Advances in the diagnosis and treatment of prostate cancer

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Abstract: Prostate cancer is a complex disease that is accompanied by a vast amount of treatment options whose effects depend on variety of factors. New strategies have been developed within the past 10 years that have brought on more effective treatments in diagnosing and treating prostate cancer. In this review, we discuss the latest diagnosis and treatments for prostate cancer and present their shortcomings to outline a future direction of development. At present, significant progress in the diagnosis and treatment of prostate cancer has been made although the limitations seen reveal that there are still more aspects to be explored.

1. Introduction

With the growth of an aging population, occurrences of prostate gland diseases in the elderly have been on the rise. Epidemiological data reveal prostate cancer to be the most prevalent non-dermatological cancer among males in western countries, and roughly 192,000 males are annually diagnosed with prostate cancer in the United States [1]. Despite the increase of prostate cancer occurrences, methods of diagnosis and treatment have also evolved to become more sophisticated and advanced in the last few years. A variety of treatment options now exist, including radical prostatectomy, radiation therapy, androgen-deprivation therapy, and the administering of radiopharmaceutical agents [2]. This review will focus on highlighting a few of the exciting technologies that have advanced the diagnosis and treatment of prostate cancer.

2. The debate between surgical intervention and watchful waiting

Elevated levels of the prostate-specific antigen (PSA), a glycoprotein produced specifically by epithelial cells of the prostate gland and released into the circulation, have been used since 1987 as a means of monitoring males with suspected or diagnosed prostate cancer [3]. However, other factors unrelated to prostate cancer may also cause an increased level of circulating PSA. These "false positives" have created controversy as to the true benefits achieved by early detection via PSA screening [4]. One of the main reasons for such controversy arises from the lack of randomized clinical trials that compare and examine the outcomes of early PSA screenings and subsequent aggressive treatments. Although the rates of death in the United States have declined since the introduction of PSA screenings, rates of death in England and Wales have similarly exhibited a decline despite lower attention and emphasis on PSA screenings [5].

A recent clinical, randomized study by Bill-Axelson et al examined the clinical benefits of early PSA screening for patients diagnosed with localized prostate cancer [6]. Researchers selected patients who were diagnosed with localized prostate cancer, were less than 75 years old, had no other known cancers, and had a life expectancy of more than 10 years. A total of 695 patients were randomly assigned to either a radical prostatectomy (RP) group or an observation group (termed "watchful waiting", WW).

After conducting a 23-year follow up, researchers discovered the RP procedure to reduce short-term patient mortality. Specifically, 200 of 347 men in the RP group and 247 of 348 men in the WW group died over the observed period, and it was estimated that 8 patients (from each group) needed treatment to prevent one death. Of the patients receiving RP, 63 deaths were due to prostate cancer while the WW group

exhibited 99 deaths attributed to cancer. Less metastases occurrences were detected in the RP group and fewer patients were eventually placed on androgen-deprivation therapy, a common second-line of defense treatment. The beneficial effect of RP was determined to be age-related, as males less than 65 years of age – in addition to those with intermediate-stage tumors – were found to have less metastases and need for palliative treatment. Despite these mentioned benefits, however, it should be noted that some patients in the RP group developed complications of urinary incontinence and erectile dysfunction within two years of the surgery. The results of this study suggest that RP after PSA screenings do not necessarily eradicate prostate cancer in the long-term but do buy the patient time and reduce the likelihood of metastasis. Clearly, more efficient detection and treatment methods are needed to minimize the number of these mortalities.

3. Comparison between MRI- and ultrasound-guided biopsies

A patient suspected of prostate cancer based off the results of a PSA test and/or a digital rectal exam would then have a biopsy taken of the prostate for further analysis. This is commonly done by performing an ultrasound-guided transrectal biopsy, which consists of inserting needles through the rectum lining to take small tissue samples from various areas of the prostate. The sextant biopsy protocol (removing six cores from around the paramedian region of the prostate) has been the standard for many years. However, it has been reported that biopsies obtained from these six cores do not detect all incidences of cancer and in fact miss about 10-30% of prostate cancers [7]. Eichler et al compared clinical findings of 20,698 patients from 13 different electronic databases to outline the relationship between the number of biopsies and cancer detection rates, and found that removing 12 biopsy cores rather than the original 6 resulted in the highest cancer detection levels (and had the least adverse effects) [8]. Interestingly, additional biopsy samples from laterally directed cores significantly increased the yield of cancer detection while increasing the amount of central cores did not produce any beneficial change. Procedures with 18-24 cores did not increase cancer detection and instead produced an increased amount of adverse events. While the 12-core ultrasound-guided transrectal biopsy exhibits 40-45% prostate cancer detection rates, there is an estimated 20-24% chance of false negatives that will occur [9,10].

Emerging technology using magnetic resonance imaging to procure these biopsies has become attractive recently due to its sensitivity and ability to distinguish between benign and malignant tissue within the prostate and adjacent lymph nodes. Schoots et al conducted a meta-analysis and reported that MRI-guided and ultrasound-guided biopsies had similar cancer detection rates in patients with clinical suspicion (i.e. visible lesions in the prostate as detected by MRI) [11]. However, Schoots et al did find that MRI-guided biopsies had higher rates of detecting significant prostate cancer (i.e. malignant) and lower rates of detecting insignificant prostate cancer (i.e. benign) when compared to similar cancer detection rates via ultrasound-guided biopsies.

Recently, Abdi et al looked at 283 out of 2,416 male patients who were suspected of prostate cancer and had received either ultrasound-guided and/or MRI-guided biopsies [12]. Of the 283 examined, 86 patients had lesions detected in their MRIs that could not be detected via ultrasound. Abdi et al concluded that MRI-guided biopsies improved the detection rate of significant prostate cancer in patients with prior negative ultrasound-guided biopsies. In an analogous study, Kim et al carried out an in-house institution study comparing MRI or ultrasound-guided biopsies in the accurate detection of prostate cancer [13]. Patients were matched by age, PSA levels, prostate size, and ethnicity. Kim et al found that patients who underwent MRI-guided biopsies had a 76% rate of prostate cancer detection while those undergoing conventional ultrasound-guided biopsy had a 56% detection rate. Similarly, Ukimura et al examined the diagnostic yield of performing MRI-guided biopsies on lesions that looked suspicious only on an MRI as opposed to lesions that seemed suspicious on both MRI and transrectal ultrasound [14]. Looking at 127 patients, they found that the suspicious lesions that could be detected only by MRI corresponded with an increased positive biopsy rate and higher Gleason score. Ukimura et al suggests greater diagnostic yield may be achieved if suspicions detected by ultrasound could be combined with information provided by an MRI to evaluate specific lesion sites within the prostate.

4. Robotic-assisted laparoscopic surgery

While radical prostatectomy has become the gold standard for treating prostate cancer patients, the procedure has been plagued by frequent morbidities. In the past few years, surgeons have been striving to improve their technique to create more effective alternatives. Due to the clarity, precision, and dexterity achieved by robotic machines, robotic-assisted laparoscopic prostatectomy (RALP) operations have drawn a lot of attention from surgeons and has increased in usage since 2010 [15]. Many changes and modifications have been made to the robotic-assisted procedure since Binder first performed in 2000 using the da Vinci Surgical System [16]. As with most newly developed surgical techniques, however, the introduction of new procedures implies a rush of newly trained surgeons and inevitably higher chances of complication rates throughout these learning curves. Vascular injuries are perhaps the most common complications in RALP procedures as they can occur during the first stages of surgery (i.e. trying to get into the abdominal cavity) as well as during intraoperative and postoperative care [17]. The risk from RALP is small, as Patel et al followed one surgeon who operated on 1500 patients and determined the risk of RALP complications to be 4.3 % of cases and concluded there to be no mortalities associated with the procedure [18].

Two major factors affecting patient quality of life after a radical prostatectomy are urinary incontinence and erectile dysfunction. Hakimi et al compared RALP procedure outcomes to human-performed laparoscopic radical prostatectomies (LRP) performed by a single surgeon [19]. They looked at 75 patients who underwent RALP and 75 patients who underwent LRP, all with similar age, preoperative PSA levels, and initial Gleason scores. Patients receiving RALPs were found to undergo shorter operation times (199 compared to 232 minutes), exhibited less intraoperative blood volume loss (230 compared to 311 ml), and had quicker times until patient discharge (1.95 versus 3.4 days). Both procedures had roughly equivalent 12-month continence rates and potency rates, though the RALP was shown to be a superior minimally-invasive option for surgically removing prostate cancer. While data is still very limited, the RALP procedure appears equivalent in restoring functions of continence and potency within a year of the operation.

To assess the potential difficulties clinicians may have in learning to operate the da Vinci system,

Trabulsi et al reviewed the experience of a single, fellowship-trained urologic oncologist in transitioning from pure LRP procedures to a RALP program [20]. The surgeon had performed a RALP on 205 patients and a LRP procedure on 45 patients. Examining operative, pathological, and functional outcomes, the study found that the transition from LRP to RALP yielded less operating time and less blood loss. The amount of RALP procedures also dramatically increased: the institution had recorded only 200 LRP procedures between 2000-2005. With the introduction of the da Vinci Surgical System, the hospital witnessed over 400 more procedures by 2008.

5. Pharmacology and the advancement of radiopharmaceuticals

Advanced prostate cancer initially depends on androgens and can be suppressed by placing a patient on an androgen deprivation therapy (ADT). ADT aims to reduce androgen levels or block androgen receptors to stop prostate cancer cells from proliferating. In cases where ADT fails and PSA levels continually rise, a secondary treatment is initiated. Autologous immunotherapy techniques have been explored in the last few years as a method of training the patient's immune system to recognize their own prostate cancer cells. Currently, the only FDA-approved prostate cancer immunotherapy treatment being used is Sipuleucel-T (Provenge). Sipuleucel-T treatment requires leukophoresis to remove the patient's immune cells. These cells, particularly immature dendritic cells, are grown in the lab and stimulated by prostatic acid phosphatase (PAP), an antigen expressed in 95% of prostate cancers. A double-blind phase III trial gave patients either Provenge or placebo intravenous infusions every two weeks for a total of three infusions [21]. Provenge prolonged patient life by 4.1 months (a median 25.7 month-survival rate compared to the 21.7 months in the placebo group). The 3-year survival rate increased in Provenge-treated patients from 23% to 31.7%. No effects on the overall disease progression were observed, however.

As prostate cancer progresses, however, the disease appears to become more independent of circulating androgen levels. This behavior minimizes the beneficial effect of ADT and similar therapies that rely on halting androgen receptor signaling pathways. In castration-resistant prostate cancer patients with the advanced form of the disease, prognosis is extremely

poor. Scher et al summarized their phase III findings using the new drug, Enzalutamide (previously known as MDV3100), to treat patients with castration-resistant prostate cancer after chemotherapy [22]. Enzalutamide is being explored for its ability to function as an androgen-receptor signaling inhibitor. Unlike other anti-androgen pharmacological agents, Enzalutamide has a greater affinity for the androgen receptor and inhibits translocation of this receptor into the nucleus. Previous phase I and II studies demonstrated anti-tumor activity and gave researchers an idea of the dosage level required to harness these effects [23]. In their Phase III trial, Scher et al performed a double-blind, placebo-controlled clinical trial and randomly assigned 800 patients to receive Enzalutamide (dosage: 160 mg per day; primary endpoint was overall survival) and assigned 399 patients the placebo. During an interim analysis (i.e. after 520 deaths), researchers found Enzalutamide to increase the overall survival rate from 13.6 months to 18.4 months.

It is only until prostate cancer spreads beyond the prostate and hormone therapies, such as ADT, are no longer effective that chemotherapy is administered. Currently, the most common chemotherapy agent given is docetaxel (Taxotere). A study by Unger et al found that of 6561 patients with metastatic prostate cancer, 1350 subsequently received chemotherapy. Of these 1350, 95% of these patients received docetaxel chemotherapy treatments. Docetaxel has replaced its predecessor chemotherapy drugs after having been shown to significantly extend patient life [24].

Once prostate cancer has spread outside the prostate, a major focus of treatment is to prevent its metastasis to the bones. Bone metastasis is painful and can induce a variety of additional problems and place the patient at high risk for fractures, spinal cord compression, and high blood calcium levels. The use of radiopharmaceuticals has been investigated due to their localization to highly metabolically active bone and ability to emit radiation that can eradicate cancerous cells. Whereas external beam radiation localizes the radiation to a certain area, injected radiopharmaceuticals hone to all areas of damaged bone simultaneously. Of the three radiopharmaceuticals available, only radium-223 dichloride (Xofigo, formerly called Alpharadin) has been shown to both relieve pain and extend life (the other two are strontium-89, or Metastron, and samarium-153, or Quadramet).

An analog to calcium, radium-223 has natural bone-honing abilities and selectively binds to newly formed bone matrix [25]. Once binding to metastatic lesions, radium-223 emits high energy α-particles within a short-range radius of 100 μm. The emitted α-particle radiation induces irreparable double stranded DNA breaks to induce cell death, while not affecting deeper, more sensitive areas like the bone marrow. A clinical trial conducted by Sartor et al gave 614 metastatic castration-resistance prostate cancer patients radium-223 and 307 patients a placebo [26]. Assessing the delay of symptomatic skeletal events, the group concluded that 33% of patients in the radium-223 group and 38% of patients in the control group developed skeletal event symptoms. Despite the similarities, radium-223 did delay the onset of skeletal events from 9.8 to 15.6 months in addition to reducing the risk of external beam radiation therapy used to treat bone pain.

As some patients have received previous administrations of docetaxel, Hoskin et al looked at the effects of previous docetaxel use on the outcomes of radium-223 treatment and showed radium-223 to be safe and effective in patients regardless of previous exposure to docetaxel [27]. Patient data was pooled from the phase 3 ALSYMPCA (ALpharadin in SYMptomatic Prostate CAncer patients) clinical trial, where patients who were or were not exposed to docetaxel in the past were given either radium-223 or a placebo [28]. Currently, both the National Comprehensive Cancer Center and the American Urological Association recommend radium-223 as a first line of defense against prostate cancer after receiving docetaxel treatment, and new clinical trials are being conducted to elucidate the optimal combination of docetaxel and radium-223 (NCT01106352).

6. Conclusions

In the last 10 years, we have witnessed the explosion of exciting technologies that equip clinicians and surgeons with better tools to more efficiently diagnose and treat early and advanced prostate cancer. Early prostate detection by PSA screenings has certainly been responsible for increasing survival rates of prostate cancer. As robotic-assisted prostatectomies are becoming more prevalent, complications associated with prostatectomies are decreasing. New immunotherapies, such as Sipuleucel-T, give the

patient the ability to train autologous immune cells to attack their own tumor cells. The development of Enzalutamide as a chemical agent with higher affinity for the androgen receptor has helped extend patient life by blocking the androgen-receptor signaling pathway in patients with castration-resistant prostate cancer where traditional androgen-deprivation therapy has ceased to work. Finally, clinicians are trying to optimize the potent, specific effects of radiopharmaceuticals, like radium-223 dichloride, along with chemotherapy treatments to prevent and treat prostate metastasis to the bone. Future technologies will most likely incorporate combinations of these therapies in a patient-specific manner to deliver the optimal prostate cancer treatment.

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