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REVIEW

Prostate cancer: clinical questions and imaging answers

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Introduction

Prostate cancer is now the commonest cancer in humans and the third commonest cancer after breast and lung cancer; both the frequency and incidence are increasing. The three main clinical questions are: (1) What is the extent of prostate cancer when radical surgery is proposed? (2) Where is the disease when there is a rising PSA and a normal bone scan and radiology? (3) What is the significance of a PSA which is in the normal range but non-zero after radical prostatectomy or radical radiotherapy? Staging is important. The prognosis falls from 80% five-year survival to 30% five-year survival if a single node is involved with prostate cancer.

The imaging questions therefore are: (1) Is the prostate capsule breached? (2) Is there local node involvement? (3) Is there extra pelvic node involvement? (4) Is the skeleton involved? The last question is usually answered with the methylene diphosphonate (Tc-99m MDP) bone scan. A recently positive bone scan will reflect the presence of metastases, whereas a persistently positive bone scan may represent the healing process continuing and the effect of hormonal therapy, rather than persistence of active metastases. Painful bone metastases may be treated using Strontium 89, or Sm-153 EHMDP radionuclide therapy[1].

Imaging

After the first suspected detection of prostate cancer (either by digital rectal examination or screening with PSA), transrectal ultrasound with multiple biopsies of the prostate is required. The number of positive biopsies provides a Gleason score; the higher the Gleason score the worse the prognosis and the greater the likelihood of the cancer spreading through the capsule or to local regional nodes. It is difficult for ultrasound, CT and MRI to demonstrate capsular involvement and particularly regional node involvement since involved nodes may not be enlarged beyond the 1 cm threshold for a 'normal' node.

It is clear that cancer cells must be present in a normal-sized node in order for their multiplication to lead to an enlarged lymph node. In principle the presence of malignant cells in a normal-sized node can be determined by nuclear medicine techniques, since their strength is identification of cancer cells, as different from normal cells and the technique does not depend solely on physical size or contrast. There is a large amplification factor.

For antigens, there may be between 5000 and 50 000 antigens expressed on a particular cancer cell with which an appropriate monoclonal antibody radiolabelled with Tc-99m or Indium-111 can bind. There may be between 5000 and 10 000 receptors on a particular cancer cell with which a radiolabelled peptide may be chosen to bind.

Most cancer cells have an increased glucose utilisation and an up-regulation of the glucose-1 transporter protein by a factor of five to ten and an up-regulation of the hexokinase enzymes by a factor of two to three. These enable the use of F-18 deoxyglucose (FDG) with a positron emission tomography (PET) camera, whose sensitivity is about 100 times greater than the conventional gamma camera. These large amplification factors mean that the radioactive pinhead may be detected

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if it has sufficient radioactivity on it and a sufficiently sensitive detector. In the context of prostate cancer[2], glucose utilisation is unfortunately at a low level in the initial stages (as compared to lung, breast or colon cancer) and only rapidly progressive metastases of prostate cancer are reliably FDG positive.

As yet no particular receptors have been identified as specific to prostate cancer. However, a number of antigens appear to be prostate cancer specific and radiolabelled monoclonal antibodies to detect prostate cancer and demonstrate its potential spread are being evaluated. Radiolabelled antibodies against PSA and against plasma acid phosphatase have not been successful, since the avidity of the circulating antigen binds the injected radiolabelled antibody and no reliable imaging is obtained of the cancer. This is not however true for monoclonal antibodies against the prostate specific membrane antigen (PSMA) whose use is becoming an important part of the management of patients with prostate cancer[3–8].

Radio-immunoscintigraphy with anti PSMA

PSMA, also sometimes called PMSA (prostate membrane specific antigen), is a 100 K Dalton glycoprotein antigen related according to different authors to the transferrin receptor, folate dehydrogenase, and a neuropeptidase. It is a trans-membrane protein with an external and internal domain. The intra-cellular domain has antigens, against which the monoclonal antibody CYT 356 labelled with Indium-111 is commercially available as Captomab pendetide (Prostascint, Cytogen Corporation). It has also been labelled with Tc-99m called CYT 351, Prostatec[9].

The extra-cellular domain has an antibody developed by Bander called MUJ-591 which has been radiolabelled with I-131[10] and with Tc-99m[11]. Experimental studies with I-131 or Y-90 radionuclide therapy agents have been undertaken with both these classes of antibody[12].

Radioimmunoscintigraphy has a number of requirements for success. The antigen should be as specific as possible to the cancer. A monoclonal antibody should be available with high avidity that binds to this cancer antigen. It should be radiolabelled with the best radiolabel: Indium-111 or preferably Tc-99m. The radiolabelling method must preserve the antibody's binding efficiency. The imaging system must be optimised for the energy of the radionuclide and the position of the patient. Single photon emission tomography (SPET) is essential and image analysis techniques are required.

The rules of radioimmunoscintigraphy are simple. Specific uptake increases with time so that an image shortly after the injection of the radiolabelled monoclonal antibody provides a tumour-free template with which the later images can be compared. Non-specific uptake after the initial distribution decreases with time as the blood level of the agent decreases. The higher the count rate, the better the detection and the smaller the lesion detected[13].

Indium-111 anti-PSMA

The product Prostascint (Cytogen Corporation) has been in use in the United States for several years, with over 22 000 patient studies, and virtually free of side effects[4–8]. The imaging protocol requires planar, squat and SPET studies at 1, 24 and 48 h. The two Indium-111 peaks at 171 and 252 Kev are summed with 15% windows. A medium-energy parallel-hole collimator is used. A 128×128 matrix with 800 Kc for planar imaging, 400 Kc for squat views, and 60 projections (360 degrees, 40 seconds per projection) for SPET. The 1 hour, planar and SPET images are compared with the later images to see if a site of specific activity increasing with time is detected in the prostate, the prostate capsule, the obturator nodes, pelvic nodes or paraaortic nodes.

Our own experience[14] concerns 49 patients, of whom 36 were untreated primary prostate cancer patients and 13 were for follow-up. Of the 36 patients, 16 had radical prostatectomy, 17 had radical radiotherapy, of whom there was extra prostatic disease on the scan in seven, and three had hormone therapy. Of the 16 patients with radical prostatectomy, eight had the perineal approach, so no histology of lymph nodes was obtained, and eight had a retropubic and lymph node dissection approach. In these eight patients with nodal histology, none of the nodes were involved. In six patients, the images of the nodes were negative, but in two patients there was positive nodal uptake on imaging. It happened that in those two patients the surgical margins contained malignancy on histology.

Of the 13 patients who underwent imaging during their follow-up where there was a rising PSA, 10 patients had positive immune scans after radical treatment, four with uptake in the prostate bed and six with pelvic or distant disease. The three patients receiving hormone therapy also had positive imaging. The conclusion from this study was that all localised prostate cancer was imaged positive; six out of eight immune scan-negative nodes were negative on histology. 13 out of 13 patients with a rising PSA had disease localised by the immune scan and treatment of patients with immune scan-positive sites led to a fall in PSA[14].

The advantage of Indium-111 as a label is that there is less bladder activity than with Tc-99m. However, the disadvantages include the requirement for a longer study period, more bowel and rectal uptake, more marrow uptake, a higher effective radiation dose to the patient and the requirement of the technical procedure to change from the usual low-energy collimator to a medium-energy collimator. The use of a thick-crystal camera is preferred.

Tc-99m labelled anti-PSMA

The antibody used in Prostascint was kindly provided to us by the Cytogen Corporation for radiolabelling with Tc-99m. The imaging protocol concerned images at 1, 4 and 24 h together with planar, squat and SPET views. A range of patients was studied: those with clinically localised prostate cancer, those in whom prostate cancer was an incidental finding after transurethral prostatectomy for prostatic hyperplasia, those who had a rising PSA on follow-up and some patients with known metastases, in whom the PSA was rising or falling. The overall accuracy was 92% and two patients were saved unnecessary prostatectomy through the demonstration of pelvic and extra pelvic metastases. Patients with a positive bone scan and a rising PSA showed uptake in the bone metastases, however, patients under treatment with bone metastases seen on the bone scan but with a falling PSA did not show uptake of the antibody. This probably reflects the bone scan representing a healing process while still positive, rather than active disease[9].

Tc-99m MUJ 591

A pilot study of radioimmunoscintigraphy of patients with prostate cancer, selected for consideration of radical prostatectomy, was undertaken in 24 patients. All patients had biopsy evidence of prostate cancer, normal bone scan and no radiological evidence of extra prostatic spread. A further four patients were imaged for suspected progression after prostatectomy. 600 MBq Tc-99m MUJ 591 was injected intravenously with planar, squat and SPET imaging at about 1 and 24 h. In three patients the demonstration of extra pelvic disease saved them from an inappropriate prostatectomy. Nine out of 14 patients received radical radiotherapy combined with adjuvant LHRH therapy. Pelvic nodal images were positive in five but no histological confirmation was possible. Three out of four patients who underwent imaging for suspected progression showed disease not detected by bone scan or by radiological techniques. In summary, all patients with prostate cancer had the prostate cancer detected by radioimmunoscintigraphy (28/28). Non-involvement or obturator and pelvic lymph nodes was confirmed in 13 to 14 patients who underwent surgery; histology was obtained. There was one false positive. Disease progression has occurred in three out of these 14 to date. Two of the patients were found to have extra pelvic disease on imaging[11].

This pilot study of prostate cancer and radioimmunoscintigraphy with Tc-99m MUJ 591 indicated that it was a promising approach to selecting patients for radical prostatectomy. In the USA the use of this antibody for therapy is being investigated, labelled either with I-131 or Y-90[12] and the antibody has been humanised and has been licensed to a commercial company.

Conclusion

Monoclonal antibodies against the prostate-specific membrane antigen whether the external domain (MUJ 591) or the internal domain (CYT 356), labelled with Tc-99m or with Indium-111, are showing promise in solving important clinical management problems in patients with prostate cancer. They aid the determination of the operability of prostate cancer. They help to resolve the problem of the slightly raised PSA after prostatectomy or radical radiotherapy and they are able to localise the soft tissue cause of a rising PSA in patients suspected of metastases but with a normal bone scan and radiology. As these imaging agents become more widely available so they will affect the general management of patients with this common cancer[15].

Questions

1. How best to demonstrate that Prostate cancer is confined to the prostate?

2. How best to evaluate the post radical prostatectomy or post radical radiotherapy patient who has a follow up PSA greater than 0.0 but less than 2.0?

3. How best to evaluate the patient with a rising PSA post primary treatment when bone scan and radiology are negative?

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