Anatomy

The prostate gland is positioned just below the base of the bladder and in front of the rectum.

In a young male the prostate weighs approximately 20 grams and is 3 x 4 x 2cm (often referred to as being the size and shape of a walnut or plum).

Through the prostate passes the prostatic urethra, which is covered by transitional epithelium. The prostate is divided into two lobes and is surrounded by a thin layer of fibrous tissue. Part of the venous drainage is to a plexus of veins lying in front of the vertebral bodies. This is possibly a reason why prostate cancer has a tendency to spread to the vertebrae.

In radiation therapy planning it is important to be able to identify the apex and the base of the prostate

Apex = inferior portion of prostate, continuous with striated sphincter.

Base = superior portion and continuous with bladder neck.

The growth and function of the prostate are controlled by hormones. Normal prostate function depends on several androgens, primarily testosterone, which is produced by the testes.

The prostate is made up of thousands of tiny fluid-producing glands. Specifically, the prostate is an exocrine gland.

Exocrine glands are so-called because they secrete through ducts to the outside of the body (or into a cavity that communicates with the outside). The fluid the prostate gland produces forms part of semen.

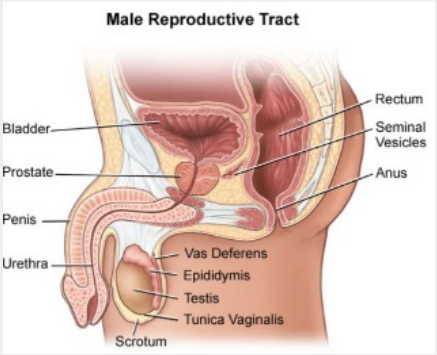
The prostate also produces a protein called **Prostate Specific Antigen (PSA)**

Anatomy (cont)

PSA is released with the ejaculatory fluid and can also be traced in the blood stream. *The testing of PSA levels in the blood is used to detect prostate cancer*

In addition to the prostate's role in producing ejaculate, it also plays a part in controlling the flow of urine. The prostate wraps itself around the urethra as it passes from the bladder to the penis. Muscular fibres in the prostate contract to slow the flow of urine.

Anatomy



Epidemiology and aetiology

The exact aetiology of prostatic cancer is unknown. It commonly presents itself in the seventh and eighth decades and is rare under the age of 40 years. There are significant differences in incidences worldwide, with the highest risk of developing prostate cancer being in Sweden, followed by the United States and Europe. The lowest incidence is in Japan.

Many factors contribute to the development of prostate cancer:diet (high fat consumption); genetics (risk increasing with positive family history); environmental factors (such as exposure to radiation, heavy metals and chemical fertilisers); hormonal factors.

Epidemiology and aetiology (cont)

Orchidectomy or administration of oestrogens may result in the shrinkage of the prostate gland in 80% of tumours.

Pathology and natural history

More than 95% of prostatic carcinomas arise in the glandular epithelium of the peripheral glands of the prostate and hence are classified as adenocarcinomas. Other histologies such as sarcomas, transitional, small and squamous cell carcinomas are rare.

Prostate carcinoma is more commonly found in the apex of the prostate, frequently involves the gland's capsule and is also multifocal. This makes the removal by transurethral resection unfeasible.

The development of clinically significant prostate cancer follows **predictable patterns**. Although growing slowly at first, as time goes on and as the tumour mass becomes larger, prostatic tumours appear to progressively dedifferentiate and become more aggressive. As the bulk of the tumour increases, there occurs extension to the capsule margins, through the capsule, and into the seminal vesicles, the neck of the bladder, and the pelvic lymphatics. Rarely do prostate tumours cross the fascial space into the rectal wall.

Metastatic spread is both lymphatic and haematogenous.

The pelvic lymph nodes near the prostate are usually affected first by lymphatic spread, which is orderly. The next area of metastasis is to the lymph nodes around the arteries and veins leading to the legs and pelvic organs. Dissemination via the blood most frequently affects the bones, producing dense osteoblastic metastases.

By **Molly**

cheatography.com/molly/

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Pathology and natural history (cont)

Liver involvement also occurs, but metastasis to the brain and other soft tissues is less common. 60% of men who die of prostate cancer have bone metastases (vertebrae, pelvis, femur, and ribs). Spinal involvement frequently extends into the epidural space and is a cause of extrinsic compression of the spinal cord that can result in leg weakness and can progress to paraplegia.

Prognosis

The rate of tumour growth can vary from very slow to moderately rapid.

As it is often not diagnosed until a man is 70 years of age or older, the approach to treatment and thus prognosis is greatly influenced by the patient's age and coexistent medical problems. Men who are younger at the time of diagnosis are more likely to die of prostate cancer, and definitive treatment is important for them.

As with other cancers, survival is related to the extent of tumour dissemination and histological grade.

When confined to the gland, prostate cancer is frequently curable. Median survival is more than 5 years whether the cancer is treated or not.

When locally advanced, prostate cancer is rarely curable. Many patients will die of the cancer, but some may live for 5 years or longer with treatment.

If spread to distant organs has occurred, cure is not possible. Median survival in such cases is 1 to 3 years, and most such patients will die of their tumour.

Prognosis (cont)

Other factors influencing prognosis are the:
patient's age;
hormone status;
acid phosphatase levels in the blood;
regional lymph node involvement;
bone scan results;
response to treatment.

As prostate cancer grows slowly at its onset, a diagnosis before spread beyond the gland would result in an excellent potential for survival with treatment. However, localised malignancy of the prostate is not easy to diagnose because it is characteristically asymptomatic.

Presentation and Workups

Screening

Prostate Specific Antigen (PSA) is a glycoprotein that liquefies semen. *The normal range of PSA is approximately 4ng/ml*. Levels above this increases the risk. **PSA levels increase proportionally to the volume of disease**, and are a valuable tool to monitor response to treatment and development of metastatic disease.

Clinical presentation

Early prostatic cancer is usually **asymptomatic** and can only be detected through a routine rectal examination. As the prostate can undergo benign enlargement, patients may experience increased frequency and difficulty in micturition (ejection of urine).

Larger tumours can produce symptoms of: hesitancy; urgency; nocturia (urination at night); poor urine stream; dribbling and terminal haematuria (blood in urine).

Presentation and Workups (cont)

Advanced disease can manifest itself as pain in the back, pelvis, shoulders and possibly over multiple bony sites. Occasionally patients may present with pathological fractures in the femurs.

Diagnostic workups and staging

Trans-rectal ultrasound (TRUS) is helpful for defining the extent of local disease but is unable to assess lymph node size.

With **rectal examination** exclusively, there is 50% understaging, and with ultrasound exclusively, understaging is 62%.

A **bone scan** to assess for bone metastasis should be part of the initial staging.

Computed Tomography (CT) scanning or Magnetic Resonance Imaging (MRI) can help evaluate the pelvic lymph nodes but have poor sensitivity and specificity

Acid phosphatase levels directly correlate with the stage of prostate cancer. Because it is rarely elevated in organ-confined disease, the acid phosphatase is a good marker for extra-capsular disease.

Pathological staging refers to histological examination of the resected specimen after surgery. It is important for determining prognosis and the need for more treatment after surgery. Surgical removal of the prostate, seminal vesicles and pelvic lymph nodes is required for complete pathological staging.

The extent of tumour is stratified to organ confined, specimen-confined, and margin negative or margin-positive disease. Histopathologic examination of the malignant tissue and histopathologic growth patterns are used to determine **grade (degree of biological aggressiveness).**

By **Molly**
cheatography.com/molly/

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Presentation and Workups (cont)

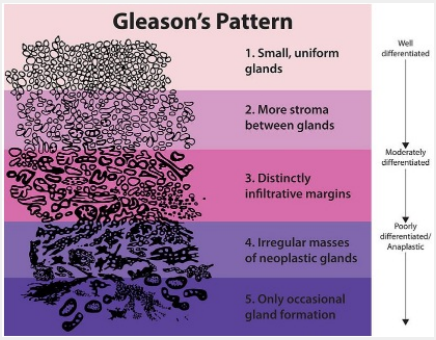
Because of the wide variability of growth patterns, cell types, degree of anaplasia, and variation from one microscopic field to another, a range of differentiation among the malignant tumours may be reported.

Gleason's score is used to report the degree of malignancy of prostate cancer. This system assigns histological grade to the predominant (primary grade) and the lesser (secondary grade) patterns of tumor on a scale of 1 to 5.

The grade numbers of the two patterns are added to obtain the Gleason score, which may **range from 2 to 10. The lower the score, the better.**

The major problem with the Gleason grading system is its reproducibility, which is only 80%.

Gleason Score



TNM Staging: Stage extent

STAGE EXTENT	
T1	Clinically apparent tumour not palpable or visible by imaging
T1a	Tumour incidental finding in 5% or less of tissue resected
T1b	Tumour incidental finding in more than 5% of tissue resected
T1c	Tumour identified by needle biopsy (e.g. due to elevated PSA)
T2	Palpable tumour confined to the gland
T2a	Tumour involves half a lobe or less
T2b	Tumour involves more than half a lobe
T2c	Tumour involves both lobes
T3	Tumour extending beyond the capsule
T3a	Unilateral extracapsular extension
T3b	Bilateral extracapsular extension
T3c	Tumour invades seminal vesicle(s)
T4	Tumour fixed or invading adjacent structures
T4a	Tumour invades bladder neck, external sphincter, rectum
T4b	Tumour invades levator muscles and/or fixed to pelvic wall

TNM Staging: Nodes

N0	No Nodes involved
N1	Single node metastases < 2 cm in diameter
N2	Single node metastases 2-5 cm in diameter or multiple nodes,none > 5 cm
N3	Node > 5 cm

TNM Staging: Metastases

M0	No distant metastases
M1	Distant Metastases

Where **N** = regional lymph nodes and **M** = distant metastasis

Treatment summary

It is very difficult to find the optimum treatment for patients presenting with early prostate cancer, as the clinical behaviour of the disease can be quite unpredictable.

The disease has a long natural history, and many patients survive 15 years or more after the diagnosis is established.

Treatment of patients using radiation when it is asymptomatic may lead to toxicity of treatment, whilst no or under treatment can lead to morbidity or cancer related death.

This is a potentially curable disease, therefore it is a fine line to balance each patient individually.

There are five options available to patients currently:

1. watchful waiting
2. hormonal therapy
3. radical prostatectomy
4. radical external beam radiation therapy
5. radical brachytherapy
- brachytherapy seed implants
- high dose brachytherapy

Patients who are expected to have a life expectancy of greater than 10 years will be offered radical treatment. In general, for patients who have a high PSA, Gleason score, and T stage, the greater the likelihood of tumour progression, and therefore the need for radical treatment.

Treatment summary (cont)

Patients who are elderly and medically unfit with less aggressive histological features are managed with watchful waiting. They also have options of hormonal treatments and palliative radiotherapy if and when the need arises.

Surgical options

Radical prostatectomy is an option when the tumour is still confined to the prostate, and the patient is medically fit.

This operation entails the removal of the entire prostate, including the capsule, a layer of the surrounding connective tissue, and the attached seminal vesicles.

The anatomical location of the prostate makes this procedure technically challenging and nerve sparing to avoid complications is an important issue.

Once the tumour has spread beyond the prostate and there are metastases, surgery is no longer an option. Side effects from this surgery include incontinence and compromised potency. Improved surgical techniques have reduced the incidence of long term complications from radical prostatectomy.

Transurethral resection of the prostate (TURP) involves removing tissue from the prostate with the use of an instrument inserted through the urethra. This surgical procedure is often done to relieve symptoms resulting from the tumour, and prior to other treatment. TURP may also be performed for patients who due to age or other illness are unable to have a radical prostatectomy.

Hormonal options

Hormonal treatments are of benefit in the reduction of testosterone circulating in the bloodstream.

Mechanisms:

Firstly is the removal of the testes;

Secondly the consumption of oral oestrogens;

Thirdly through the administration of monthly or three monthly injections.

Early intervention with hormonal therapy reduces complications of the disease such as pathological fractures, however it does not appear to improve survival. Hormonal treatment also has a role in reducing prostate volume before treatment (“downsizing”), due to reduced benign prostate hyperplasia (BPH) of the gland.

Radiation Therapy Options

Radiation therapy has been employed as the treatment of choice for several decades. As prostate cancer is highly sensitive to radiation, it is an appropriate treatment of choice.

Most patients are diagnosed in the **early/clinically localised stage**, which can be **treated curatively with radiation therapy alone.**

Innovative methods such as brachytherapy, three dimensional conformal radiation therapy (3D-CRT), intensity modulated radiation therapy (IMRT), and volumetric modulated arc therapy (VMAT) are able to deliver very high tumouricidal doses to the diseased prostate, with minimal side effects to the surrounding tissue.

Radiation therapy combined with hormonal treatment can be curative in **locally advanced disease.**

Radiation Therapy Options (cont)

Radiation therapy is very effective in alleviating symptoms of metastatic prostate cancer (bone metastases, spinal cord compression, and bladder outlet obstruction).

External beam radiation therapy (EBRT), alone or in combination with other treatment modalities, such as hormonal therapy or brachytherapy, has become an alternative treatment to radical prostatectomy in patients with low-risk tumours. Yet the long natural history often observed in these patients makes an accurate assessment of the impact of any therapy on survival more difficult.

EBRT treatments are conventionally given from one or more fixed gantry angles. For deep seated targets with adjacent critical normal tissues such as prostate and its close proximity to the rectum, or where there is complex geometry, as many as 6-9 beams are utilised to optimise the geometric dose parameters.

3D Conformal Radiation Therapy (3DCRT)

A technique where the beams of radiation used in treatment are shaped to match the tumor.

Retrospective dose escalation studies using 3DCRT provide clear evidence for a dose-response relationship in various subgroups of patients with prostate cancer.

The RTOG 9406 trial investigated changes in toxicity with increasing radiation doses. They report no significant difference in acute and late toxicity up to the highest dose level of 79.2 Gy.

The vast majority of 3DCRT studies showed a direct relationship between high doses and no biochemical evidence of disease.

Volumetric Modulated Arc Therapy (VMAT)

VMAT is a type of intensity modulated radiation therapy (IMRT) treatment technique which can be delivered on a linear accelerator and delivers the radiation therapy treatment using a rotational or arc geometry rather than several static beams.

There are three mechanical variable in VMAT delivery; gantry rotation, multi-leaf collimator (MLC) motion, and dose rate modulation

Both the MLC aperture and the dose rate can be simultaneously adjusted in an arc of 360 degrees or less, whereas gantry speed is modulated as needed.

During a VMAT treatment, the Linear Accelerator rotates around the patient while the radiation beam is shaped and reshaped as it is continuously delivered from virtually every angle in a revolution.

During a VMAT treatment, specialised software algorithms will vary the three parameters simulateously; the speed of rotation around the patient, the shape of the MLC aperture, and the dose delivery rate.

The target volume dose does not change when using VMAT. The amount of scatter and leakage radiation dose to the rest of the body is reduced compared to conventional IMRT.

VMAT for prostate treatment and planning is more widely accepted in Australian clinical practice, many centres deliver 78Gy in 39 Fractions using.

For the treatment of prostate cancer, there is an involvement of tissues such as bone, rectum, and bladder, which all have different tissue heterogeneities. Hence, it is important to have an accurate tissue heterogeneity correction while calculating dose in the situation when tissues of different densities are involved in the beam path.

By **Molly**
cheatography.com/molly/

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Brachytherapy

Brachytherapy (BT) can be used as mono-therapy, mainly for low-risk patients with smaller prostate volumes.

Combined EBRT, followed by a temporary brachytherapy (BT) boost, is effective in **low-risk patients** (T2a, initial PSA <10 ng/ml, Gleason score<6), but these patients also do well with permanent brachytherapy alone.

The greatest advantage of EBRT plus temporary BT (total dose of 20–25 Gy) seems to be in **intermediate- and high-risk patients** (T1b–T3b or PSA>10 ng/ml or Gleason>6).

Common side effects: Transient urinary morbidity related to radiation induced urethritis (inflammation of the urethra) or prostatitis (inflammation of the prostate gland)

Irritative and obstructive lower urinary tract symptoms may develop over the first few weeks as a result of implant trauma.

These side effects are of a temporary nature. In addition to the urethral dose, the presence of obstructive symptoms secondary to pre-existing benign prostatic hypertrophy before brachytherapy has been correlated with an increased incidence of acute symptoms, including urinary retention.

Late side effects, such as incontinence, chronic cystitis, urinary retention, dysuria, frequency and late grade 3 urinary complications, that require medical or surgical intervention **may occur in approximately 2%–5% of patients**.

Combined modality (with EBRT) can cause about 20% of patient's grade 2 and 8% grade 3 toxicity.

Late rectal complications, including proctitis with diarrhea, perineal pain, tenesmus, or rectal bleeding **may occur in 2 – 19% of patients**.

Prostate Cancer Simulation

It is well established the prostate can move internally, despite the body remaining completely still. Therefore, **bony anatomy is not a reliable method of determining precise prostate position.**

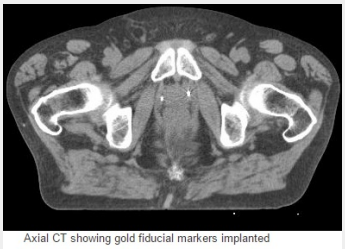
Many clinical centres have an established **gold seed or fiducial marker** implantation programs, whereby 3 gold seeds or fiducial markers are implanted into the prostate prior to simulation.

A Urologist or Radiologist inserts the fiducial markers using ultrasound guidance in a procedure similar to the prostate biopsy.

The fiducial markers are then visible on the CT and verification images to accurately localise the prostate and ensure treatment is delivered accurately, minimising dose to critical structures such as the bladder and rectum.

As with all radiation therapy treatment sites, the simulation procedure will be based on the same fundamental principles of collecting the required information and data to effectively reproduce the appropriate treatment plan over the course of the patients treatment.

Gold seed markers



Axial CT showing gold fiducial markers implanted

Close up of fiducial markers as insert

Simulation: Stabilisation and localisation

The standard radical set-up for prostate cancer radiation therapy includes placement of devices for the head, support for the pelvis region, the knees and feet.

Simulation: Bowel and bladder preparation

The anatomical position of the prostate varies depending on bladder and bowel filling

Simulation imaging and treatment require patients to follow bowel and bladder preparation protocols. Patients will receive instructions on the preparations and procedures required prior to their simulation appointment.

Most clinical centres follow **full bladder and empty bowel** protocols during simulation and treatment.

Filling the bladder reduces the area of bladder that will fall within or close to high dose regions of the treatment volume.

Simulation: Example

An example of a prostate simulation procedure that could be used for radical 3DCRT or IMRT/VMAT treatment:

Fiducial Gold seeds implanted under ultrasound guidance one week prior to CT.

Clinical centre protocol for bowel and/or bladder preparation instructions given to the patient prior to simulation appointment.

Prior to CT establish if the patient has complied with the bowel and/or bladder preparation instructions.

Patient scanned supine using the stabilisation devices as per the clinical centre protocol. These generally include some form of knee and foot stabilisation devices.

Simulation: Example (cont)

Trans-axial CT Data-Set acquired.

Scan from L5 to Perineum 2 - 5mm slices (centre dependent)

No contrast requested

Limitations of CT for Prostate delineation

CT is able to differentiate various tissues solely on the basis of differences of attenuation coefficients.

Since the prostate, rectal and bladder wall, levator ani muscle, and penile bulb all have similar attenuation coefficients they **cannot be readily differentiated on CT.**

Many clinical centres use CT/MRI fusion for radical treatment planning of prostate cancer protocols but the use of CT/MRI fusion will vary from one clinical centre to the next.

Some centres may use MRI for IMRT planning, while others may use it for dose escalation, or not at all. The soft tissue contrast of T2 weighted MRI images has been demonstrated to result in better definition of both prostate and critical structures.

Planning

A large number of randomised studies have demonstrated that radiotherapy doses of </=70 Gy are less than ideal as curative prescriptions for the treatment of localised prostate cancers.

Most of these studies are based upon measures of freedom from biochemical failure and it should be noted that “no randomised study so far has demonstrated the survival benefit from dose escalation”

Dose and fractionation regimes

The dose fractionation regimes used for 3DCRT and IMRT/VMAT radical treatment of prostate cancers vary slightly.

Planning (cont)

Dose fractionations are evidence based and may vary due to individual Radiation Oncologists preferences, actual treatment technique used (3DCRT or IMRT, and IGRT protocols) and individual patient variations.

Volume and organ delineation

After patient simulation and acquisition of CT scans of the treatment area, the first stage of the planning process is to use the CT scans to delineate target structures as well as organs at risk.

There is convincing published evidence that favours the use of additional imaging modalities such as magnetic resonance imaging (MRI), as it provides superior soft tissue visualisation compared to CT.

Compared to MRI, CT leads to a larger volume than that derived by MRI, which also facilitates a more precise definition of the prostate apex.

Standard protocol for IGRT and IMRT prostate planning to delineate the following anatomical structures:

1. Prostate
2. Seminal Vesicles or part thereof (this is a clinical decision).
3. Rectum - Some prescribing RO’s prefers to mark the rectum and anal canal as one organ.
4. Bladder
5. Head & Neck of Femurs

Inter observer errors often occur in the delineation of the apex of the prostate – this is when one observer would delineate the apex of the prostate differently to the next observer.

Contouring errors at the apex result in the overestimation of prostate volume in the vast majority of cases.

Planning (cont)

Once the prostate volume and OAR have been delineated, the addition of beams to the treatment plan can commence. The ICRU point for dosimetry is in the centre of the Planning Target Volume (PTV).

Treatment

An important aspect of prostate EBRT and clinical quality assurance is **treatment verification.**

Verification procedures have been established that improved patient set-up accuracy, such as ultrasound localisation systems, kV and MV imaging systems, cone beam CT scanners, CT on rails and implanted gold seeds or fiducial markers.

These systems offer the possibility of visualising the prostate (or markers within the prostate) immediately before treatment to assure optimal target positioning.

This procedure is called **image-guided radiotherapy (IGRT)**. It is important to note that when considering imaging protocols the following points are taken into account:

1. Dose received by the patient from imaging (this is often factored into the total dose delivered)

2. Time taken to acquire, assess and act on imaging results – the effect of this on the time the patient is on the treatment couch.

3. Will images be assessed before or after treatment – this is referred to as online or offline review.

4. Equipment and imaging options available

5. Overall, impact of imaging on achieving accurate, reproducible treatment that allows or high dose to be delivered to the tumour with minimal impact on organs at risk

By **Molly**
cheatography.com/molly/

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Treatment (cont)

Specific to prostate patients it is important to ensure any patient preparation instructions for bladder and bowel must be strictly adhered to. Patients cannot be treated unless all conditions are the same as simulation.

Complications and Toxicity

External beam RT is generally well-tolerated; the most common side effects are: grades 1–2 acute rectal morbidity, tenesmus, diarrhoea, urinary symptoms (frequency, dysuria, urgency, nocturia) requiring conservative medication.

Serious persisting complications that require corrective surgical intervention are rare.

Bladder Toxicity

Two major predicting factors for acute bladder toxicity: more than 30% of the bladder receiving doses of 65 Gy or higher and neoadjuvant hormonal treatment (because of rapid volume shrinkage and more normal tissue exposed to irradiation).

In addition, the relative risk of developing late bladder complications (bleeding, strictures) also increased as the percentage of the bladder receiving 65 Gy or more of radiation increased.

Rectal Toxicity

There is a significant correlation between the percentage of the rectum treated to 70 Gy or higher and the likelihood of late rectal toxicity (bleeding, rectal wall ulcer, severe diarrhoea, incontinence).

Patients with more than 25% of the rectal wall treated to 70 Gy or a higher dose had a 37% risk of grade 2 rectal toxicity compared to 13% in patients who had less than 25% of the rectal wall exposed to this dose.

Complications and Toxicity (cont)

In recent years, the addition of a hydrogel 'spacer' placed between the prostate and rectum has helped to minimise dose to the rectal wall by displacing it outside the high-dose region. This has the potential to reduce radiation induced rectal toxicity, thus allowing dose escalation to occur to improve disease control.

By **Molly**
cheatography.com/molly/

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