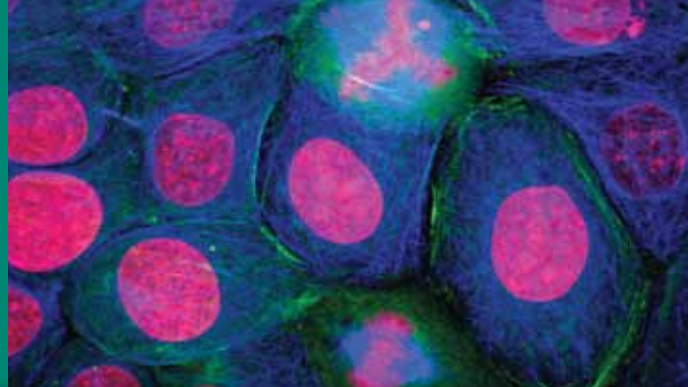




CEDARS-SINAI

**SAMUEL OSCHIN COMPREHENSIVE
CANCER INSTITUTE**



ADVANCES IN CANCER

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Case Study: Postoperative Radiation Therapy for Prostate Cancer

Howard M. Sandler, MD

Prostate cancer is a common problem for US men. Once patients are initially diagnosed, they are often treated with either surgery or radiation therapy. For those whose initial treatment is radical prostatectomy, recurrences of cancer can be detected at an early stage by monitoring the blood levels of prostatic specific antigen (PSA). Once the PSA level becomes detectable, radiation therapy delivered to the pelvic area can often completely eradicate the cancer that is the source of the PSA. Radiation therapy is delivered in a highly focused manner, treating the prostate bed (and sometimes nearby lymphatic drainage sites), and the treatment is associated with minimal side effects.

Presentation

A 69-year-old gentleman was found to have prostate cancer in late 2000 with a PSA elevation to 3.6 ng/ml, a significant rise compared with previous values. A prostate biopsy revealed Gleason 7 adenocarcinoma. In March 2001, he underwent radical retropubic prostatectomy and bilateral lymphadenectomy. Pathology confirmed Gleason 7 adenocarcinoma with a positive apical margin. Initially his postoperative PSA was undetectable, but gradually it became elevated and by May 2009 was 1.0 ng/ml. He had no clinical symptoms to suggest metastatic disease, and he was evaluated for a course of radiation therapy. Because of the PSA of 1.0 ng/ml, he was evaluated with a high field strength, 3T pelvic MRI, and no gross residual disease was seen in the prostatic fossa. Additionally, he had no evidence for metastatic disease on bone scan.

The patient had a radiation therapy treatment planning CT scan to create a 3-dimensional model of the pelvic region. The appropriate radiation therapy target (prostatic fossa in this case) was defined, as well as nearby organs (i.e. rectum and bladder) that should be avoided.

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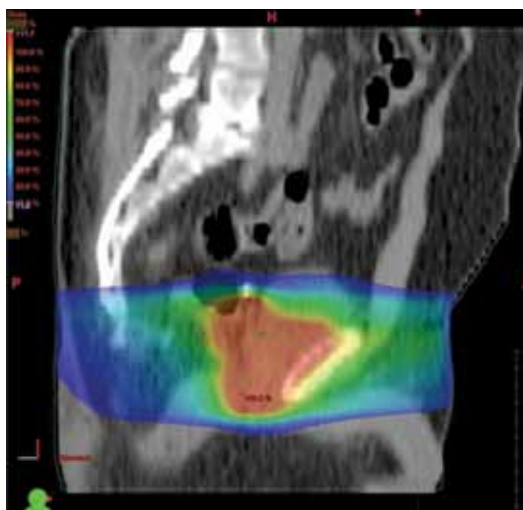


Figure 1: Sagittal view of the pelvis from treatment planning CT scan. Colorwash shows the highly conformal nature of the radiotherapy exposure; red indicates the full treatment dosage, while green and blue represent substantially lower amounts of radiation.

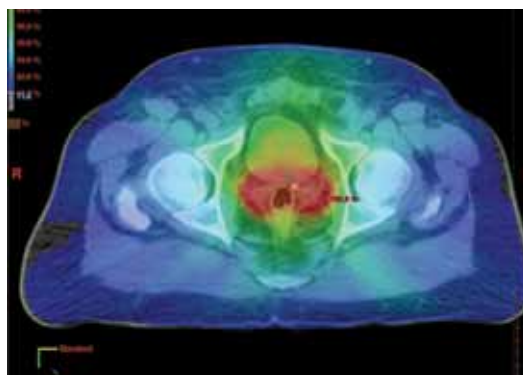


Figure 2: Axial view of the pelvis with a similar colorwash shows the intended target area (prostate bed), located between the bladder (above the prostate bed) and rectum.

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Neoadjuvant Therapy for Renal Cell Carcinoma

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Widespread use of abdominal imaging has increased the incidental detection of renal tumors (note 1). Currently, surgical resection remains the standard treatment; however, better multimodality treatment strategies are needed for management of large renal masses, which carry a significant risk of recurrence. Furthermore, large renal tumors often require radical nephrectomy, which decreases renal function and may increase the risk of future cardiovascular morbidity and death (note 2).

Neoadjuvant therapy has the potential to reduce the risk of recurrence and downstage tumors, making them amenable to organ-sparing surgeries that maximize renal function. Until recently, however, no therapies were available that significantly reduced tumor size. The recent FDA approval of sunitinib for renal cell carcinoma (RCC) provides an opportunity to evaluate neoadjuvant approaches. In patients with metastatic disease, sunitinib decreased the size of target lesions in the majority of patients (note 3). We conducted a pilot trial to determine the safety of neoadjuvant sunitinib and measure the response of the primary tumor to preoperative sunitinib therapy (IRB #I95206, Pro00019812).

Case study

A 59-year-old Caucasian gentleman was referred for management of an incidentally identified left renal mass. The tumor was centrally located and compressed the collecting system (Figure 1). The patient had normal renal function with a serum creatinine of 0.8 mg/dL. His only comorbidity was a history of hypertension, which was well-managed medically. His metastatic

workup was negative. The patient elected to participate in a clinical trial of neoadjuvant sunitinib.

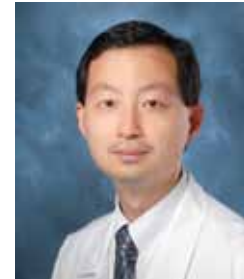
Percutaneous, CT-guided biopsy of the renal mass revealed a Fuhrman grade 3, clear cell renal carcinoma. He received sunitinib 37.5 mg daily for a total of three months. A repeat CT performed two months after starting sunitinib showed a 28 percent decrease in diameter of the tumor and a 46 percent decrease in cross-sectional area of the tumor (Figure 2). Measure of CT density following contrast enhancement showed that tumor perfusion was decreased when compared to the baseline CT.

Sunitinib was continued up to the day of surgery and the patient successfully underwent a laparoscopic partial nephrectomy. There were no complications and the patient was discharged to home on the second postoperative day. His final pathology revealed a T3a, Fuhrman grade 3, clear cell renal carcinoma with negative margins. The diameter of tumor was 3 cm on the pathologic specimen. Postoperative CT showed successful removal of the tumor with good perfusion of the remaining left kidney (Figure 3). Postoperative serum creatinine obtained two months following surgery was 0.9 mg/dL.

Discussion

This is an example of a patient with a high risk RCC localized at the time of diagnosis. The patient would have faced a significant risk of recurrence despite successful resection of the tumor. Preoperative sunitinib therapy may have reduced his risk of recurrence. Future large-scale, randomized studies with long-term followup will need to

be performed to determine if neoadjuvant sunitinib decreases the recurrence risk. For this patient, the use of preoperative sunitinib therapy did not result in unexpected surgical complications, and the tumor was down-sized, making laparoscopic partial nephrectomy feasible and maximizing the preservation of his renal function.



Dr. Kim is Associate Director for Surgical Research at Cedars-Sinai's Samuel Oschin Comprehensive Cancer Institute and Director of Academic Programs for the Division of Urology.

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2. Go AS, Chertow GM, Fan D, et al.: Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. *N Engl J Med.* 2004; 351: 1296-1305.
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Figure 1: Preoperative CT showing a 5.4 cm left renal mass.



Figure 2: CT showing that the tumor decreased to 3.8 cm after the patient received two months of neoadjuvant sunitinib.



Figure 3: Postoperative CT showing successful removal of the left renal mass and mild perinephric stranding expected in the immediate postoperative setting.

Prostate Cancer Metastasis: Emerging Science, Technological Advances

Leland W. K. Chung, PhD

Recent uro-oncology research at Cedars-Sinai has focused on several key areas with strong potential to improve the prognosis for metastatic prostate cancer. These include (1) studying cancer cell signaling networks (2) developing near-infrared (NIR) fluorescence imaging and (3) testing a microglobulin antibody to target radiation- and chemotherapy-resistant cancer.

Cancer cell signaling networks

Cancer cells have shown the ability to use previously wired cell signalling networks to “cross-talk” with neighboring cells. Such communication may facilitate osteomimicry (the ability of cancer cells to mimic bone, gaining growth and survival advantages when metastasizing to bone) and epithelial to mesenchymal transition, or EMT (the ability of cancer cells to mimic embryonic development). A collaboration between Haiyen E. Zhau, PhD and Dan Luthringer, MD has studied such signaling networks, confirming their existence in clinical prostate cancer specimens.

Also in this area, a collaboration under development by Jian Liu, PhD, Stuart Holden, MD and Mahul Amin, MD will attempt to track prostate cancer cells circulating in the bloodstream and predict the ability of those cells to metastasize. The team will use a highly sensitive and specific quantum-dot multiplexed technology developed at Cedars-Sinai to assess cell signaling networks at the single cell level. This technology has already been successfully used to differentiate localized human prostate cancer from bone metastatic human prostate cancer in archival primary tumor tissue specimens (Fig. 1A and B), and further study will involve a large bank of prostate cancer tissues with confirmed bone and visceral organ metastases (IRB #3979).

Near-infrared (NIR) fluorescence imaging

Cedars-Sinai investigators have discovered that a unique class of non-toxic, NIR indocyanine fluorescence dyes accumulates in human prostate tumor xenografts (IACUC #2999), as well as in transgenic mice bearing prostate cancer. Because of the unique affinity and transport properties of these dyes in tumor tissues, Cedars-Sinai initiated a joint research program with the University

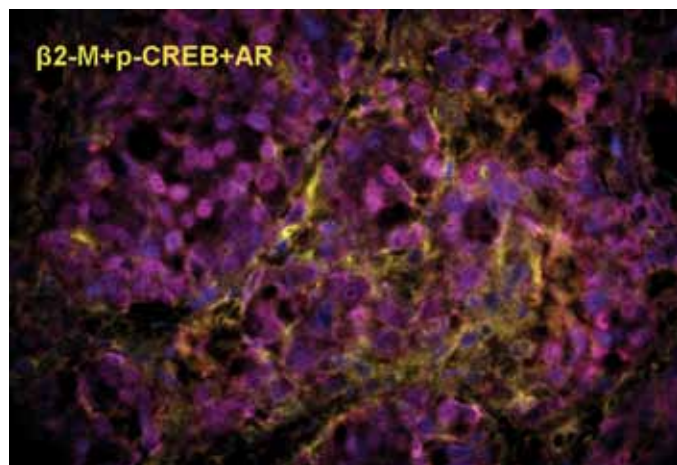


Figure 1A: Multiplexed quantum dot technology was applied to human prostate cancer tissues for the detection of three cell-signaling-associated markers.

of Illinois to examine the development of this class of dyes as potential diagnostic and therapeutic drugs. The research team synthesized a number of organic dye-drug conjugates, which were found to be extremely effective in eradicating the growth of pre-established human prostate tumors in mouse skeleton (Figure 2). We are optimistic about the prospects of this technology to be further developed, validated and applied in preclinical models.

Targeting treatment of resistant and recurrent cancer

Another promising area of investigation was opened when Cedars-Sinai uro-oncology researchers discovered a new pleiotropic cell signaling pathway mediated by an unexpected immune-responsive modulatory protein – β -2 microglobulin. We found that targeting this protein-mediated cell signaling network causes massive cell death in many types of human solid and liquid cancers, including prostate cancer (IACUC #2999).

As a result, Cedars-Sinai researchers devised a strategy to use either radiation or chemotherapy in combination with anti- β -2 microglobulin antibody for the management of prostate cancers that are considered radiation and/or chemotherapy resistant. We found that anti- β -2 microglobulin antibody lowered the resistance of prostate cancer cells to oxidative stress and decreased DNA repair and androgen receptor-mediated survival signaling, contributing to differential cancer cell-kill without affecting the growth of normal cells. The combination of this antibody with either radiation or chemotherapy could restore the sensitivities of recurrent prostate cancer cells that are currently considered radiation- or chemotherapy-resistant (Figures 3A and 3B).

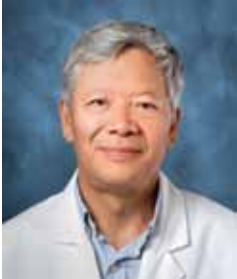
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Localized PCa Tissue	Gleason Grade	Metastatic State	No. of Cancer Cells Counted	% Triple Positive
1	3	No	300	3.3
2	4	No	200	74
3	4	No	200	0
4	3	No	100	0
4	4	No	100	0
5	4	No	200	0
6	3	No	200	0
7	3	Yes	100	59
7	3	Yes	100	55
8	3	Yes	100	61
8	4	Yes	100	73
9	3	Yes	100	48
9	4	Yes	100	78
10	4	Yes	200	90

Figure 1B: Triple positive labeling of β 2-M/p-CREB/AR in human prostate cancer archival tissues is an excellent predictor of the progression of prostate cancer from primary to bone metastasis.

Metastasis: continued from Page 3

The Cedars-Sinai research community is positioned to continue making important new discoveries related to prostate cancer. With prostate cancer affecting one in six men in the United States, it is our hope to rapidly translate such bench discoveries to the clinic as rapidly as possible for the benefit of cancer patients.



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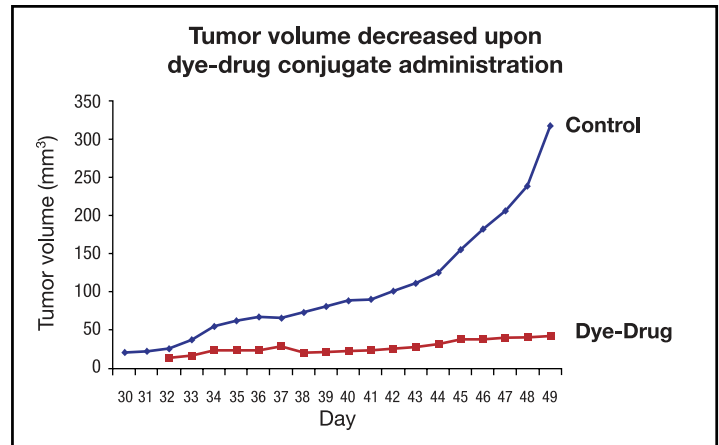


Figure 2: The marked growth-inhibitory effect observed by intraperitoneal injection of a dye-taxotere conjugate on the growth of subcutaneous human prostate tumors in mice. No systemic toxicity was noted in mice treated with this dye-taxotere conjugate, whereas the unconjugated taxotere-treated mice lost 50 percent of body weight.

Radiation: continued from Page 1

Treatment planning consisted of intensity modulated radiation therapy (IMRT) using inverse planning with dose constraints on the rectum and bladder. A planned dose of 70.2 Gy in 1.8 Gy fractions was devised. Therapy was delivered using a new image-guided IMRT technology that quickly and painlessly circles the patient while thin lead shielding devices move quickly back and forth under computer control. This method comprehensively treats the intended target while minimizing dose to rectum and bladder. The entire daily treatment session can be delivered in two minutes.

Prognosis

The patient tolerated his full dose of 70.2 Gy with minimal acute morbidity. Overall, his prognosis is excellent, and he will be carefully monitored with PSA testing every six months.

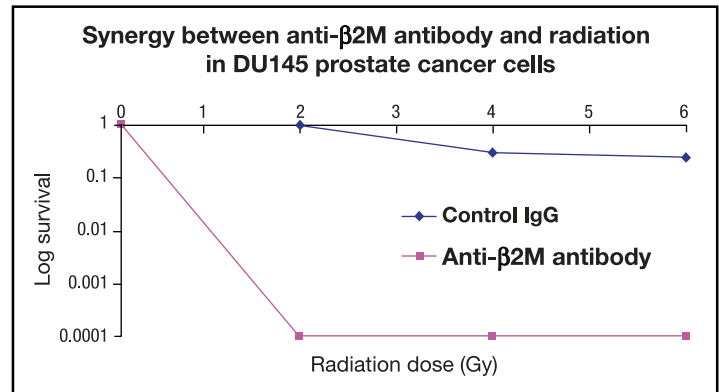


Figure 3A: Anti-β2M antibody can synergistically enhance cytotoxicity induced by ionizing radiation on the growth of radiation-resistant human prostate cancer cells in culture.



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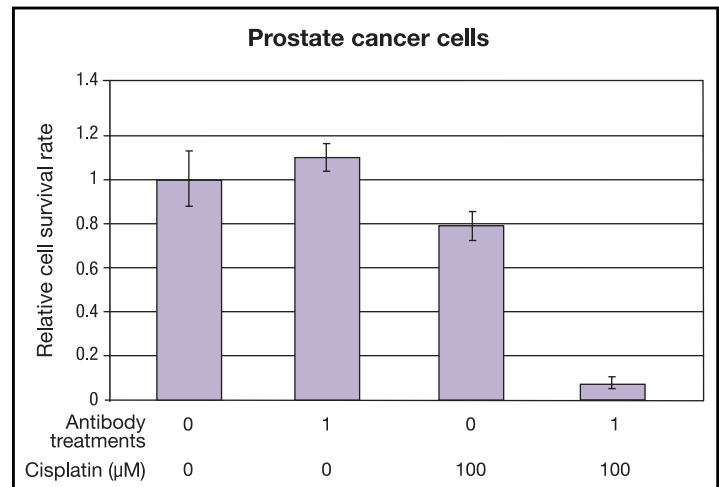


Figure 3B: Similarly, cytotoxicity in chemotherapy-resistant human prostate cancer cells can be markedly enhanced by the combined treatment of these cells with anti-β2M antibody plus chemotherapy, such as cisplatin.