MedicineToday 2013; 14(9): 44-52

PEER REVIEWED FEATURE
POINTS: 2 CPD/2 PDP

Prostate cancer: what's new

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Although there is still no recommended prevention policy for prostate cancer, advances are being made in its earlier detection and treatment.

Key points

- **The overall philosophy in prostate cancer screening is to detect significant cancers in those who could benefit from their diagnosis.**
- **The increased use of active surveillance for patients with low-risk prostate cancer is reducing overtreatment.**
- **New tests now available are the Prostate Health Index (PHI) and the urinary PCA3 test. The PHI has better sensitivity but not specificity than the PSA test; the PCA3 test offers little over the PSA test.**
- **Improved imaging with multiparametric MRI shows promise in appropriate detection of prostate cancer as well as localising and ascertaining the nature of tumours.**
- **Improved surgical and radiotherapeutic options plus focal therapies under investigation are likely to change the way prostate cancer will be managed in the next five to 10 years.**

The controversy about prostate cancer screening continues with further debate over when to test and when to treat. Some prostate cancers are clearly indolent and others are clearly highly aggressive, and an individual approach is therefore mandated. This makes it very difficult to have a universal policy regarding early detection. Furthermore, although the trials of prostate cancer screening have shown some benefit they have also shown considerable overdetection of insignificant cancers.

The good news is that the increased use of active surveillance for patients with low-risk prostate cancer is reducing overtreatment. Improved imaging with multiparametric MRI shows promise in appropriate detection and screening for prostate cancer. Improved surgical and radiotherapeutic options plus some of the less-tested focal therapies are changing the way prostate cancer will be managed in the next five to 10 years. This article is an update of many on the controversies in the area of prostate cancer.

PREVENTION

There is still no recommended prevention policy for prostate cancer. Although the 5α-reductase inhibitors have been shown to be effective in reducing the incidence of low-risk cancers, there has been a slight concern about their increasing the risk of high-grade cancers; while this concern continues, they will not be widely used.[1]

Dietary and lifestyle modification has also been proposed to prevent prostate cancer, based on population studies. Patients should be advised to:

- have a healthy-heart diet, minimising saturated fats and refined sugars
- avoid obesity
- maintain normal levels of cholesterol, blood pressure and blood glucose through diet and exercise or prescription medication.

Evidence is emerging of improved prostate cancer outcomes with maintenance of normal levels of cholesterol, blood pressure and blood

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RISK FACTORS FOR PROSTATE CANCER

Men with one or more of the following risk factors are at high risk of developing prostate cancer:

- significant family history – a first degree relative diagnosed at younger than age 55 years
- PSA more than 1.0 ng/mL at age 40 years
- African American race
- *BRCA1* or *BRCA2* gene mutation

INFORMATION FROM PROSTATE SPECIFIC ANTIGEN (PSA) BLOOD TESTS

PSA level

- PSA levels rise with age – check age-matched ranges of PSA levels to determine if high (see Table 1)

Free to total PSA ratio (%fPSA)

- If below 10% then more likely to be cancer
- If above 25% then more likely to be benign prostatic hyperplasia

PSA velocity

- An increase of more than 0.75 ng/mL per year for over-65-year-olds is significant
- An increase of more than 0.4 ng/mL per year for under-65-year-olds is significant

Prostate health index (PHI)

- The ratio of pro-PSA (an isoform of free PSA that is a precursor of PSA) to PSA has improved sensitivity but not specificity for prostate cancer detection compared with PSA and %fPSA testing

glucose as well as avoidance of obesity.

Although vitamin D and selenium deficiency have been linked with an increased risk of prostate cancer, there is no high level evidence to suggest that supplementation reduces risk.

EARLY DETECTION AND SCREENING

Four randomised screening trials on screening have now been completed. Two from Europe, have now shown a survival benefit of screening men for prostate cancer.[2-5] The Goteburg trial showed a 50% reduction in prostate cancer mortality over 14 years in the screened group.[3] In this trial, the number needed to treat to save one life was 12, a comparable figure to breast cancer screening.

The overall thrust has now been to direct early detection at a younger age group and particularly those at a higher risk, after informed consent (see the box on this page). A single prostate specific antigen (PSA) test at the age of 40 years, as advocated by the Urological Society of Australia and New Zealand, has been shown to be predictive of the lifelong risk of developing life-threatening prostate cancer. This could further help stratify patients into high and low-risk categories. Early detection of prostate cancer still requires a combination of PSA testing and digital rectal examination.

New tests now available for prostate cancer are the Prostate Health Index (PHI) and the urinary PCA3 test. The PHI is a measure of pro-PSA (an isoform of free PSA that is a precursor of PSA), which has been found in higher levels in men with prostate cancer than in men with benign prostatic hyperplasia. It has improved sensitivity but not specificity for prostate cancer detection compared with PSA and %fPSA (the ratio of free to total PSA) testing (see the box on this page).

PCA3 is a urinary biomarker (a prostate-derived mRNA) that is overexpressed in prostate cancer. The urinary PCA3 test is useful in predicting patients requiring a repeat biopsy but disappointing as a first-line screening tool as it offers little over PSA testing.

PSA testing

The most accurate predictor of prostate cancer is the absolute level of PSA relative to age and PSA velocity (i.e. the increase in PSA level per year). The average PSA level and upper limit of the normal range for men of various ages are given in Table 1.

Other information derived from PSA blood tests is also useful, as listed in the box on this page.

Age at testing

Traditionally PSA testing has been recommended from the age of 50 years, and usually ceases when life expectancy is less than 15 years. More recently, PSA testing from the age of 40 years has been recommended, and earlier cessation of PSA testing should be considered to maximise the potential benefit.

TABLE 1. PSA VALUES BY AGE GROUP IN WESTERN MEN

Age (years)	Serum PSA (ng/mL)	
	Median	Upper limit
40 to 49	0.65	2.0
50 to 59	0.85	3.0
60 to 69	1.39	4.0
70 to 79	1.64	5.5

Informed consent

Informed consent is strongly recommended before PSA testing and early detection. A minimum requirement is to explain that although there is evidence for a decrease in prostate cancer mortality though early detection, particularly in younger patients, there is also strong evidence for overdetection and overtreatment. A more detailed description of informed consent can be obtained on various websites including www.prostate.org.au and www.prostatescreenaustralia.com.au.

Targeted patient screening

A suggested guide to the frequency of testing for prostate cancer and when it is inappropriate is given in Table 2.[6]

Early detection in the future

Two recent publications add weight to the theory that MRI improves detection of prostate cancer at initial biopsy.[7,8] Although MRI is not at present standard of care in prostate cancer detection, a possible future algorithm for early detection of prostate cancer could well include this imaging. The role of MRI in this algorithm would be to better select patients requiring biopsy and to safely decrease the number

TABLE 2. RISK-ADJUSTED TESTING FOR PROSTATE CANCER: A PROPOSED REGIMEN IN A PATIENT WITH 'NORMAL' RISK (NO HIGH RISK FACTORS)*[6]

	Age (years)			
	40 to 59†	60 to 69†	70 to 74†	75 and older†
PSA level (ng/mL)				
Below 0.6	Return in seven years or age 60, whichever comes first	No further screening	No further screening	No further screening
0.6 to 1.0	Return in five years	No further screening	No further screening	No further screening
Above 1.0 to 1.5	Return in two years	Return in two years	No further screening	No further screening
Above 1.5 to 2.0	Annual PSA	Return in two years	No further screening	No further screening
Above 2.0 to 3.0	Annual PSA	Annual PSA	No further screening	No further screening
Above 3.0	Refer to urologist	Refer to urologist	Consider annual PSA if below PSA 6.5 ng/mL Refer to urologist if PSA 6.5 ng/mL or above	Refer if PSA greater than age-specific reference range
Digital rectal examination				
Abnormal result	Refer to urologist	Refer to urologist	Refer to urologist	Refer to urologist

ABBREVIATIONS: DRE = digital rectal examination; PSA = prostate specific antigen.

* This is not a validated algorithm; however, it is evidence based. For further information see reference 6.

† Screening should not be undertaken if life expectancy due to age or comorbid illness is less than 10 years.

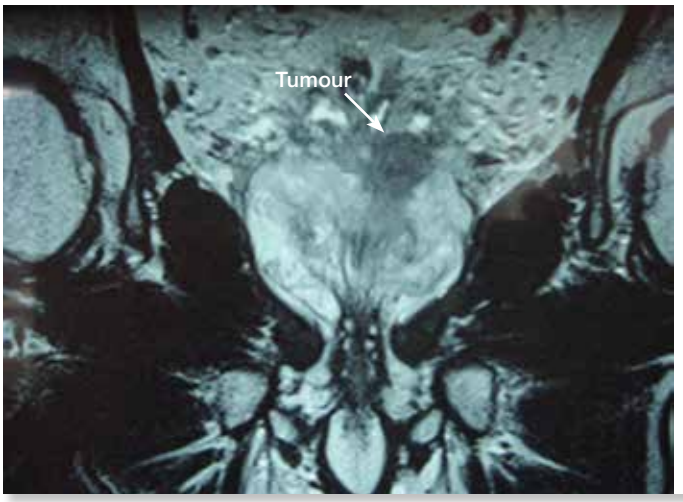


Figure 1. MRI showing a prostate cancer with extracapsular extension at the left base.

of repeat biopsies for the patient without missing significant cancer diagnoses. MRI would also help avoid the overdetection of low-risk cancers.

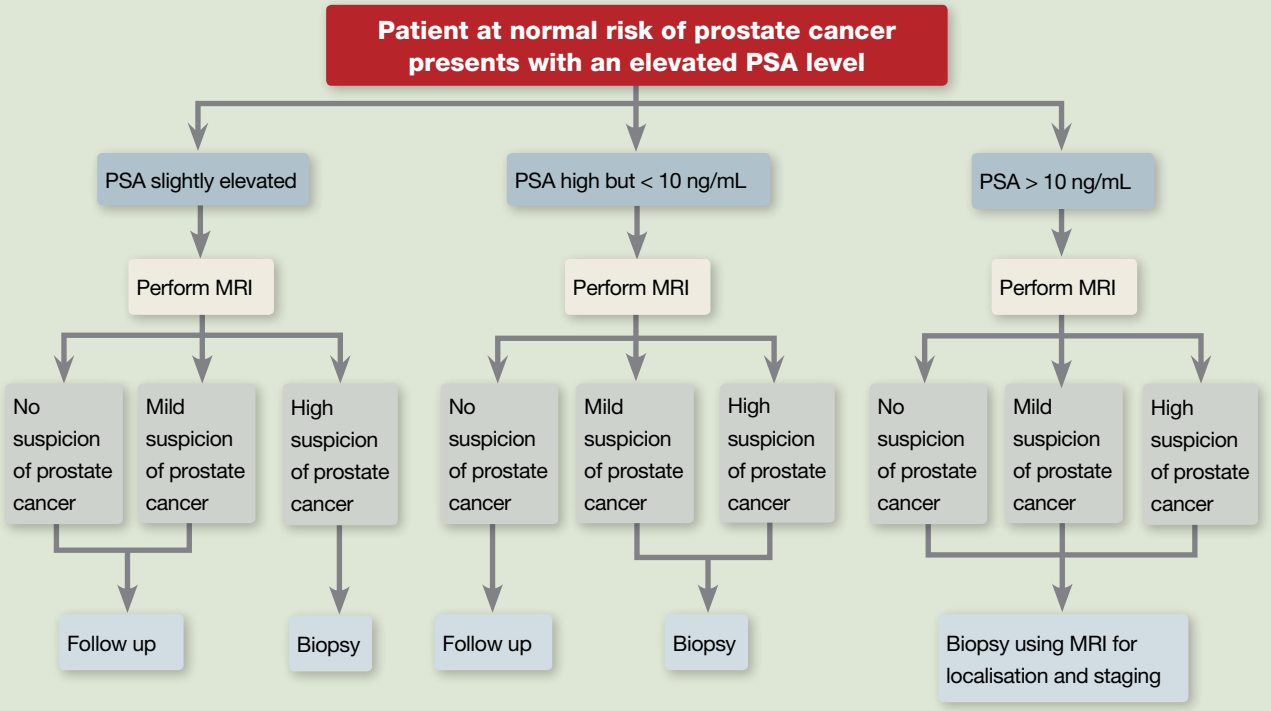
An algorithm for the use of MRI in biopsy decision-making proposed by one of the authors (Associate Professor Stricker) is shown in the flowchart on this page. MRIs should be ordered by a urologist as close interaction is required with the radiologist and the procedure is often followed by biopsy (Figure 1).

BETTER BIOPSY TECHNIQUES

Transrectal ultrasound-guided (TRUS) biopsy is the standard approach for prostate biopsy; this technique takes an average of 12 to 24 biopsy cores per procedure. Transperineal biopsy is a newer approach that has the benefit of increased sampling of the anterior part of the prostate, where cancers can be missed, as well as a much lower risk of infection as the biopsy needles do not pass through the rectal wall. Disadvantages of this technique are that it is performed under general anaesthesia and requires more equipment than a TRUS biopsy.

The use of MRI to more accurately target prostate biopsy is being investigated. This can be done either with an MRI-guided

A PROPOSED ALGORITHM FOR THE USE OF MRI IN BIOPSY DECISION-MAKING*



ABBREVIATIONS: MRI = magnetic resonance imaging; PSA = prostate specific antigen.

* A proposed algorithm by Associate Professor Stricker for the use of MRI in biopsy decision-making. This is likely to miss very few cancers but would markedly reduce overdetection. It is most accurate in smaller prostates. MRIs should be ordered by the urologist in close communication with a credentialled radiologist.

TABLE 3. DIFFERENTIATING SIGNIFICANT AND INSIGNIFICANT PROSTATE CANCERS

Insignificant cancers	Significant cancers
Tumour factors	
Gleason score 6 or below	Gleason score 7 or higher
Gleason score 7 where Gleason pattern 4 makes up less than 5%	Clinically palpable tumour (T2 or higher)
Low volume disease (fewer than two biopsy cores, less than 30% of core involved)	PSA level greater than 10 ng/mL at presentation
Patient factors	
Patients more than 75 years old at diagnosis	Patients less than 60 years old at diagnosis
Patients with life expectancy less than 10 years	Patients with life expectancy more than 25 years
Significant comorbid illness	Little or no comorbid illness

PROSTATE CANCER: CHOOSING TREATMENT

Patient factors
- Age
- Comorbidities
- Lower urinary tract symptoms
- Pelvis (previous surgery, radiotherapy)
- Medications (e.g. clopidogrel, warfarin)
- Geographical, financial issues
- Patient priorities

Prostate factors
- Gleason score
- Prostate volume
- Prostate tumour volume
- Extracapsular extension
- PSA level at diagnosis

biopsy within the MRI machine or alternatively with MRI–ultrasound fusion technology (the overlaying of an MRI image on a real-time ultrasound image). Overall these new emerging techniques will lead to fewer biopsy cores being taken and a more selective choice of patients to undergo biopsy. It will also minimise the chance of missing tumours, thus minimising multiple repeat biopsies.

DISTINGUISHING SIGNIFICANT AND INSIGNIFICANT CANCERS

The overall philosophy in prostate cancer screening is to detect significant cancers in individuals who may benefit from their diagnosis. Ideally, insignificant cancers would not be detected; however, many are, and patients with such cancers should be educated, counselled and regularly monitored (active surveillance). The features of significant and insignificant prostate cancers are listed in Table 3.

When classifying a patient with an insignificant cancer, such as a low-volume Gleason 6 tumour, it is mandatory to ensure that a higher grade cancer is not being missed in the biopsy process. It is often recommended that performing repeat TRUS biopsy with more core samples (typically 30 to 50 samples, known as a saturation biopsy), initial transperineal biopsy or multiparametric MRI can help avoid the underdetection of these high-grade tumours. This can increase confidence that an insignificant cancer can be monitored safely with active surveillance without the concern that a significant lesion has been missed.

BETTER IMAGING FOR PROSTATE CANCER

MRI

Multiparametric MRI is a new technique that incorporates T2-weighted imaging, diffusion-weighted imaging, dynamic contrast-enhanced imaging and proton MR spectroscopy to assess the likelihood of significant prostate cancer. These techniques not only report anatomical detail within the prostate but also biological properties of the tissues, giving a 'signature' of prostate cancer. The technique's negative predictive value is more than 90% and its positive predictive value more than 80%, and it is most accurate in smaller prostates and in the peripheral zone.

The use of multiparametric MRI is, however, extremely user-dependent and probably requires credentialling of radiologists to avoid inaccurate diagnosis. It should therefore be ordered by a urologist, and close collaboration with a radiologist and the GP is then needed to individualise decision-making to the patient. It is not standard care, nor currently rebated through Medicare.

Multiparametric MRI is currently used to select patients to have biopsies, to identify tumours that have been missed on the initial biopsy and to enable more accurate biopsy and also more accurate staging before surgery and radiotherapy (thereby allowing appropriate nerve-sparing techniques). It also provides a more accurate and less invasive means of active surveillance.

PET/CT scan

A positron emission tomography (PET)/CT scan gives both metabolic information (from the PET scan) and anatomical information (from the CT scan). Prostate

cancers generally do not metabolise glucose, hence PET/CT scans using a choline-based radiotracer are proving to be more accurate than scans using a glucose analogue-based radiotracer in the detection of metastatic prostate cancer, particularly to lymph nodes.

Sodium fluoride F-18 is another new radiotracer used in PET/CT scans, and more accurately stages prostate cancer for metastatic disease that has spread to bone than does 18F-fludeoxyglucose PET. It is more sensitive at picking up smaller bone secondaries but with lower specificity.

AN UPDATE ON TREATMENT

Generally the final decision on treatment for prostate cancer should be made after the patient has been counselled by a specialist with expertise in multiple options or multiple specialists with expertise in different modalities. For more difficult cases, multidisciplinary meetings should take place. Factors influencing the choice of treatment are listed in the box on page 49.

Robot-assisted laparoscopic surgery

Evidence is increasing that an experienced robot-assisted laparoscopic radical prostatectomy (RARP) gives equal oncological results with quicker recovery and return to normal activities and lower blood loss than the previous gold standard of surgery of a well-performed open radical prostatectomy often in association with an extended lymph gland dissection. There is early evidence from meta-analyses that RARP may deliver better functional outcomes, such as early return to continence.[9] In addition, patients are now selecting robot-assisted surgery more often as the technology has become more available. However, surgeon experience has been shown to be more critical than the technology used.

Dose escalation radiotherapy

It has recently been appreciated that a higher dose of radiation is often necessary to eradicate prostate cancers than has previously been used. Both intensity-modulated radiotherapy (IMRT) and high-dose rate brachytherapy (HDR) can deliver higher doses of radiation with less damage to surrounding structures.

Intensity-modulated radiotherapy and HDR are often combined with hormone therapy, particularly in patients at higher risk of prostate cancer. The decision between the two modalities is often dictated by factors such as involvement of the seminal vesicles, previous transurethral resection of the prostate (TURP) and the size of the prostate. Increasingly, radiation oncologists are appreciating the need to irradiate the lymph node chain draining the prostate, particularly in the case of high-risk cancers.

Low-dose rate brachytherapy

Low-dose rate brachytherapy (LDR) is now a well established treatment for high-volume Gleason 6 tumours and some Gleason 3+4=7 tumours. The long-term results appear to be equal to the

TABLE 4. HORMONE THERAPIES FOR METASTATIC PROSTATE CANCER*

Drug	Comments
Traditional agents	
GnRH agonists (goserelin, leuprorelin, triptorelin)	Cause feedback inhibition of LH and FSH secretion from pituitary
Antiandrogens (bicalutamide, cyproterone)	Blocks testosterone action at the androgen receptor
New agents	
Abiraterone	CYP17 enzyme inhibitor, blocks androgen synthesis at testis, adrenal and tumour level
Degarelix (GnRH antagonist)	Blocks hypothalamic secretion of GnRH. Rapid drop in testosterone without flare
Enzalutamide (not yet TGA-approved)	Binds androgen receptor with five times the affinity of bicalutamide

ABBREVIATIONS: CYP = cytochrome P450; FSH = follicle-stimulating hormone; GnRH = gonadotropin-releasing hormone agonist; LH = luteinising hormone.
* All patients on hormone therapy should be strongly counselled to adopt an appropriate diet and exercise program. Regular monitoring of physical health and blood tests as well as bone mineral densitometry is recommended.

long-term results of surgery. Documented side effects differ from those of treatments such as surgery and HDR. Patients treated with LDR have less severe sexual side effects but more irritative urinary symptoms. The ideal candidate is a slightly older patient with a tumour that has low to intermediate risk features not meeting the criteria for active surveillance.

Active surveillance

About 40 to 50% of patients with low-volume low-risk prostate tumours may be suitable for active surveillance. The Prostate Cancer Intervention versus Observation Trial (PIVOT) showed that there was no difference in overall survival at 12 years between observation and intervention for low-risk prostate cancers.[4] It is crucial that at least one saturation biopsy is done and/or multiparametric MRI to ensure that a high-grade tumour has not been missed.

An active surveillance program involves:

- PSA tests every three to six months
- periodic biopsy (at between 12 and 48 months from the start of the program until life expectancy is less than 15 years)
- multiparametric MRI at entry and potentially again at 12 to 24 months to reduce the need for repeat biopsies
- progression to active treatment if cancer significantly progresses.

There is now 15 years of follow-up information for the larger studies of active surveillance, suggesting this is a safe approach to managing low-risk prostate cancer.[10] It avoids many of the concerns of overtreatment, although unfortunately this group still sometimes suffers with anxiety, being concerned about the 'cancer' diagnosis, and also has a small risk of sexual dysfunction due to multiple biopsies.

HORMONE THERAPY SIDE EFFECTS

- Metabolic syndrome (weight gain, glucose intolerance, dyslipidaemia)
- Osteoporosis
- Decreased libido
- Hot flushes
- Depression, mood swings, decreased concentration
- Lassitude

Multimodal therapy for locally advanced prostate cancer

It is now well established that multimodal therapy is needed for patients with locally advanced prostate cancer. The two modalities generally used are either a combination of surgery plus follow-up adjuvant radiotherapy or a combination of high-dose radiation with hormone therapy (androgen deprivation therapy). It is no longer adequate to give unimodal therapy in this group of patients.

Focal therapy

In highly selected individuals where there is an identified index lesion (largest or significant tumour focus within the gland) that is higher grade than appropriate for simple active surveillance, there is an increasing trend worldwide to consider ablating that lesion and continuing the patient on active surveillance. As yet, such focal therapy has no long-term track record and is generally confined to those patients where an index lesion is less than one-quarter of the prostate in size and has a significant Gleason 4 component, and the patient refuses standard surgery or radiotherapy options but wants more than active surveillance alone.

Ablative techniques used include high-intensity focused ultrasound, laser, cryotherapy, brachytherapy and the NanoKnife system. At this stage probably fewer than 10% of patients are suitable.

This therapy is not currently standard of care and should only be undertaken in

specialised units as part of a clinical trial or after careful informed consent.

Metastatic prostate cancer treatment

Hormone therapy is the first-line treatment for metastatic prostate cancer, and the traditional and newer agents are listed in Table 4. Hormone therapy has side effects, and all patients taking hormone therapy should be strongly counselled to adopt an appropriate diet and exercise program and undergo regular monitoring for complications (see the box on page 51).

Debate continues on the roles of intermittent hormone therapy versus continuous hormone therapy.[11] This debate is still largely unresolved and although the gold standard remains continuous therapy, there appears to be a group of patients in whom intermittent hormone therapy would be a suitable option. The benefit of intermittent hormone therapy is the minimisation of side effects.

Osteoporosis is particularly common in patients with metastatic prostate cancer. Bisphosphonates were the mainstay of treatment but have been superseded by the human monoclonal antibody denosumab. Denosumab is indicated in patients with bone metastases from prostate cancer for the prevention of skeletal-related events. It has a different mechanism of action to the bisphosphonates and is associated with a lower risk of osteonecrosis of the jaw.

Experimental work is in progress on treating oligometastatic disease (fewer than five secondaries) with targeted stereotactic radiotherapy. This is in its infancy and there are very few follow-up data at this stage.

CONCLUSION

Debate continues on when to test for prostate cancer and when to treat identified cancers. The overall philosophy in prostate cancer screening is to detect significant cancers in those who could benefit from their diagnosis. The increased use of active surveillance for patients with low-risk prostate cancer is reducing overtreatment.

The major factors likely to impact on the management of prostate cancer in the next five to 10 years are biomarkers predicting the natural history of the cancer, focal treatments aimed at treating the index lesion, better imaging (including multiparametric MRI and PET/CT scanning), improved delivery of radiation and the increased use of surgical treatments using modalities such as intensity-modulated radiotherapy, the CyberKnife system and robot-assisted surgery. MT

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COMPETING INTERESTS: None.