MCD Year 2: – Tutorial 3 – Prostate cancer – Take-home messages

In 1998, prostate cancer came a close second to lung cancer in male cancer incidence (18.1% and 18.3% respectively). However, while lung cancer deaths are declining, mortality rates from prostate cancer have nearly trebled over the last 40 years. Although prostate cancer is a disease of older men, with just 7% of prostate cancer deaths occurring in men under 64 years of age, the increase in incidence and mortality cannot be solely attributed to the aging population.

Causes of the increasing risk of prostate cancer are not clear. It is heterogeneous and may have the 4th highest genetic component of common cancers, but no genes have been found which can account for >10% of familial cases. It is the androgen-signalling pathway that appears to be disrupted in the vast majority of tumours (see below). Inactivation of the potential tumour suppressor gene PTEN (linked to brain, breast, endometrium and kidney cancers) also shows robust links to familial prostate cancer. Loss of PTEN may have a direct impact on androgen-independent activation of the androgen receptor, since PTEN has been demonstrated to antagonize androgen signalling, or may facilitate anti-apoptotic pathways. The gene BRCA2, known to be involved in familial breast cancer predisposition, has also been linked to prostate cancer in up to 5% of familial cases.

The prostate provides components of the seminal fluid and it is probably important for fertility. Prostatic hyperplasia, whether benign or malignant, leads to problems with urination due to the physical location of the prostate (surrounding the urethra). More rarely, the patient may suffer from lower back pain or blood in the urine. Prostate tumours may spread to the adjacent organs, the seminal vesicles and bladder, and metastasise to the lymph and bone. The majority of deaths from prostate cancer are due to metastatic disease the major symptom of which is severe bone pain.

PSA testing and screening for prostate cancer

The prostate is an exocrine gland. Secretions from the luminal epithelial cells are released in to the duct and thence into the urethra, to form part of the seminal fluid. PSA is a component of the seminal fluid and normally epithelial gap junctions, the basal cell layer and basement membrane prevent PSA entering the tissue and blood serum, so PSA levels in the blood serum of men with no prostate disease is usually undetectable. Any damage to the prostate allows PSA escape in to the serum and generally a cut-off concentration of 4ng/ml serum is taken to indicate the possibility of prostatic disease. However, this test is unable to distinguish between damage due to malignant disease or benign disease (BPH). Benign prostatic hyperplasia affects the majority of men older than 50 years and may be problematic due to constriction of the urethra, causing the same symptoms as prostate cancer. Other causes of raised PSA include mechanical damage (e.g. bike riding, biopsy) and prostatitis (infection of the prostate). Hence, further tests are required to determine the cause of the raised PSA count.

Biopsy and subsequent Gleason scoring is used for detecting and grading tumours after a positive PSA result and digital rectal exam. In one report, it was estimated that needle biopsies underestimated the tumour grade in 36% of cases and overestimated it in 18%. Extended sampling techniques and repeat biopsies have been recommended to improve accuracy. Also, biopsy and grading is not generally useful for predicting prognosis. Prognosis is very variable as by no means in all cases will prostate cancer behave in an aggressive manner and result in death of the patient. Prostate tumours are relatively slow growing and there is evidence from post-mortem examinations that many men die *with* rather than *from* prostate cancer. In many cases the latent foci are too small to cause any symptoms. Unfortunately, at present there is no reliable way of differentiating histologically or via the PSA test between those cancers which will remain latent and those which will progress to life-threatening metastatic disease. These are sometimes termed, respectively, “pussycats” and “tigers”.

A strong argument against routine PSA screening of men with no symptoms is that, once a raised PSA count is detected, the man will have to have further, invasive, tests as well as a period of acute anxiety until the results are known. If malignancy is detected he will then undergo treatment which has unpleasant side-effects and can reduce quality of life dramatically. Meanwhile, there is a not inconsiderable possibility that the lesion, if left alone, would not have been problematic during his lifetime. Many laboratories are trying to identify a new test for prostate cancer which is (a) specific for malignant disease) and (b) able to predict which cancers are likely to become life-threatening. Since testing body fluids such as serum, urine or semen is easy in the clinic, they are focussing on detectable changes in these, using techniques such as proteomics or nuclear magnetic resonance. Researchers are also screening for markers of aggressive prostate cancer using many of the latest technologies. For instance, recently results of a microarray study

were published showing that expression of the Polycomb group gene EZH2 appears to be increased in prostate cancers which subsequently become metastatic.

Treatment options for prostate cancer

Although doing nothing may seem unsatisfactory once malignant disease has been established, it can be the best form of “treatment” for some prostate cancer patients, due to the possibility of the tumour remaining latent for the patients lifespan. This “watchful waiting” or “active observation” is favoured in older patients with low-grade tumours.

Radical prostatectomy (removal of the prostate) is only effective for tumours confined to the prostate gland and has reported side-effects of incontinence and/or impotence in the majority of people who undergo the operation due to the proximity of nerves controlling these functions to the prostate. For many surgeons, the criteria for operability include PSA levels <10-12ng/ml and age <70 years, giving the group with the highest chance for survival.

External beam radiotherapy is a possibility if the tumour has spread outside of the prostate capsule but has not affected other organs. Computer planning is used to limit the toxicity to the bowel and bladder. If the tumour is contained in the prostate, brachytherapy can be used, where radioactive “seeds” are implanted into the prostate. For both types of radiotherapy, side effects of incontinence and sexual dysfunction are common.

Metastatic prostate cancer requires hormone therapy, sometimes in combination with one of the above treatments. Hormone therapy involves bilateral orchidectomy to remove the main source of testosterone, the testes. This is now usually performed by chemical rather than surgical castration using an LHRH analogue. Although LHRH itself, released by the hypothalamus, acts on the pituitary to cause release of LH and production of testosterone, these analogues over-stimulate the pituitary receptor, causing them to become desensitized such that they no longer response to LHRH. LH and testosterone production ceases. However, weak androgens are still produced by the adrenal glands so anti-androgens are also used. These bind to the androgen receptor to prevents its activation by androgens, and may also actively repress androgen target genes. Side-effects of hormone therapy include osteoporosis, loss of libido, anaemia, muscle atrophy, memory loss and gynaecomastia.

Progression of prostate cancer to “androgen independence”

Since the prostate is an androgen-dependent organ, hormone therapy is designed to remove circulating androgens and/or oppose the effects of androgens at the level of the androgen receptor. This works well initially in the majority of cases, however, at a median of 13 months from the initiation of hormonal therapy patients show biochemical evidence of relapse. Symptomatic relapse occurs two years later and is followed by death within a median of 7 months. This advanced form of the disease is often aggressive and is referred to as "androgen-independent". However, expression of the androgen receptor (the ligand-activated transcription factor that mediates response to androgens) is not lost and is often increased by over-expression or gene amplification, implying that androgen receptor signalling is required for prostate cancer progression. Possible causes of this growth in the absence of high circulating androgens include amplification of the response to low residual levels of androgen, or weak androgens, present in the patient by increased levels of androgen receptor or other proteins required for androgen receptor signalling (co-activators); decreased levels of co-repressors; or mutation of the androgen receptor causing it to become activated by other ligands (oestrogen, anti-androgens). Such mutations of the androgen receptor are rare in primary tumours but increase in frequency in advanced, metastatic hormone-independent disease, being detected in up to 30-50% of such tumours. Amplification or over-expression of the androgen receptor is seen in a similar percentage of advanced disease. Amplification of co-activator proteins has been reported in hormone-independent breast cancer and is being studied in prostate cancer. Another pathway could be ligand-independent activation of the androgen receptor by, for instance, growth factors as has been shown for the oestrogen receptor in breast cancer. Alternatively, the androgen receptor pathway could be bypassed altogether for instance by loss of PTEN function.

Reviews: Waxman, J and Mazhar, D (2003) “How are we treating prostate cancer?” *Q J Med* **96**:1-5; Grossman, M, Huang, H and Tindall, D (2001) “Androgen receptor signalling in androgen-refractory prostate cancer” *J Nat Cancer Inst* **93:**168701697; Shi, X, Gumerlock, P and White, R (1996) “Molecular biology of prostate cancer” *World J Urol* **14:**318-328; Walker, M N Editorial comment (Prostate biopsies and Gleason grading) *BJU Int* **90**:698-9