IIIA
T3-4	N0	M0	Any	1-4	IIIB
Any T	N0	M0	Any	5	IIIC
Any T	N1	M0	Any	Any	IVA
Any T	Any N	M1	Any	Any	IVB

NOTE: When either PSA or Grade Group is not available, grouping should be determined by T category and/or either PSA or Grade Group as available.

TNM: tumor, node, metastasis; AJCC: American Joint Committee on Cancer; UICC: Union for International Cancer Control; PSA: prostate-specific antigen.

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Risk stratification schema for localized prostate cancer, according to the National Comprehensive Cancer Network (NCCN)

Risk group	Clinical/pathologic features
Very low	▪ T1c AND ▪ Grade group 1 AND ▪ PSA <10 ng/mL AND ▪ Fewer than 3 prostate biopsy fragments/cores positive, ≤50% cancer in each fragment/core AND ▪ PSA density <0.15 ng/mL/g
Low	▪ T1 to T2a AND ▪ Grade group 1 AND ▪ PSA <10 ng/mL AND ▪ Does not qualify for very low risk
Favorable intermediate	▪ No high or very high risk features ▪ No more than one intermediate risk factor: • T2b to T2c OR • Grade group 2 or 3 • PSA 10 to 20 ng/mL AND ▪ Grade group 1 or 2 AND ▪ Percentage of positive biopsy cores <50%
Unfavorable intermediate	▪ No high or very high risk features ▪ Two or three of the intermediate risk factors: • T2b to T2c • Grade group 2 or 3 • PSA 10 to 20 ng/mL AND/OR ▪ Grade group 3 AND/OR ▪ ≥50% of positive biopsy cores
High	▪ No very high risk features AND ▪ T3a OR ▪ Grade group 4 or 5 OR ▪ PSA >20 ng/mL
Very high	▪ T3b to T4 OR ▪ Primary Gleason pattern 5 OR ▪ Two or three high-risk features OR ▪ >4 cores with Grade group 4 or 5

PSA: prostate-specific antigen.

Adapted from: NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®): Prostate Cancer. Version 4.2018.

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Selection of treatment depends on risk stratification and patient characteristics/choice

- Very low, low and *favourable intermediate* risk patients may be considered for active surveillance alone or definitive local treatment (noting that in *intermediate* group risk of developing metastatic disease higher compared to definitive treatment)
- Active surveillance NOT indicated for *unfavourable intermediate* risk patients
- High and very high risk patients may also have definitive local treatment

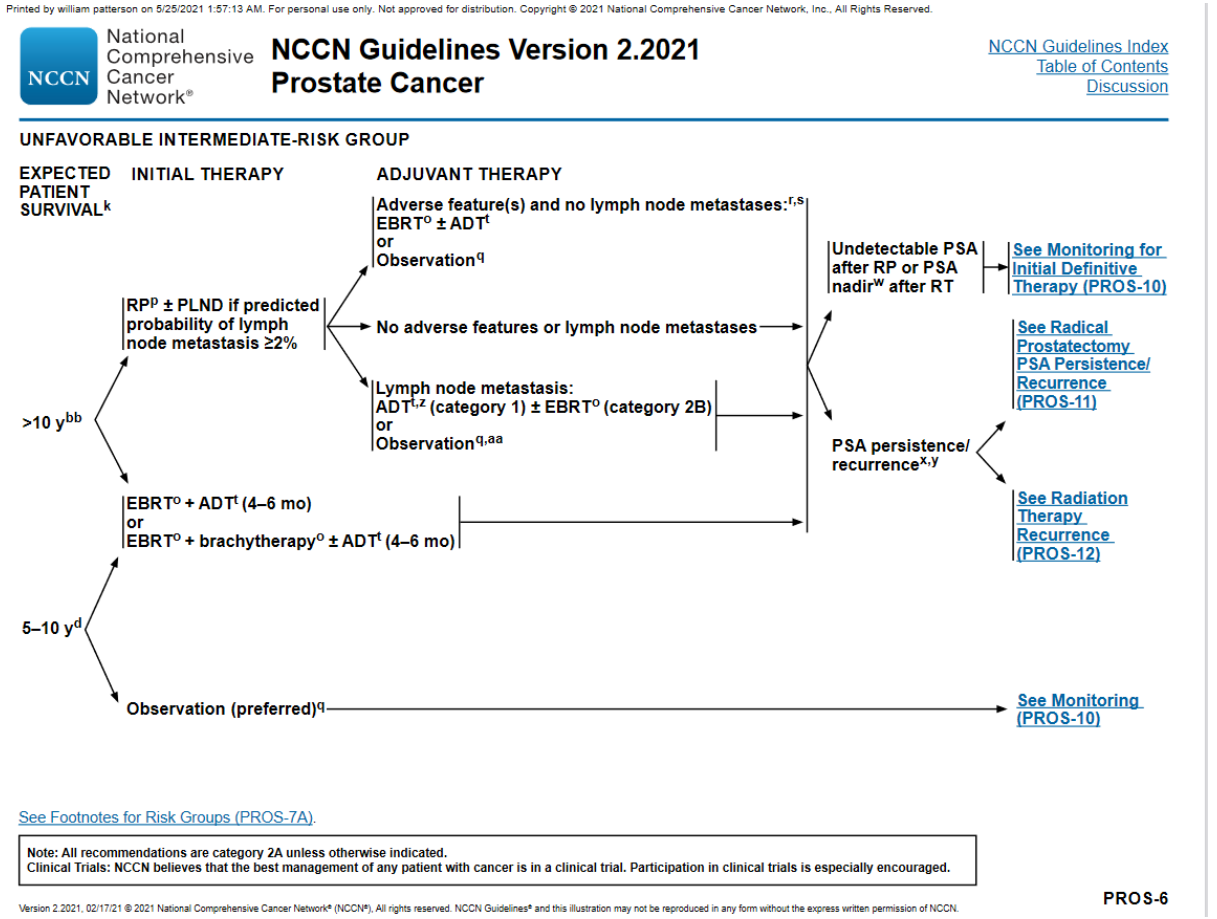
Definitive local treatment

- Radical prostatectomy
- External beam RT with or without brachytherapy

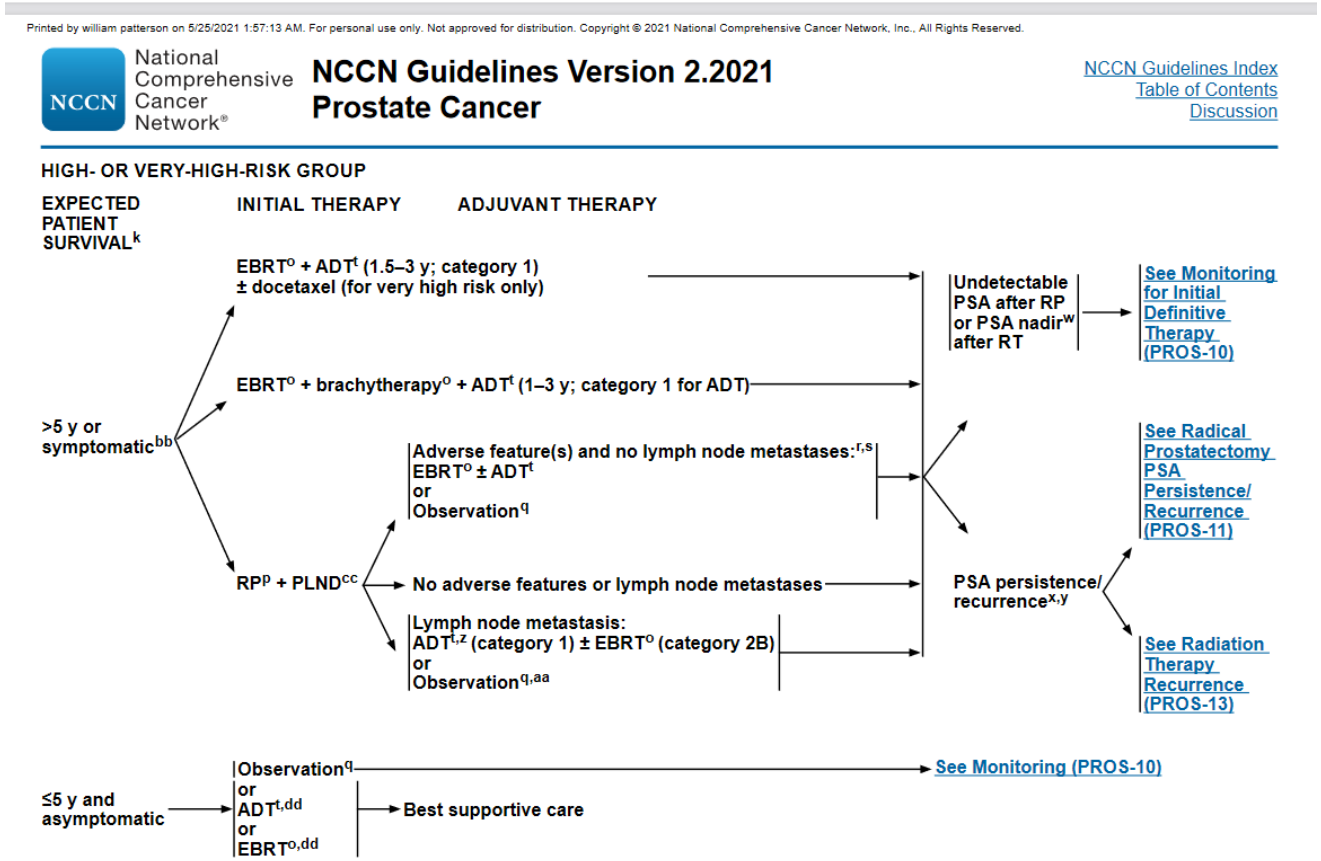
Systemic treaments for localised prostate cancer

- Androgen deprivation therapy (ADT) may be achieved with orchidectomy or chemical castration (GNRH agonist or direct antagonist)
- Cytotoxic chemotherapy (docetaxel in early stage disease)

Unfavourable intermediate risk – NCCN guidelines



High and very high risk groups



Chemotherapy for early stage, hormone sensitive prostate cancer (very high risk)

- Docetaxel given 3 weekly for 6 cycles in combination with ADT has been shown to improve PFS and OS
- Cost is additional toxicity associated with cytotoxic chemotherapy

Anti-androgen treatments

- Orchiectomy, GNRH agonists (goserelin) and GNRH direct antagonists (degaralix)
- Cyproterone acetate is a steroidal antiandrogen blocks androgen receptor and inhibits synthesis. Side effects include increased risk venous and arterial thrombosis, liver toxicity.
- Older anti androgens (bicalutamide, flutamide, nilutamide) block binding at androgen receptor.
- Second generation antiandrogens, abiraterone blocks steroid synthesis, enzalutamide acts at multiple sites in androgen signalling pathway

Other systemic treatments

- Ketaconazole inhibits steroid hormone synthesis
- Glucocorticoids (prednisolone, dexamethasone), several mechanisms of action
- Megesterol acetate/estrogens not commonly used because of thrombotic side effects

Initial approach hormone sensitive metastatic prostate cancer

- Androgen deprivation cornerstone of treatment (GNRH agonist with 4 weeks antiandrogen to cover “flair” or GNRH antagonist which leads to more rapid decline in testosterone levels and may be preferred if rapid response needed)
- Significant side effects of ADT may lead to consideration of intermittent treatment
- NOT generally indicated for overt metastatic disease but if rising/elevated PSA level only then may be considered

What to add to ADT??

- The addition of 6 cycles docetaxel to ADT improves overall survival in men with metastatic prostate cancer. Benefit greatest in high volume disease (visceral metastases, >4 bone lesions) but may be considered in lower volume disease.
- The addition of abiraterone to ADT improves survival in men with high risk disease (high grade, > 3 bone lesions, visceral mets) and possibly low risk disease – NOT PBS LISTED
- Similar benefits with the addition of enzalutamide or apalutamide to ADT in denovo MPC.
- No direct comparison of docetaxel vs newer antiandrogens

Castratation resistant prostate cancer - CRPC

- Men with advanced prostate cancer who have disease progression whilst being managed with ADT and have castrate levels of testosterone.
- Does NOT imply that disease is totally independent of androgens and resistant to further androgen directed treatments.

Treatment options CRPC

- Choice of treatment depends on disease characteristics (volume of disease, symptoms, PSA level and doubling time), age/comorbitities and patient choice.
- General agreement that ADT should continue with the addition of other therapies

Treatment options CRPC

- Addition of newer antiandrogens
- Enzalutamide, apalutamide and darolutamide are orally administered agents acting at multiple levels and have been shown to improve outcomes
- Abiraterone which blocks intracellular synthesis of androgens also improves OS
- No direct comparison of enzalutamide vs abiraterone
- Very small benefit from treating with abiraterone post enzalutamide failure

Treatment options CRPC

- Cytotoxic chemotherapy
- Mitoxantrone and prednisolone showed activity in CRPC
- Docetaxel and prednisolone superior outcomes compared to MP
- Cabazitaxel non inferior to docetaxel in chemo naïve setting and shows activity post docetaxel failure (PBS indication is in setting of docetaxel failure or intolerance)
- Choice of treatment depends on disease/patient characteristics

Other treatment options CRPC

- Radioligand therapy – PSMA is an antigen expressed on prostate cancer cells and ligands can be linked to radio-isotopes for diagnostic and therapeutic purposes
- Trials with LUT 177 plus ligand have shown good activity in terms of PSA response when compared to cabazitaxel
- No reimbursement in Australia, cost $10,000 per treatment and 3-4 treatments needed

Other treatment options CRPC

- Radium-223 is an alpha emitting particle that is bone seeking and may be used to treat bone metastases
- Immunotharapy - Sipuleucil-T is an autologous prepared dendritic cell vaccine
- Pembrolizumab (anti PDL1 monoclonal antibody) shows activity in MSI hightumours and PDL1 overexpression. No current reimbursement.
- Recycle older antiandrogens like cyproterone acetate

Bone metastases CRPC

- Zoledronic acid delays time to SREs compared to placebo in men with CRPC and bone metastases
- No benefit in Hormone sensitive disease
- Denosumab (monoclonal antibody against RANK LIGAND which mediates osteoclast activity) superior to zoledronic acid in CRPC
- No trials in hormone sensitive disease
- ***4 weekly denosumab for 2 years indicated in CRPC with bone mets noting major S/E Osteonecrosis Jaw associated with poor dental hygiene***

Urothelial Cancer

- Arises in transitional cell epithelium most commonly in bladder but may involve renal pelvis, ureters and urethra.
- Most common histology in USA/Europe (>90%)
- May be non muscle invasive (superficial) which is most common and treated with local therapies (surgical excision, fulguration, intravesical BCG or chemotherapy)
- May be muscle invasive and locoregional only or metastatic disease

Muscle invasive –locoregional disease

- Cystectomy with urinary diversion usually treatment of choice.
- Combined modality TURBT/RT/CT may be appropriate for organ preservation.

Adjuvant treatment

- There is randomised and meta-analysis evidence for the use of cisplatin based adjuvant chemotherapy following cystectomy for high risk disease
- 4 cycles cisplat/gemcitabine or 3-4 cycles MVAC or dose dense MVAC usually recommended
- For cisplat ineligible patients observation or RT (selected patients)
- Combination RT/CT has been trialled and shown to improve local control rates

Adjuvant treatment – what's new

- Adjuvant nivolumab for advanced urothelial carcinoma (March 2021)
- Adjuvant checkpoint inhibitor immunotherapy is under investigation in select patients with advanced urothelial carcinoma and high-risk (eg, muscle-invasive or node positive) disease after radical cystectomy. In a phase III trial of over 700 patients with high-risk disease after radical cystectomy who had received neoadjuvant chemotherapy or were ineligible for adjuvant cisplatin-based chemotherapy, one year of adjuvant immunotherapy with nivolumab improved disease-free survival compared with placebo (median 21 versus 11 months) [1]. While promising, adjuvant immunotherapy remains experimental for patients with advanced urothelial carcinoma and high-risk disease after radical cystectomy, and we await regulatory approval before incorporating this approach into routine clinical practice.

Neoadjuvant chemotherapy

- Treatment administered prior to surgery
- Administration of neoadjuvant chemotherapy has consistently shown survival advantage.
- Meta analysis of 11 trials comparing cisplatin based chemotherapy plus local therapy to local therapy alone showed improved OS (50 vs 45%) and lower risk of recurrence.
- Optimal regime not established but should be cisplatin based (GC, MVAC, ddMVAC).
- Results from early phase trials of immune checkpoint inhibitors (atezolizumab, pembrolizumab, durvalumab) have shown very promising results with pCR rates 30-40%. CONFIRMATION AWAITED

Kidney cancer

- Commonest tumours arise in renal cortex (85%) with clear cell predominant histology
- Treatment of early stage disease surgical
- No established role for systemic adjuvant treatment
- Ongoing trials with immune checkpoint inhibitors.

Kidney cancer – metastatic disease