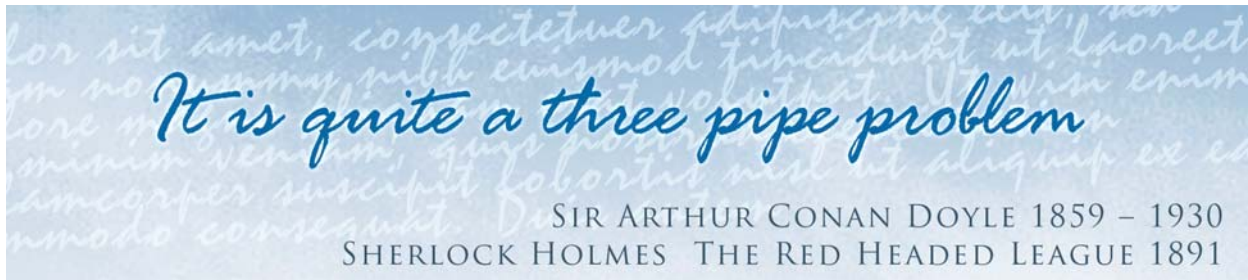




Angel Falls - Venezuela

Adenocarcinoma of the prostate is a malignant tumour arising from the glandular elements of the prostate. It is the most common male cancer.



The prostate is a small gland situated beneath the bladder. The prostate produces the majority of the seminal fluid. One function of the prostate is to produce a sugar called fructose. Fructose feeds the sperm in the semen.

Incidence

Prostate cancer accounts for 12% of all cancers and 23% of all male cancers in the UK. There has been a huge increase in incidence in the last two decades. The mortality rate has not increased commensurately so that the rise in incidence is probably due to earlier diagnosis rather than a true rise in incidence.

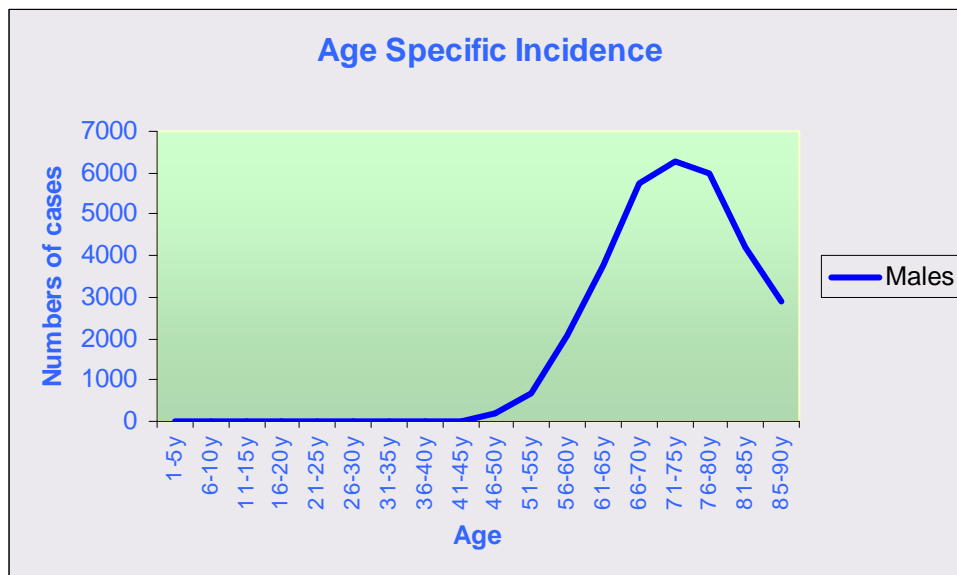
New cases UK	Mortality UK
32000	10000

Age

Prostate cancer incidence is directly proportional to age.



Angel Falls - Venezuela

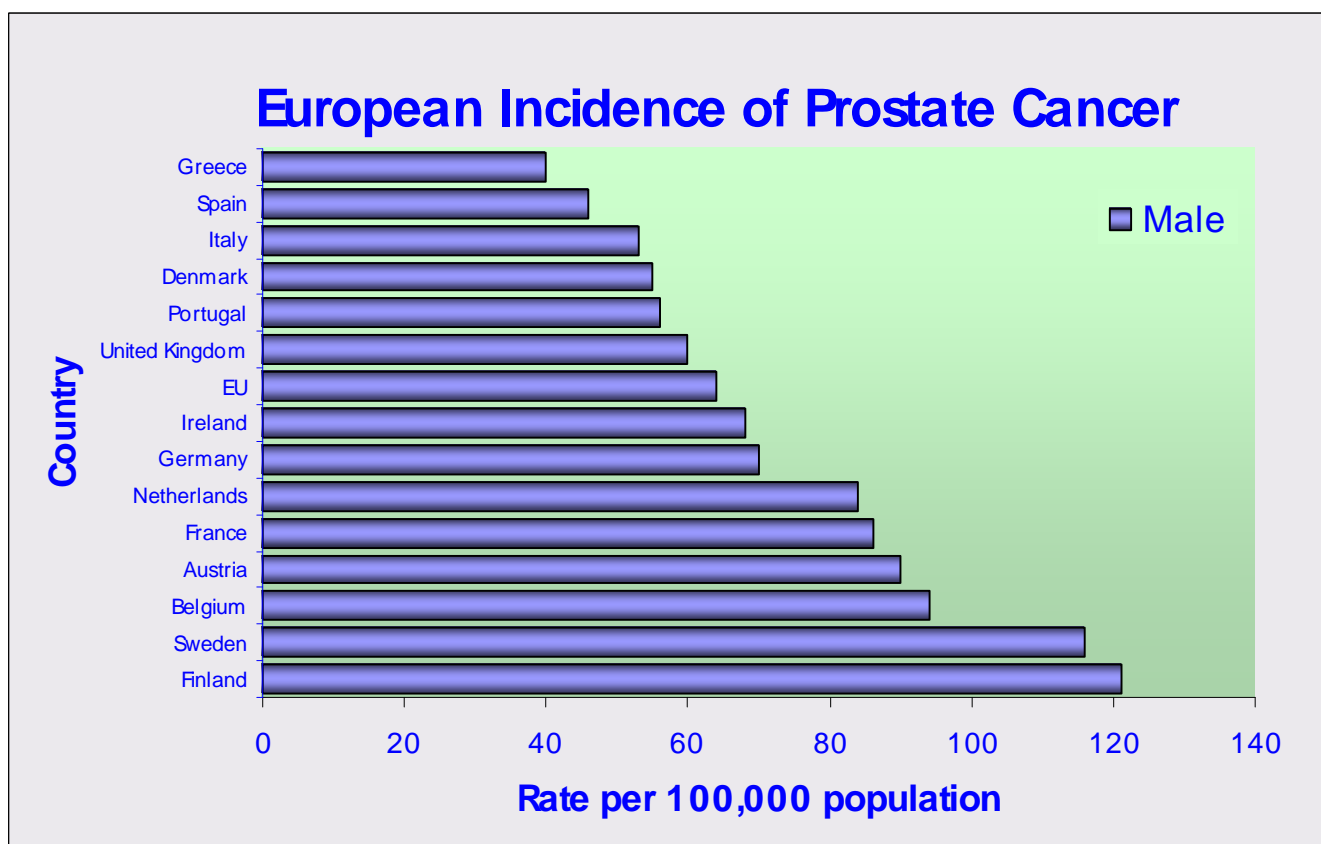
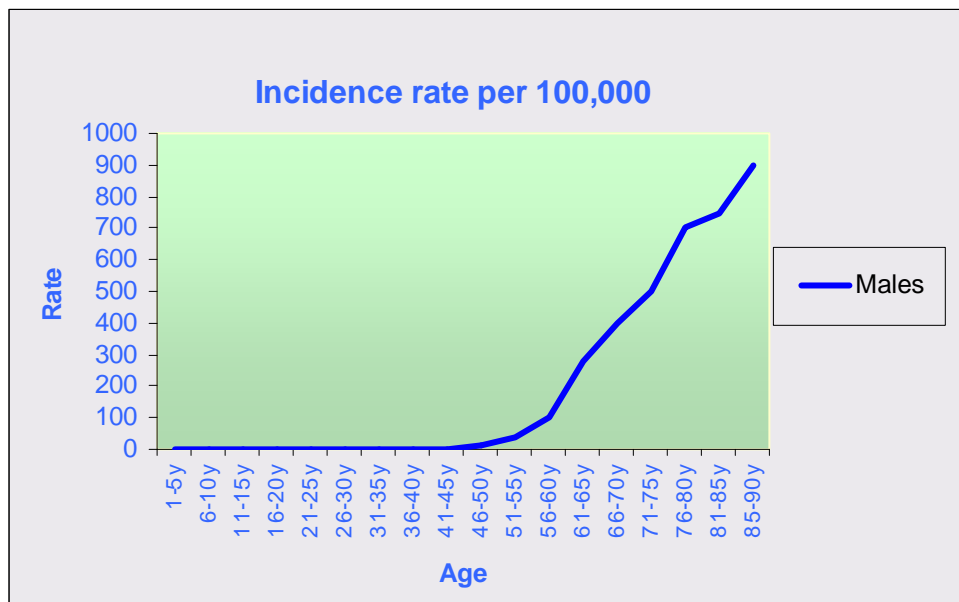


As the graph shows the number of cases rises until 80 years. After this there is a fall in the absolute numbers but the number of cases per 100,000 of the population continues to rise. This is because the number of people alive at 85+ is proportionately much less.

Age band	Cases per 100,000
65 - 75	450
75 - 85	725
85 +	900

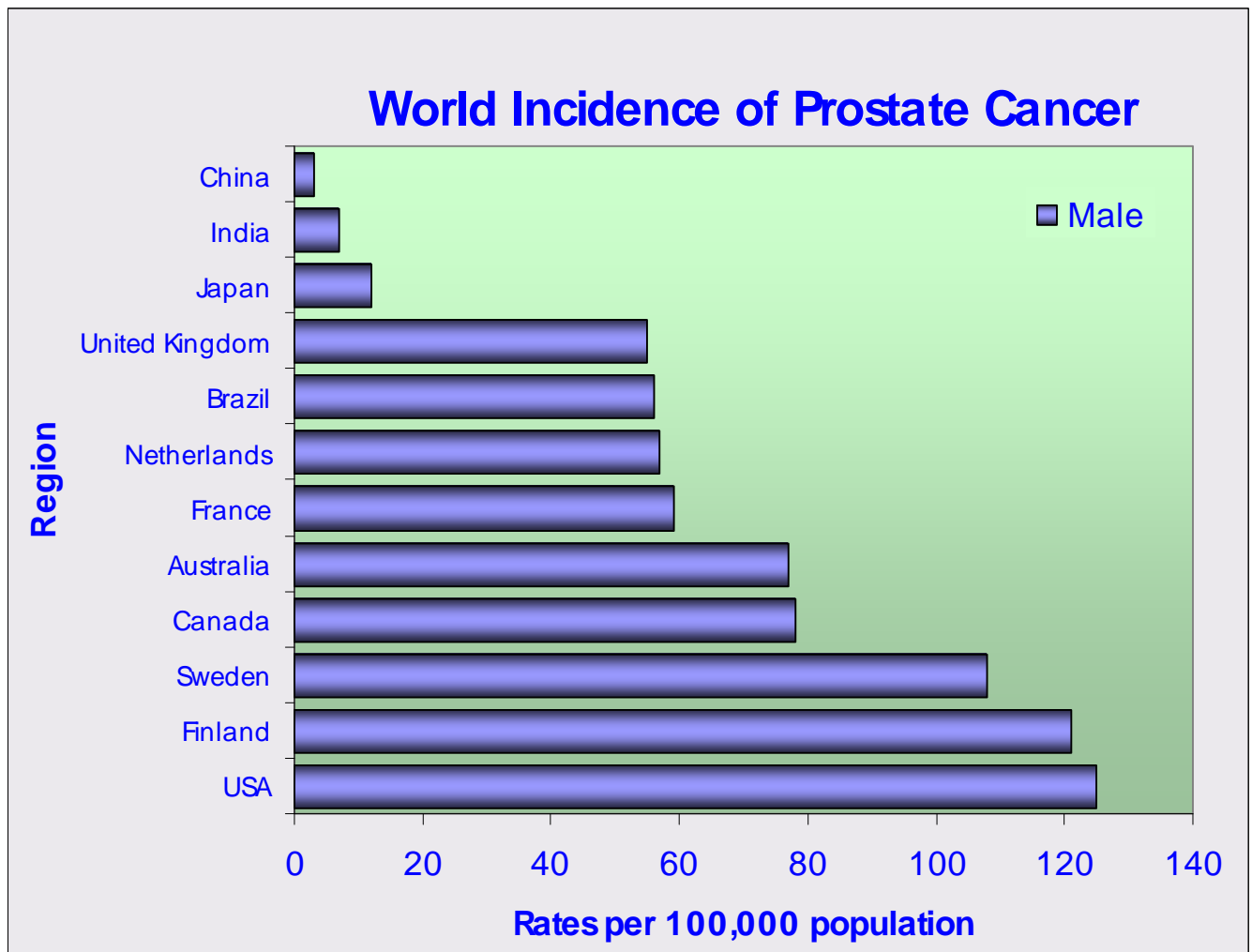


Angel Falls - Venezuela





Angel Falls - Venezuela



Worldwide there are nearly 700,000 new cases each year. The high rates in the USA may reflect the high rates of PSA testing in America.

Sex

It is only found in males

Predisposing factors

The precise cause of prostate cancer is unknown.

There is definitely a correlation with age. It is rare in men under 50.



It is more common in patients who have close relatives with the disease such as a father brother or uncle. Negroes who live in North America have the highest incidence of the disease whilst Asians have the lowest.

A diet high in animal fat increases the risk. Obesity also increases the chances.

In some families an inherited faulty gene may predispose to breast cancer. This gene may also give rise to prostate cancer in the male members. These genes are called BRCA 1 and BRCA 2.

IGF-1 is insulin-like growth factor. This substance is definitely linked to prostate cancer. It is not certain if it can actually cause cancer or whether it is released by prostatic malignant cells. In the latter instance IGF-1 may be a marker for the disease.

The exact role of testosterone is unknown. . There is no conclusive evidence that it causes cancer but castrate men very rarely form prostate cancer. There is no doubt that it can accelerate cancer when present.

Studies have shown that men who regularly take aspirin or non-steroidal anti-inflammatory drugs have a lower incidence.

It is thought that men with diabetes have a lower incidence of prostatic cancer. It is known that IGF-1 levels are reduced in diabetic patients.

Tomatoes contain a substance called lycopene. This is thought to be protective against prostate cancer.

Selenium may also protect against prostate cancer but the case is not definitely proven.

One recent Australian study showed that frequent ejaculation may be protective.

Types

Most cases of prostate cancer are adenocarcinomas.

1% of prostatic tumours are transitional cell carcinomas. These form in the prostatic urothelium.



Presentation

In some cases there may be no symptoms whatsoever.

If the prostate enlarges because of the tumour then the patient may present with obstructive symptoms.

- Hesitancy
- Poor urinary flow
- Post voiding dribbling

There may also be irritative symptoms

- Nocturia (rising at night to pass urine)
- Frequency of micturition
- Urgency

The patient may not fully empty his bladder.

Prostate cancer can sometimes present with a urinary tract infection.

Occasionally haematuria (blood in the urine) may be the presenting symptom. This is a relatively uncommon presenting feature.

All of these symptoms are in themselves not diagnostic of prostate cancer. Benign prostatic enlargement can produce all of these symptoms as well.

If there are bone deposits then the patient may experience pain at the site of the secondaries.

In advanced cases patients will present with the general manifestations of malignancy.

- Poor appetite
- Weight loss
- Tiredness
- Lethargy

The patient may have a PSA blood test in a screening programme which may be raised. This is becoming more common as more men are being tested for PSA



Angel Falls - Venezuela

Screening

There is no official screening programme in the UK for prostate cancer.

Screening for prostate cancer has been a contentious issue. The PSA blood test has been used. PSA is prostate-specific antigen. It is a protein issued by prostate cells. The main problem with the PSA is its lack of specificity. The upper limit of normal for the test is dependent on the age of the patient. There are many different assay kits used to measure the PSA. None of the kits have been standardised. This produces a variation from laboratory to laboratory.

A patient with a PSA level between 4 and 12 has a 25% risk of having a cancer. Therefore up to 75% do not. Because of this, unnecessary investigations are therefore being performed.

A small percentage of patients with prostate cancer will have a normal PSA.

The indiscriminate use of PSA for screening should be avoided. All patients having a PSA must be fully cognisant of the many potential pitfalls. Care must be exercised in requesting a PSA in an asymptomatic patient.

Digital rectal examination and trans-rectal ultrasound are not routinely used in screening.

Examination

Abdominal examination may be normal. The bladder may be palpable as a suprapubic mass arising from the pelvis.

The prostate can be examined directly by digital rectal examination. The normal prostate has two palpable lobes that are soft and of equal size. In carcinoma the central sulcus (groove) between the lobes can be obliterated. Nodules can be felt in one or both lobes. The prostate may be firm or hard in consistency. The lateral margins may be indistinct and fuse with surrounding structures.



Investigations

- Blood tests** A full blood count will detect the presence of any anaemia. A renal profile will assess kidney function.
- Tumour Markers** Prostate-specific antigen (PSA) is a protein released by prostate cells. It is raised in prostate cancer. Unfortunately it can also be raised in other prostatic conditions such as prostatitis. Urinary tract infections, digital rectal examination and endoscopic examinations may also raise the PSA.
- Ultrasound** Ultrasound assesses any hydronephrosis in the kidneys. It can also be used to identify any liver deposits. Trans-rectal ultrasound (TRUS) visualises the prostate directly. This examination is often associated with trans-rectal biopsy of the prostate. It has been shown that TRUS is not any more superior to DRE in assessing capsular penetration.
- Biopsy** If there is a suspicion of a prostatic tumour then biopsies are carried out. It is customary to take 3 – 4 biopsies from each lobe and a further biopsy from each lateral margin. The biopsies are carried out via the trans-rectal route or the trans-perineal route.
- MRI scanning** Magnetic resonance images are used to stage prostate cancer. Commonly the pelvis is scanned. The prostate gland is assessed. The primary cancer is staged. In particular capsular breaches can be seen. Also the scan can identify bilateral disease. Any lymph node involvement is assessed. Nearby bony metastases are seen in the pelvic bone.
- CT scanning** CT scans look at the body in slices. They use Xrays and computers to do so. CT scans are not routinely performed for this condition. MRI is the preferred method of scanning.



Angel Falls - Venezuela

Bone Scans This is an isotope study using a gamma camera. It detects the increased blood supply to bones found in bone metastases. It is a useful examination to visualise the whole skeleton in one scan. Less than one quarter of one percent of patients with a PSA below 20 will have a positive bone scan.

Plain Xrays Any doubtful areas seen on the bone scan can be further assessed by Xraying the bone in question.

Grades

Tumours used to be graded into 3 categories

Grading of Prostatic Cancer

Grade	Category	Gleason Score
G1	Well differentiated	2 – 4
G2	Moderately differentiated	5 – 7
G3	Poorly differentiated	8 - 10

Staging

TNM Staging

The TNM classification system is commonly used to stage tumours.

The “T” refers to the primary **T**umour

The “N” refers to the lymph **N**odes draining the bladder

The “M” refers to all other distant **M**etastases



Angel Falls - Venezuela

Stages of Prostate Cancer - Tumour

T _x	Primary tumour unknown
T ₀	No evidence of primary tumour
T ₁	Primary tumour not palpable
- T _{1a}	- Incidental tumour < 5% of tissue
- T _{1b}	- Incidental tumour > 5% of tissue
- T _{1c}	- Incidental tumour found by needle biopsy
T ₂	Tumour confined to the prostate
- T _{2a}	- Tumour involves < 50% of one lobe
- T _{2b}	- Tumour involves > 50% of one lobe
- T _{2c}	- Tumour involves both lobes
T ₃	Tumour extends beyond prostatic capsule
- T _{3a}	- Unilateral or Bilateral extracapsular extension
- T _{3b}	- Seminal vesicles invaded
T ₄	Tumour invading other structures

Secondary node involvement is staged as follows:

Stages of Prostatic Cancer - Nodes

N _x	Lymph node status unknown
N ₀	No metastases in lymph nodes
N ₁	Metastases in lymph nodes



Angel Falls - Venezuela

Distant metastases are staged as follows:

Stages of Prostate Cancer - Metastases

M _x	Metastatic status unknown
M ₀	No distant metastases
M ₁	Distant metastases
- M _{1a}	- Distant metastases non regional lymph nodes
- M _{1b}	- Distant metastases in bone
- M _{1c}	- Distant metastases in any other site

There are 4 stages of testicular tumours in the American Joint Committee on Cancer system.

AJCC System Prostate Cancer

Stage	Tumour	Nodes	Metastases	Grade
1	T _{1a}	N ₀	M ₀	G ₁
2	T _{1a} T _{1b} T _{1c} T ₁ T ₂	N ₀ N ₀ N ₀ N ₀ N ₀	M ₀ M ₀ M ₀ M ₀ M ₀	G ₂₋₃ any G any G any G any G
3	T ₃	N ₀	M ₀	any G
4	T ₄ Any T Any T	N ₀ N ₁ Any N	M ₀ M ₀ M ₁	any G any G any G

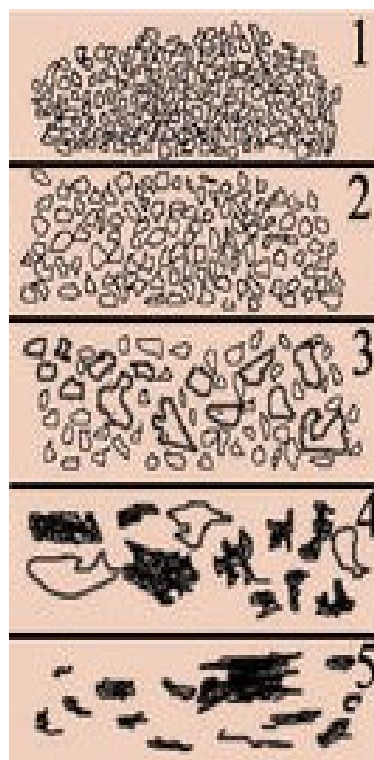


Angel Falls - Venezuela

Gleason Score

The Gleason scoring system applies to the pathological grading of the tumour. The pathologist assigns a grade to the most common pattern seen under the microscope. He then assigns a second grade to the next common grade. These grades range from 1 to 5. The two grades are added together to produce the final score. The minimum score is therefore 2 and the maximum is 10. A score of 2 is the least aggressive and a score of 10 indicates the most aggressive cancer. The Gleason score aids in the prognosis.

Gleason score



1 Small uniform glands

2 More spaces between glands

3 Infiltration of cells from glands at margin

4 Irregular masses of cells with few glands recognisable

5 Sheets of cells, no recognisable of glands



Angel Falls - Venezuela

Treatment

Watchful waiting

This modality is active surveillance of the prostate cancer. It has been controversial but it has a role to play. Generally in patients over 70 years or patients who are not fit for other treatment this option may be the best choice. Whilst PSA is not a very good screening agent it is a good monitor of the disease. In those patients who do not want to expose themselves to the side effects of surgery or radiotherapy this option allows them to maintain their standard of life for longer. By monitoring the PSA the patient will know if his disease is progressing. At that point he can decide on further treatment. If this option is exercised then regular follow up is advised.

Surgery

Radical Prostatectomy

Radical prostatectomy is an operation to remove the entire prostate and seminal vesicles. The bladder is then anastomosed to the urethra. A pelvic lymphadenectomy is very occasionally performed with it. The operation is also performed laparoscopically (keyhole) or by a robot. These procedures are performed in specialised units. They require a lengthy training period especially for the open and laparoscopic methods. The robotic method has a shorter training period for the surgeon. The robotic method is gaining popularity. Nerve sparing procedures are also done to reduce the incidence of impotence. The effectiveness of these nerve sparing procedures is dependent on the staging of the disease. This is a difficult procedure to perform after a transurethral prostatectomy. The first radical prostatectomy was performed by Hugh Young at the John Hopkins Hospital in 1904 via a perineal incision.



Angel Falls - Venezuela

The operation is performed on patients with histologically proven adenocarcinoma of the prostate. The patient must be fit enough to undergo the procedure. He should also have a life expectancy in excess of 15 years to justify the operation. His PSA should ideally be below 15. If the PSA is between 15 and 20 then a lymph node is sampled at the start of the operation and sent for frozen section. A pathologist will then inform the surgeon if the nodes are involved whilst the patient is still asleep. If the nodes are clear then the radical prostatectomy will proceed. It can be performed via a retropubic or a perineal incision.

Stage 1 and 2 disease may be cured by a radical prostatectomy. 30% of patients require further treatment within 4 years of the operation. This may be due to the operation not totally removing the tumour. In this case the surgical margins will have disease present.

The procedure is not without its complications. These include:

Urinary incontinence

Up to 30% need to wear pads

Up to 65% report some kind of wetness problem. These figures vary from unit to unit but more specialised units will achieve better figures.

Urethral stricture

Impotence

Up to 60% in some series

The PSA should fall to zero within 4 weeks of the operation. Any subsequent rise means the patient has more cancerous tissue still present.

The 30 day mortality rate is 0.5%. Major complications have been reported in 28%. Comorbidity can be significant in the outcome of the operation.



Angel Falls - Venezuela

Transurethral prostatectomy

This operation is an endoscopic procedure. It will not cure prostate cancer. It can be performed in those patients either not undergoing a radical prostatectomy or not wishing to have a radical. It is performed for bladder outflow obstruction.

Radiotherapy

Radiotherapy kills cancer cells using high energy rays. This can be curative or palliative. There are two types of local treatment

External beam radiotherapy

External beam radiotherapy (EBRT) is administered to the prostate by a radiotherapy machine which focuses the rays from outside the body. The total dose of the xrays is usually given in 30 sessions over a 6 week period. The angle of the beam is changed in order that the prostate receives the total dose while the surrounding structures receive less irradiation.

Brachytherapy

In this procedure tiny radioactive seeds are implanted into the prostate under ultrasound control. The radioactive isotopes used include iodine125 (I^{125}). With a trans-rectal probe scanning the prostate a grid is applied to the perineum. The seeds are inserted evenly throughout the prostate via the grid. The procedure is operator dependent in order to achieve an even dose throughout the prostate. Patients undergoing this procedure should have a PSA <15 with a Gleason score 2-7 and a small volume prostate.



Angel Falls - Venezuela

Radiotherapy has complications

Acute cystitis

Proctitis

Haematuria

Dysuria

Frequency

Urgency

Incontinence - 7%

Impotence - up to 40 – 60%

All of these complications will vary in incidence and intensity.

Hormone Therapy

The male hormone testosterone acts as catalyst for prostate cancer. By denying prostate cancer cells this hormone the cells cannot divide and grow. The cells die in a process called apoptosis. Hormone therapy is used to treat advanced prostatic cancer.

Bilateral subcapsular orchiectomy

This procedure is an operation in the scrotum. The substance of both testes is removed preserving the capsule of each testis. In effect the testes are reduced in size. In this case testosterone can no longer be produced. The operation has been the gold standard of hormone therapy.

LHRH super agonists

Luteinising Hormone Releasing Hormone (LHRH) is a peptide released by the hypothalamus in the brain. This peptide causes the pituitary gland (beneath the brain) to secrete Luteinising Hormone. Luteinising Hormone in turn stimulates the testes to produce and release testosterone. This process of releasing testosterone is governed by a negative feedback system. As the level of testosterone rises then the production of LH and LHRH is suppressed. LHRH super agonists initially stimulate the system but thereafter block it. The initial stimulation would increase the testosterone temporarily. It is known as the flare reaction. This phenomenon can be blocked by giving an anti androgen just before and after the first treatment.



Angel Falls - Venezuela

Goserelin (Zoladex®) and leuprorelin (Prostap®) are two of the commonest drugs in this category. They are administered by subcutaneous injection in one month or three month depots.

Anti androgens

These drugs counteract the effects of testosterone. They do not influence the production of testosterone. These drugs are used as second line treatment after LHRH agonists or orchiectomies have failed. They are also used to prevent the flare reaction that occurs with the first LHRH agonist injection. There are two classes of drugs – steroidal and non steroidal.

Cyproterone acetate

This drug is a steroidal anti androgen. Prostatic cells have receptor on the surface which accept the testosterone molecule. Cyproterone (Cyprostat®) has a similar molecular structure to testosterone. Both are steroid molecules. It occupies the receptor sites hence nullifying the effects of testosterone. Side effects include gynaecomastia (tenderness and swelling of the breast), nausea, vomiting and diarrhoea. Long term use can interfere with liver function. This may need to be monitored if the drug is given long term.

Bicalutamide

Bicalutamide (Casodex®) is a non steroidal anti androgen. It also blocks the effects of testosterone. Side effects include gynaecomastia, nausea itching and hot flushes.

Flutamide

Flutamide (Drogenil®) is also a non steroidal anti androgen. It acts in the same way as Bicalutamide. Side effects include gynaecomastia, diarrhoea and tiredness.



Angel Falls - Venezuela

Diethylstilboestrol

Diethylstilboestrol (Stilboestrol®) is a hormone preparation. It reduces the amount of testosterone in the blood by increasing the female hormone oestrogen. Its use nowadays is limited owing to side effects. The main side effect is an increase in cardiovascular incidents such as coronaries and strokes and pulmonary emboli. Other side effects include gynaecomastia, fluid retention, nausea and vomiting.

Cryotherapy

This treatment freezes the tumour. It is given intermittently. It is as yet an experimental treatment. It is only suitable for small tumours. Cryotherapy is used in patients with a PSA <15. The prostate ideally should be small. The tumour Gleason score should be 2- 7. The temperature within the prostate drops to -140°C. The long term results are not known.

HIFU

High Intensity Focussed Ultrasound heats the tumour to ablate it. It is another experimental treatment under review. The incidence of impotence is high with this treatment. Long term results are not known.

The problem with these last 2 newer unproven treatments is whether the treatment modality has in fact dealt with the entire tumour. Frequent follow up and repeat biopsies may be necessary. Also a radical prostatectomy offers the patient the best possible chance of cure. Ideally these treatments should be used in clinical trials until their efficacy is known.

Chemotherapy

This form of treatment is not commonly given for prostate cancer. It is used in advanced hormone refractory disease.



Angel Falls - Venezuela

Follow up

All patients should be followed up with serial PSA estimations and DREs. This is not dependent on which treatment modality is chosen. Additional investigations will be performed dependent on the PSA and clinical status of the patient.

Prognosis

5 year survival figures relate to the percentage of patients alive 5 years after presentation. The overall 5 year survival rate is 70% compared to 30% over 30 years ago. This apparent improvement may represent the fact that more cancers are now being diagnosed at an earlier stage. The concomitant 10 year figures are 55% and 20% respectively.

All Cases – Improvement in survival

	1970	2000
1 year survival - all cases	65%	90%
5 year survival - all cases	30%	70%
10 year survival - all cases	20%	55%

The stage of the presenting tumour also affects the prognosis. Prognosis is also affected by the Gleason Score grading. Virtually 100 % of all early stage patients will be alive at 5 years. 92 % of these patients are alive at 10 years and 61% at 15 years.

10 year survival of Prostatic Cancer - stage 1 and 2

Radical Prostatectomy	93%
Radiotherapy	75%
Watchful Waiting	85%



Angel Falls - Venezuela

It is difficult to accept that the radiotherapy arm is worse than the watchful waiting arm. It may represent different patient selection in each group rather than a true difference.

Over one third of all advanced tumours will be alive at 5 years.

Further information

BUPA

0800 600 500

www.bupa.co.uk

Cancerbackup

0808 800 1234

www.cancerbackup.org.uk

Cancer Research UK

020 7009 8820

info.cancerresearchuk.org

www.cancerhelp.org.uk

National Cancer Institute

www.cancer.gov