Chapter 58
What are the treatments for organ-confined prostate cancer and how effective are they?

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Organ-confined or localized prostate cancer is a malignancy in which there is no outgrowth or extension of tumor beyond the capsule of the prostate. The prostate gland is an accessory sex organ in men which provides a component of seminal fluid during ejaculation. However, with age, 1 out of 8 men will develop tumors in the prostate gland and 1 out of 41 men will die from this disease. The adenocarcinoma develops in the peripheral region of the prostate gland. In general, prostate cancer is slow growing in the majority of the patients as it takes decades to develop; however, in some patients it eventually metastasize to various parts of the body (e.g., lymph nodes, lung, brain and bone) and becomes deadly. In this chapter we will discuss how the organ-confined/localized prostate cancer is diagnosed, what the hallmarks of organ-confined prostate cancer are, and what the current treatment options for organ-confined prostate cancer and their effectiveness are.

How to detect an organ-confined prostate cancer?

The clinical course of newly diagnosed organ-confined prostate cancer can vary. Prostate cancer is diagnosed by evaluating serum concentration PSA (prostate specific antigen), digital rectal examination (DRE), magnetic resonance imaging (MRI), computed tomography (CT) scan, bone scan and prostate biopsy.

PSA (also known as kallikrein III, seminin, semenogelase, γ-seminoprotein and P-30 antigen) is a 34-kDa secretory glycoprotein serine protease produced in all mature glandular epithelial cells of the prostate gland as well as by prostate cancer cells. In adult men, blood PSA level ranges from 0.5-4 ng/ml and its level increases with the development of prostate cancer (above 4 ng/ml to 600ng/ml or more). Using blood PSA as a screening tool is controversial due to the fact that it is also increased in benign prostatic hyperplasia

(BPH) and prostatitis; however, it is the easiest and most commonly used test we have at this point. PSA concentrations reaching between 4 to 10 ng/mL are considered suspicious. Once PSA level is suspicious, digital rectal examination of the prostate through the wall of the rectum is generally performed. Hard or nodular areas in the surface of the prostate gland indicate that cancer may be present and require further investigations.

MRI is performed to obtain a detailed picture of the prostate gland and the surrounding tissues. MRI helps the urologist decide whether the patient needs a biopsy, and which areas of the prostate should be targeted for needle biopsy. Similarly, CT scan can be done after a prostate biopsy to determine if the cancer has spread outside the prostate to the surrounding lymph nodes. To determine if the lump of tissue is malignant or not, a thin needle biopsy is used to take small pieces of tissue from the prostate. Histological assessment of the tissue is essential to determine if a malignant tumor has formed. Biopsy results also show how aggressive the cancer is (how likely it is going to spread outside the prostate gland). Under the microscope, pathologists give a Gleason score or grade based on the patterns of epithelial cells in its surrounding stroma (Fig. 1). The Gleason grade is given from 1 to 5. The Gleason score is determined by adding together two Gleason grades. The first is the most prevalent grade in the entire samples collected and the second is the highest grade within the tissue biopsy. When these two grades are added together, the total is called the Gleason score. For example, if the biopsy samples from a patient show that most of the cancer seen is grade 3, and the highest grade of any other cancer seen is grade 4, then the Gleason score will be 7 (3+4). It is also important to note that individual scores are also very important. For example a Gleason score of 4+3 dictates that the cancer is relatively more aggressive compared to a score of 3+4, as there is more grade 4 cancer, although the total Gleason score is 7 in both cases. In some patients the Gleason score could be made up of two of the same Gleason grades, such as 3+3, this means that no other Gleason grade was seen in the entire biopsy samples. A Gleason score of 6 (3+3) will be low risk compared to a Gleason score of 10 (5+5) which is a high risk. In addition to Gleason scores, Gleason 'grade group' is also a newer system for describing how aggressive a patient's prostate cancer is likely to be. A grade group (1 to 5) is given based on the

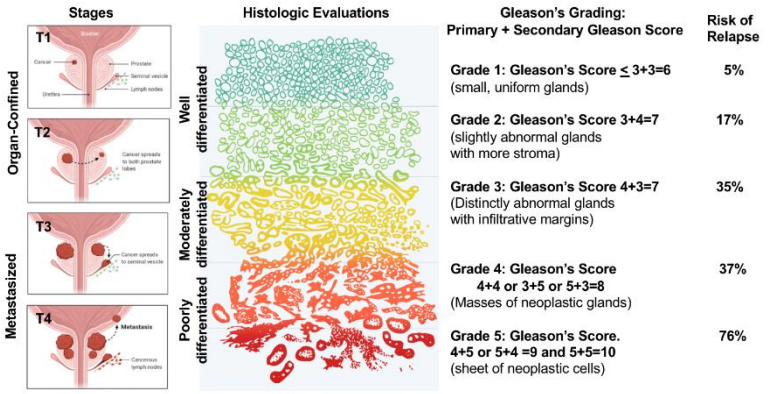

Figure 1. The cartoon showing stages of organ-confined and metastatic prostate cancer with histologic features (well-differentiated, moderately-differentiated and well-differentiated) and Gleason scores (created with BioRender).

Gleason score. A Gleason score of 6, is equivalent to grade group 1, suggests the cancer is likely to grow very slowly, if at all, for example localized prostate cancer. Whereas a Gleason score of 7, will be equivalent to a grade group 2 or 3, suggests the cancer may grow at a moderately quick rate and a Gleason score of 8, 9 or 10, will be equivalent to grade group 4 or 5, indicates the cancer may grow more quickly. In addition to the Gleason score, MRI and CT scan results can be used to determine if there is any metastasis of cancer cells and how far they has spread. This staging system is usually recorded using the TNM (Tumor-Nodes-Metastases) system. The T stage shows how far the cancer has spread in and around the prostate. The N stage shows if the cancer has spread to surrounding lymph nodes and the M stage shows if the cancer has spread to other parts of the body. T1 prostate cancer can't be felt during a DRE or scans; however, it can be detected during the evaluation of tissue biopsies. T2 prostate cancer can be detected during a DRE or can be seen on MRI or CT scan, but is still contained inside the prostate. This staging can be subdivided as T2a: when the cancer is in half of one side (lobe) of the prostate, or less; T2b when the cancer is in more than half of one of the lobes, but not in both lobes of the prostate; and T2c: dictates the cancer is in both lobes but is still inside the prostate. Higher stages (T3 and T4) indicate that the prostate cancer

has spread outside the prostate and is no longer an organ-confined prostate cancer. The N stage diagnosis means the cancer has spread to the lymph nodes near the prostate. For example, if patient's blood PSA is less than 10 ng/ml, cancer Gleason score is 6 or less (grade group 1), and the stage of cancer is as T1-T2a, N0 (no cancer can be seen in the lymph nodes) or NX (lymph nodes were not looked at, or the scans were unclear) and M0 (no metastasis), it is likely that cancer is completely localized within the prostate gland and has not spread to the lymph nodes or other parts of the body.

What are the treatment options for organ-confined prostate cancer and what are expected outcome?

Most of the organ-confined or localized prostate cancer grows very slowly, and therefore, might not need treatment at all. However, localized cancer needs to be monitored on a regular basis by active surveillance or watchful waiting.

Active surveillance is suitable for those patients with low risk prostate cancer. It can also be recommended for patients with intermediate risk prostate cancer, but not for high risk prostate cancer. During active surveillance patients should be monitored with regular blood PSA tests, MRI and biopsies. If any of these tests find changes from the previous tests then the patient might need treatment or complete removal of the cancer by surgery, or external beam radiotherapy or brachytherapy.

Watchful waiting is a way of monitoring a patient's prostate cancer that isn't causing any symptoms or problems. The objective is to monitor cancer growth and serum PSA levels to avoid cancer treatments. However, if symptoms develop, a hormone therapy to control the cancer growth could be used to help manage symptoms. Watchful waiting involves fewer tests than active surveillance and is generally suitable for patients with other health problems and not fit for surgery or radiotherapy. It might also be suitable for older patients whose prostate cancer isn't likely to cause any problem over their lifetime.

The main treatments for localized prostate cancer are: 1) surgery (radical prostatectomy), 2) external beam radiotherapy, and 3) brachytherapy. High-intensity focused ultrasound (HIFU) or cryotherapy can also be used but they are less common. Radical prostatectomy is a surgery to remove the prostate, including the cancer inside it. It can be done in three ways: laparoscopic (keyhole) surgery by hand or by robot-assisted and open surgery. External

beam radiotherapy (high-energy X-ray beams) can be used to destroy cancer cells from outside the body. In high risk patients, hormone therapy, also known as androgen suppression therapy is generally used to shrink the prostate and the cancer, making it easier to perform the surgery or to treat with external beam radiotherapy. There are many options such as, LHRH agonist or antagonist and fist and second-generation anti-androgens. Brachytherapy is a type of internal radiotherapy. It can be used together with external beam radiotherapy to give an extra dose of radiotherapy to the prostate. High-intensity focused ultrasound (HIFU) and cryotherapy use ultrasound to heat and destroy cancer cells. Cryotherapy uses extreme cold to destroy cancer cells. There's no overall best treatment for organ-confined prostate cancer. Each treatment has its own advantages and disadvantages and the type of side effects develop depends on the treatment being performed. Recently, a new technique known as CyberKnife or stereotactic body radiation therapy (SBRT), is used as a better non-surgical option for localized prostate cancer where it destroys tumors by providing beams of radiation at the cancer from multiple directions while sparing healthy tissues surrounding it. It is a very accurate, and effective treatment option for localized tumors in particularly hard to reach areas. Since it uses a combination of computers, image-guided cameras, and robotic technology, it can directly target tumor cells while sparing the nearby healthy tissue. Since there is no surgery involved, patients do not feel any discomfort during the treatment or experience minimal or no side effects. The patient needs less than five sessions, compared to traditional radiation therapy, which may require as many as 40 sessions. Moreover, it does not require anesthesia, incisions, or blood loss, therefore, recovery is quicker than traditional radiation therapy.

Conclusion

Because of the slow growth of prostate cancer, the majority of patients with organ-confined prostate cancer will survive. In fact, the majority of the patient may not need any treatments, watchful waiting or active surveillance will be good enough. However, some patients will need radical prostatectomy and targeted external beam radiotherapy (Cyberknife) is a very effective treatment options for organ-confined prostate cancer with a 5-year biochemical recurrence-free survival rate of about 90%. However, we must understand that prostate cancer is a multifocal disease. Currently

focal targeted therapy depends on the removal of prostatic foci based on saturation biopsy. So the potential risk of incomplete treatment might miss some cancer foci and might cause relapse of cancer again. Since we still do not have appropriate biomarkers for aggressive prostate cancer, it is hard to determine which organ-confined cancer foci will grow aggressively and which will be indolent. Therefore, future discoveries of better biomarkers for aggressive prostate cancer and technical advances in imaging tools would greatly improve the targeted therapy for men with organ-confined prostate cancer, so that organ-confined prostate cancer will no longer be a deadly disease.

Suggested reading

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