Breast Cancer Clinical and Translational Research: Analogies and Implications for Prostate Cancer

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Breast and prostate cancer, respectively, are the most common cancers in women and in men in the United States. The management of locally advanced prostate cancer involves a multidisciplinary approach, bearing similarity to the therapeutic approach to breast cancer. Better understanding of the molecular biology of these cancers and the identification of the role played by the cancer stem cells and the tumor microenvironment may translate into better clinical decision making regarding risk classification and treatment allocation. A systematic assessment is presented of the many parallel evolutions in defining and treating high-risk breast cancer as they pertain to prostate cancer.

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Breast and prostate cancer, respectively, are the most common cancers in women and in men in the United States. Although most patients present with early disease, those presenting with locally advanced and metastatic disease or experiencing recurrence account for the 40,460 women and the 27,060 men who are estimated to die in 2007 of their disease.[1]

For prostate cancer, early disease is initially managed with either surgery or definitive radiation therapy, without any systemic intervention. It is in the management of locally advanced prostate cancer that a multidisciplinary approach is common, bearing similarity to the therapeutic approach for breast cancer.

The past few decades have brought on a dramatic change in the treatment of breast cancer. A condition uniformly treated with an extensive and disfiguring surgery—radical mastectomy—has evolved into a disease often manageable by more conservative surgery, with breast preservation becoming a common option (Figure 1). Most importantly, breast cancer is now recognized as a heterogeneous group of neoplastic processes, best treated with a tailored multidisciplinary approach, customized to the individual patient's tumor characteristics. These changes were made possible by concurrent advances in surgical techniques and in adjuvant therapies such as radiation therapy, chemotherapy, and hormonal therapies. The clinical translation of the laboratory insight of the pathogenesis of mammary tumors and the incorporation of targeted therapies usher us into a new era, with a promise of dramatically altering the natural course of disease and improving survival.[2-4]

The role of tumor, nodes, metastasis (TNM) classification, based on initial breast tumor size and extent of nodal involvement, has been extensively revisited, and today the treatment of each patient is informed by tumor markers and patient characteristics, such as the menopausal status at the time of diagnosis. For instance, large tumor size at presentation, classified as locally advanced breast cancer (LABC), was revealed to be a heterogeneous group of diseases, inclusive of a subset of patients with long-term survival. Still the most common form of breast cancer worldwide, LABC is on the decline in the United States where most breast tumors are detected earlier and a large component of the female population undergoes routine screening mammography. However, it is still responsible for 25% of breast cancer mortality.[5] Other subsets of patients with breast cancer, particularly those carrying a "triple negative" phenotype (negative estrogen and progesterone receptors and negative HER-2*neu* receptor carriers), have been shown to have a uniquely aggressive course, warranting a more aggressive systemic treatment.[6,7] These patients frequently present with small primary tumors, with a propensity for early spread to the draining regional lymph nodes and a dismal outcome due to an intrinsic resistance to systemic therapy.

The development and incorporation of genomic information has enabled a better characterization of high-risk breast cancer patients. The definition of high-risk prostate cancer patients could also be revisited, and a multidisciplinary approach similar to that currently used in breast cancer can be explored. In this article, we conduct a systematic assessment of the many parallel evolutions in defining and treating high-risk breast cancer as they pertain to prostate cancer.

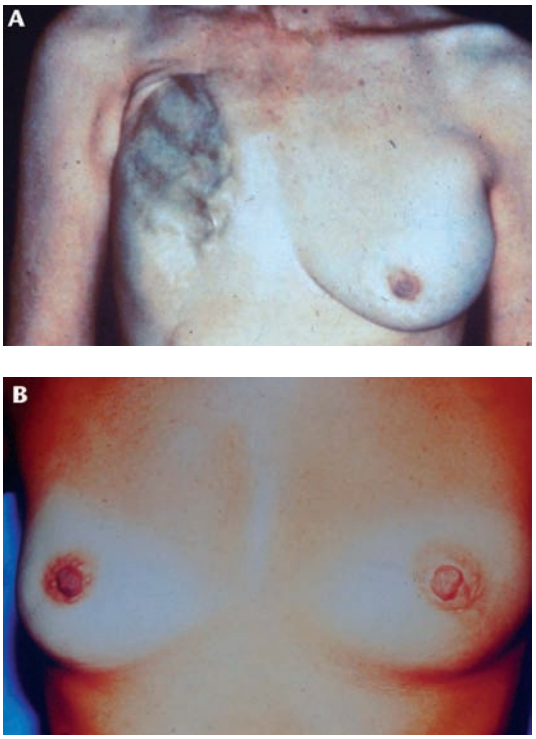

Figure 1. **(A)** *Cosmetic result in a 42-year-old woman after a radical mastectomy in 1978 for a T1N0M0 invasive ductal carcinoma. The image was taken 6 years after surgery.* **(B)** *Cosmetic result of a 39-year-old woman treated with segmental mastectomy and level 1-2 axillary dissection, followed by 6 weeks of adjuvant radiation therapy. The left breast presents residual hyperpigmentation at a 6-month follow-up visit after completion of radiation. The periareolar scar is barely detectable.*

Assessing the Initial Tumor: Improved Imaging and Diagnostic Workup

Technological advances in cancer imaging have rapidly pervaded the multidisciplinary management of both breast and prostate cancer. Similar to that of breast cancer, the diagnosis of prostate cancer is confirmed by biopsy. In men with serum prostate-specific antigen (PSA) levels of 4 to 20 ng/mL, biopsy results will be positive for cancer in 25%.[8] Once a diagnosis is made, imaging is needed to evaluate local extension or the existence of distant disease. Extent of disease remains a crucial step in assessing

long-term prognosis and allocation of patients to a specific local treatment. Although conventional gray-scale ultrasound is mainly used by urologists for guiding systematic prostate biopsies, the development of new ultrasound techniques, such as color and power Doppler ultrasound, and the introduction of ultrasound contrast agents, may change the role of ultrasound for prostate cancer detection.[9] These new techniques may improve on the sensitivity and specificity of prostate biopsies and decrease the need for repeat biopsies.

Because of its greater sensitivity and anatomic accuracy, magnetic resonance imaging (MRI) is becoming a key tool to assess both breast and prostate cancer. In prostate cancer, it is primarily used for presurgical staging and preradiation therapy planning, but it is also used for monitoring patients with low-volume disease and a low Gleason score (≤ 6) who choose watchful waiting.[10] In addition, the added metabolic information offered by magnetic resonance spectroscopy (MRS) can guide the clinician in targeting biopsies and in diagnosing disease recurrence in patients with increasing PSA. MRI/MRS also improves the ability of diagnosing regional disease with lymph node involvement.

A study comparing digital rectal examination (DRE), transrectal ultrasound (TRUS)-guided biopsy, and endorectal MRI in the detection and localization of prostate cancer confirmed the superiority of MRI in terms of greater accuracy in determining the location and extent of the tumor and the presence or absence of extracapsular extension, seminal vesicle invasion, and lymph node or bone metastases.[11]

^{111}In-capromab pendetide (Capromab) is a monoclonal antibody that specifically binds to prostate-specific membrane antigen (PSMA). PSMA has several optimal characteristics for targeting by antibodies: it is a nonsecreted protein anchored to the plasma membrane; it is highly prostate restricted, with its expression gradually increasing as the tumor grade increases, in metastatic sites, and as the tumor becomes androgen independent.[12] Capromab imaging was approved by the US Food and Drug Administration (FDA) because it proved better at detecting small-volume soft-tissue (but not bone) disease than computed tomography (CT) or MRI—modalities, capable of detecting only adenopathy exceeding 5-10 mm in diameter. In the presurgical patient, fusion imaging of Capromab with CT or MRI may improve the detection of small-volume nodal disease. After treatment, it is a valuable tool to identify local-regional disease in a setting of biochemical recurrence. A similar tool would be extremely useful in breast cancer, but unfortunately no such specific surface marker has been identified to date.

Positron emission tomography (PET) uses radiopharmaceuticals to detect metabolic alterations within cells, thus providing functional and metabolic information. The most commonly used agent for cancer imaging is the glucose analogue fluorodeoxyglucose (FDG).[13] Cancer cells usually have increased uptake and metabolism of FDG. Whole-body images depict regional FDG metabolism. In breast cancer, PET has multiple uses: in newly diagnosed patients it is used to detect regional or distant disease, and in the course of post-treatment follow-up, for the detection of locoregional or distant recurrence. In prostate cancer, the use of FDG PET has resulted in contradictory findings, probably due to renal elimination, which produces an accumulation in the urinary tract and thus hinders accurate visualization of the prostate and ilio-obturator nodes.[14] Another problem is the overlap with uptake due to inflammatory processes and benign hyperplasia of the prostate. Choline PET has recently emerged as a more promising approach for prostate cancer. Choline is a substance present in cell membranes, and choline marked at carbon 11 (^{11}C choline) has a specific affinity to damaged prostatic tissue, allowing differentiation of malignant tissue from benign processes. In addition, because choline does not require renal elimination it is a particularly attractive tracer for prostate cancer imaging. Preliminary data suggest that fusion imaging through PET-CT combining anatomic and metabolic data will aid the clinician in all stages of patient treatment, including diagnosis of extent of disease, radiation treatment planning, and evaluation of treatment response and detection of loco regional and distant recurrence.[14]

Positron emission tomography and computed tomography will aid the clinician in all stages of patient treatment.

Contemporary patients are routinely assessed by modern imaging, with improved accuracy in detecting regional and systemic spread of the disease. This progress has inevitably resulted in a "stage shift" effect, which needs to be kept in consideration when the results of modern interventions are compared to historical series. For patients with breast or prostate cancer, imaging is rapidly evolving, and the radiologist is likely to become a central player in the interdisciplinary clinical management of these diseases.

Patient Characteristics and Tumor-Related Prognostic Factors

Once the correct extent of disease is assessed, the main challenge to the interdisciplinary team of treating clinicians is the correct identification of prognostic indicators of aggressiveness and metastagenicity of the index tumor. In breast cancer, menopausal status at the time of disease presentation has enabled clinicians to divide patients into 2 main groups. Although other important variables associated with tumor markers and nodal involvement may supercede menopausal status, in general breast cancer in postmenopausal women appears to be associated with a more indolent course and a higher likelihood of responding to hormonal manipulations.

Although a similar division based on age exists for prostate cancer, it appears to be mostly confined to the type of local treatment offered to patients. Chodak and colleagues[15] performed a pooled analysis from 6 nonrandomized studies conducted in 4 countries. The outcomes of 828 untreated patients with localized cancer were reported. Grade 3 disease (Gleason, 8-10) and age under 61 years at diagnosis significantly influenced disease-specific mortality. The specific mortality at 10 years was 66% for those with grade 3 disease. The only randomized trial to compare radical prostatectomy with watchful waiting, in 695 men with early prostate cancer, was reported in 2005 by Bill-Axelson and colleagues.[16] The authors found that the reduction in disease-specific mortality by radical prostatectomy was most significant in patients 65 years old or younger, again indicating that younger age selects for a more aggressive form of the disease, similar to breast cancer. On multivariate analysis this finding was partly attributable to the differences in PSA level and Gleason score distribution between older and younger men. The fact that the benefit of an intervention tends to be detectable only in younger patients can also be explained with the relative slow disease progression characteristic of most prostate cancer, making survival advantage evident only in patients with a life expectancy of 10 years or more.[17]

Nomograms to Guide Treatment

In breast cancer several nomograms have been proposed to calculate the recurrence risk and survival impact based on the patient's age and tumor stage and markers. Once the individual patient's risk is assessed the impact of chemotherapy and/or hormonal therapy is calculated in terms of their predicted efficacy in reducing the risk. The patient is presented with both numbers and plots that help visualize the effect of a systemic therapy intervention for her specific case. Adjuvant! Online (www.adjuvantonline.com) is an evidence-based program designed on the basis of the Surveillance, Epidemiology, and End Results (SEER) database; the overviews of clinical trials; individual clinical trial results; and a general review of the pertinent literature. The program was subsequently validated using data on 4083 women from the British Columbia Breast Cancer Outcomes Unit database.[18] The program provides the treating clinician with an estimate of the 10-year risk of recurrence and 10-year risk of death based on a patient's age and clinical and pathological parameters such as size of tumor, hormone receptor status, and number of involved nodes. It also generates an estimate of the absolute benefit that can be expected to be derived by the individual patient with various therapeutic interventions such as adjuvant hormonal and distinct chemotherapy regimens. At the time of the initial consultation, it enables the medical oncologist to communicate to the patient quantitative information on her specific risk and potential risk reduction, to enable a rational, objective discussion of available treatment options.

The use of nomograms in prostate cancer is different. A variety of nomograms, predictive tables, and risk stratification strategies have been validated. Each of these approaches were derived from well established prognostic factors in prostate cancer, including palpable or imaging-identified evidence of extraprostatic extension (clinical stage T3-T4), high biopsy Gleason scores (8-10), and/or serum PSA levels of 20 ng/mL or higher.[19-22]

The main challenge in prostate cancer remains the accurate prediction of true high-risk patients; that is, those who are very likely to die of prostate cancer. Insights about the role of the initial tumor characteristics were originally provided by 2 important epidemiological studies.[23,24] Albertson and colleagues reported on the long-term survival of men in Connecticut diagnosed with localized prostate cancer during 1971 to 1984. After a 15-year follow-up period, disease-specific (DS) death closely correlated with Gleason score at biopsy: with Gleason 2-4, the risk of DS death was 4% to 7%; with Gleason 5, it was 6% to 11%; with Gleason 6, it was 18% to 30%; with Gleason 7, it was 42% to 70%; and for Gleason 8-10, it was 60% to 87%.[23] In a recent update, the same authors confirmed high Gleason score as the strongest predictor of DS death, regardless of the age of the men at initial diagnosis.[24] It is worth noticing, though, that in the PSA screening era, a higher percentage of men present with a smaller volume of disease, even among men with higher Gleason score, who could possibly have a more favorable prognosis. Longer follow-up is needed to test

this hypothesis because a clear definition of the contribution of local extent toward prognosis is missing. In fact, it is possible that locally advanced prostate cancer is as heterogeneous as a group as its locally advanced breast cancer counterpart.[25,26]

Multidisciplinary Approach in Locally Advanced Disease

It is in locally advanced disease that breast and prostate cancer bear the most similarities. Local and distant relapse after single modality treatment of locally advanced prostate cancer is as high as 70% for patients presenting with PSA greater than 10 to 20 ng/mL and/or Gleason scores of 7, warranting the development of alternative multidisciplinary approaches.[27-30] The combination of surgical and systemic therapies have long been used in the treatment of breast cancer. Although many early studies lacked power to demonstrate survival benefit, the publication of the meta-analyses by the Early Breast Cancer Trialists' Collaborative Group has provided level 1 evidence on the benefit of systemic therapies such as tamoxifen, ovarian ablation, and chemotherapy.[31-33] The use of these interventions, sequentially or in combination, was shown to reduce relative risk of recurrence and death by more than 50%, a benefit still evident after a 15- to 20-year follow-up.[34] In recent years, the introduction of newer agents such as aromatase inhibitors, taxanes, and trastuzumab has further improved disease-free survival and in some studies, overall survival.[35-37] The role of adjuvant radiation following breast conserving surgery is also well established in breast cancer, although some controversies remain regarding postmastectomy radiation.[38] In locally advanced breast cancer, whereas preoperative (neoadjuvant) systemic treatment, either hormonal or chemotherapy, decreases tumor bulk and reduces extent of surgery, evidence of disease-free or overall survival benefits are still controversial.[39] Pathologic CR (pCR = lack of persistent invasive cancer in the surgical specimen) of 22% to 31% has been reported in studies utilizing anthracyclines and taxanes. Significantly improved disease-free and overall survival in patients achieving complete responses were reported in the National Surgical Adjuvant Breast and Bowel Project (NSABP)B-18 and the European Organization for Research and Treatment of Cancer (EORTC) 10902 trials.

Combination therapies have been explored in prostate cancer, although the published information is not as robust and a meta-analysis of the results is lacking.

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Radiation Therapy and Hormonal Therapy

When combined with radiation therapy (RT), the potential advantage of hormone therapy is to reduce tumor size enabling a more conformal radiotherapy field with less morbidity, by reducing the volume of normal structures irradiated, while delivering adequate dose to control the tumor. Over the past 2 decades, several RTOG trials and 1 European trial have investigated the use of androgen blockade (AB) in combination with radiation. In RTOG 86-10, radiation therapy alone was compared to the combination of AB with goserelin (Zoladex) and flutamide (Eulexin) started 2 months before and continued throughout radiation therapy (for a total of 4 months) in patients with clinically bulky T2-T4 tumors, with or without lymph node involvement.[40] The majority of patients had tumors with Gleason scores of 6-7 (58%) and T3-T4 tumors (70%). At the 8-year follow-up, patients receiving the combination arm had a significant improvement in local control (42% vs 30%), disease-free survival (33% vs 21%), and cause-specific mortality (23% vs 31%).[41] Subset analysis indicated marked improvement in all endpoints for patients with Gleason score of 2-6, but no clear benefit from short-term AB was detected for patients with Gleason score of 7-10. A secondary analysis of the effect of subsequent AB at relapse showed no differences between patients retreated with AB (after receiving it as primary therapy and then recurring) and those who were originally randomized to radiation alone, had recurred, and received AB as salvage. The 5-year survival rate after salvage AB of 41% for both groups of patients and the 8-year overall survival rate of 50%, was identical for both groups of relapsing patients.[42] The results of this secondary analysis demonstrate that short-term AB treatment does not affect the benefit from subsequent AB treatment at relapse, dismissing the concern that initial exposure to AB might develop resistance to future treatment.

In patients with locally advanced prostate cancer, following primary radiation therapy, 2 randomized trials have investigated the use of adjuvant androgen blockade (AAB) versus deferring the same treatment to be offered at relapse. Both studies demonstrated a survival advantage for patients receiving the adjuvant therapy. In RTOG 85-31, 944 patients with

cT3 tumors or with positive lymph nodes (documented either by imaging or by pathology) were randomized to receive RT with AAB versus RT with delayed AAB, at the time of progression.[43] Adjuvant androgen blockade was started on the last week of RT. The majority of patients had lymph-node–negative disease (71%) and Gleason scores of 6-7 (54%). A recent update showed a significant decrease in 10-year local failure rate (23% vs 38%), a decrease in distant metastasis (24% vs 39%), and an increase in 10-year overall survival rate (49% vs 39%) in favor of the adjuvant hormonal therapy arm.[44] Whereas in earlier publications the survival benefit was evident only on subset analysis,[45,46] with sufficient follow-up time, all subsets of patients demonstrated a significant benefit for each endpoint.

The EORTC published results from a randomized trial comparing RT and AAB with cyproterone for 1 month followed by goserelin for 3 years versus RT alone, in 415 patients with stage cT1-T4 N0 prostate cancer.[47] Patients receiving the AAB had significantly better disease-free and 5-year overall survival, 85% versus 48% and 79% versus 62%, respectively.

The RTOG 92-02 trial compared short-term goserelin and flutamide (neoadjuvantly for 2 months and then concurrent with radiation) to the same combination treatment but prolonged for 2 years after completion of radiation. After 5.8 years of follow-up, the longer AB appeared to delay disease recurrence but did not improve overall survival.[48] At subset analysis, a survival benefit could be detected for patients with Gleason scores of 8-10 receiving long-term AB, with overall survival rate of 81% versus 70.7%.

A trimodality therapy involving external beam radiotherapy (EBRT), interstitial brachytherapy, and hormonal intervention (both neoadjuvant and concurrent) was also tested in locally advanced prostate cancer patients (defined as Gleason score of 8-10, initial PSA level >20 ng/mL, clinical stage T2c-T3, or positive seminal vesicle biopsy, or 2 or more of the following: Gleason score 7, PSA level greater than 10-20 ng/mL, or stage T2b). The preliminary 5-year results show a biochemical relapse-free rate of 86%.[49] Longer follow-up will reveal whether this approach reflects a promising survival rate.

In summary, the optimal combination of radiation therapy and hormonal therapy continues to be defined, particularly among patients at higher risk of relapse for whom the ideal timing of the treatment and the treatment duration warrant further clarification.

Chemotherapy and Locally Advanced Prostate Cancer

Traditionally chemotherapy was used only in the treatment of hormone-refractory prostate cancer. Recently, its early introduction in the management of locally advanced disease was explored, based on the high rates of distant failure in these patients and based on promising results from a similar approach in other solid tumors such as breast cancer.

Several pilot studies tested neoadjuvant chemotherapy. Although biochemical and partial objective responses were recorded, no pCR was detected at surgery, including a study that combined neoadjuvant chemotherapy and AB.[50-53]

Zelefsky and colleagues[54] reported on the feasibility of estramustine and vinblastine given neoadjuvantly and concomitantly with radiation, in 27 patients with locally advanced prostate cancer. The regimen was tolerated well, and a longer follow-up was required to assess efficacy.

Adjuvant chemotherapy following definitive treatment with either radical retropubic prostatectomy (RRP) or RT was also explored. The National Prostate Cancer Project (NPCP) evaluated the use of either cyclophosphamide or estramustine following RRP (NPCP protocol 900) or RT (NPCP protocol 1000). Adjuvant cyclophosphamide showed no benefit when compared to observation alone, but adjuvant estramustine following RT led to an improvement in the recurrence rate in patients with positive lymph nodes (60% vs 81%).[55,56]

Several larger trials are currently evaluating adjuvant or neoadjuvant chemotherapy for high-risk patients. CALBG 90203 is evaluating neoadjuvant docetaxel and estramustine before radical prostatectomy (RP), and SWOG 9921 is comparing RP and adjuvant hormonal therapy with or without mitoxantrone and prednisone. In addition, TAX 3501 will randomize men with a risk of post-RP recurrence of 60% or more (based on the Kattan nomograms) to either observation, adjuvant hormonal therapy for 18 months, or AB with docetaxel.[57]

Noticeably, in all these trials no pathological complete response after neoadjuvant systemic therapy was reported, a fundamental difference from the neoadjuvant experience in breast cancer. In breast cancer, evidence has emerged that the achievement of complete pathological response following primary chemotherapy is predictive of survival, with patients who achieved a pCR having 0.36 times the risk of death.[58] This difference is an indication of the current lack of effective systemic chemotherapy for prostate cancer, as demonstrated by the limited progress in improving survival in locally advanced disease.

Chemoradiation and Locally Advanced Prostate Cancer

The activity of taxanes in hormone-refractory prostate cancer[59] and data of their radiation-sensitizing properties[60] make taxanes ideal candidates for

chemoradiation studies. Inspired by a successful experience in locally advanced breast cancer, a pilot feasibility study (NYU 00-05) of chemoradiation was recently concluded at our institution, and the results are currently being analyzed. The study, open to high-risk prostate cancer patients (defined as clinical stage T2-T3, and/or lymph node involvement [per pathology or CT or MRI], and/or PSA level of 20 ng/mL), accrued its target number of 22 patients and demonstrated feasibility and maximum tolerated dose (MTD) of delivering standard radiation with concurrent twice-weekly paclitaxel (30 mg/m^2) during AB. Secondary endpoints were local control and time to PSA failure. MTD of concurrent chemoradiation was 73.8 Gy, total dose. At a median follow-up of 27 months, DFS is 72%. One patient has died of prostate cancer. Five others are alive with recurrence, 3 with distant metastases and 2 with biochemical failures only.

Adjuvant Radiation

Post-RP radiation has been studied in the attempt to increase local control in patients at high risk for local recurrence (T3 tumors, positive resection margins, involvement of seminal vesicles).[61] A parallel situation in breast cancer is the setting of postmastectomy radiotherapy for women with tumors larger than 5 cm at initial diagnosis (pT3), 4 or more involved lymph nodes at axillary dissection, or positive margin of the mastectomy specimen.[62,63]

Thompson and colleagues[64] reported the results of a large multiinstitutional randomized trial, enrolling 425 patients with T3N0 tumors. All patients underwent RP and were then randomized to adjuvant RT (60-64 Gy) or observation. At 10-year follow-up, distant relapse was observed in 35% of those receiving adjuvant RT, compared to 43% who did not. However, no difference in overall survival was detected.

In the postmastectomy radiation therapy series, a better local control reflected on better survival outcome in each patient subset, but the reproducibility of that data has been questioned in the contemporary era of modern, more aggressive adjuvant systemic therapy.[65]

Whether the additional value of adjuvant hormonal therapy could be beneficial in these patients is currently being explored in a national randomized trial (INT 0086), in which patients with pT3 tumors undergo RP and adjuvant radiation and are randomized to AAB versus observation.

Converging Cancer Care With Quality of Life Issues

The past 20 years have seen a big improvement in the quality of life of both breast and prostate cancer patients. Breast conservation surgery has gradually superceded the indiscriminate use of mastectomy, and whenever mastectomy remains the best surgical choice for specific patients, it is routinely offered with immediate or delayed breast reconstruction.

Although RRP remains the surgical gold standard in the treatment of localized prostate cancer, the associated long-term complications have remarkable implications on the patient's quality of life. Stanford and colleagues[66] reported on incontinence and impotence following RRP in the Prostate Cancer Outcomes Study, a population-based longitudinal cohort study encompassing 1291 men and with up to 24 months of follow-up. At 18 or more months following radical prostatectomy, 8.4% of men were incontinent, and 59.9% were impotent. An improved anatomic understanding and recognition of the importance of the neurovascular bundle coursing posterolaterally to the prostate gland[67] have led to the development of nerve-sparing RRP (NSRRP). The 2 most commonly used surgical approaches are the apical approach described by Walsh and the lateral approach described by Ruckle and Zincke.[68] The reported rates of potency preservation vary greatly between studies, depending on both the surgeon's expertise and the age of the patient—with greater success rates in centers of excellence and in patients younger than 65 years. The major concern with NSRRP is the rates of positive surgical margins (PSM), which have been shown to adversely affect recurrence-free survival after surgery.[69] Most authors agree that an ideal candidate for NSRRP should be a fully potent patient with an organ-confined cancer stage T1-T2b, with a preoperative PSA of < 10 ng/mL and a Gleason score of ≤ 7.

An emerging new surgical technique is laparoscopic radical prostatectomy with the initial results similar to open surgery. A study comparing the 2 techniques has shown comparable results with PSM rates of 7.3% versus 7.8% and potency rates of 65% versus 55% in laparoscopic versus open surgery, respectively.[70] Robotic-assisted laparoscopic radical prostatectomy is yet another evolving technique to improve the precision and accuracy of anatomic dissection. Rozet and colleagues[71] described a series of over 2500 laparoscopic radical prostatectomies of which over 130 were robotic-assisted. The intraoperative and short-term postoperative outcomes were found to be similar, but a longer follow-up is needed to evaluate long-term complications as well as disease-free and overall survival.

Issues concerning quality of life during and after treatment have acquired a central role in the interdisciplinary discussion of patients as well as in the doctor-patient initial consultation. Information delivered to

the patient is no longer limited to survival rates and risk of recurrence, as both breast and prostate cancer are now managed with 2 approaches with comparable results.[72,73] Quality of life issues such as short- and long-term complications, length of treatment, and sexuality are now an important part of patient education.[74,75]

Prostate and breast cancer survivors and advocates have played a crucial role in informing this discussion as well as in affecting federal policies and in increasing research funds allocation.[76]

The Role of Genomics

The emerging understanding of the complex molecular basis of prostate cancer encompassing gene mutations, altered gene expression, altered regulation, and pathways cross-talk has demonstrated heterogeneity of the disease and the possibility of reclassifying it consistently. Again, similar to what is found for breast cancer, carriers of these subtypes display unique clinical behavior and prognosis and therefore warrant a different therapeutic approach.

Gene expression arrays test over 20,000 genes and identify altered gene expression in a variety of cancers distinguishing them from benign diseases and normal tissue. In breast cancer, the differential expression of the most relevant genes has identified several distinct subtypes. Recent cross-platform verification has demonstrated the robustness of the approach.[77] One of these subtypes, the basal type, bearing some characteristics of basal or myoepithelial cells in normal breast tissue, predicts for a uniquely aggressive disease. This subtype accounts for 25% of the grade 3 infiltrative ductal carcinomas, and is characterized by high proliferation index and hormone receptor negativity.[21] These adverse features lead to a high recurrence rate, shorter disease-free survival, and overall survival.[4]

The improved understanding of genetic signature and its ability to predict clinical behavior can also help predict the relative benefit of therapeutic interventions and, most importantly, chemotherapy.[78] An example of such application is available for breast cancer. Paik and colleagues[79] have applied a commercial 21-gene assay (Oncotype Dx) in a retrospective validation study using the archived paraffin blocks of tumors taken from women accrued to NSABP B-20. This study was a randomized trial of chemotherapy and tamoxifen versus tamoxifen alone, in the treatment of women with estrogen-receptor positive breast cancer and negative nodes. This 21-gene panel included genes involved in tumor cell proliferation and hormonal response, which in a preliminary pilot study were shown to correlate with chemotherapy response. The authors were able to devise a recurrence score that enables the assignment of patients into high-, intermediate-, and low-risk groups. The high-risk group was found to derive maximum benefit from chemotherapy, whereas the low-risk group derived minimal benefit. The intermediate group's benefit was less clear and is now being assessed in a new, prospective randomized trial.[80]

Assays like the one mentioned previously are quickly becoming important tools for the clinician to complement the more traditional clinical and pathological parameters when assessing risk of recurrence. Similar research is ongoing for prostate cancer. Gene expression arrays have identified several genes with altered expression in prostate cancer such as hepsin with a role in proteolysis and metastatic spread, and FKBP-5 and ANKH involved in androgen metabolism.[81] The clinical relevance of these genes is not always clear at this point. Lapointe and colleagues[82] identified 3 subclasses of prostate tumors based on distinct patterns of gene expression. One of the subtypes (III) was associated with lymph node metastases. High tumor grade, advanced stage, and early recurrence were associated with gene expressions characterizing tumor subtypes II and III. To further characterize the subtypes, the authors used as surrogate markers 2 genes differentially expressed. MUC1 is a gene highly expressed in subgroups with aggressive clinicopathological features and associated with an elevated risk of recurrence. AZGP1 was also correlated with increased risk of recurrence. Positive staining of either gene was a strong predictor of tumor recurrence independently of tumor grade, stage, and preoperative PSA levels. Although the approach enables the identification of high-risk subjects, whether it can enable successful individualization of treatment remains to be verified.

Cancer Stem Cells: The Future of Oncology?

The idea of a cancer stem cell is not a new one; it was suggested as early as the 1960s, when seminal work in tumor transplantation in animal models demonstrated that tumors are comprised of heterogeneous subpopulations.[83-85] These subpopulations differ in their ability of self-renewal and reconstitution of the tumor upon transplantation. Progress in developmental biology has made possible the revival of this concept thanks to the new ability to identify and purify the putative stem cells based on cell surface markers. Putative cancer stem cells were proposed in several human malignancies including hematopoietic neoplasms such as acute myeloid leukemia,[86] and several solid tumors including breast[87] and brain[88] cancers. The existence of a myeloid stem

cell was proved with experiments of stem cell transplants in irradiated mice. Myeloid stem cells are now widely used in the treatment of human patients with leukemia, undergoing bone marrow ablation to eradicate their cancer and salvaged with stem cell transplant.

In breast cancer, Al-Hajj and colleagues[87] were able to distinguish the tumorigenic (tumor initiating) cells from the nontumorigenic cancer cells based on cell surface marker expression. As few as 100 cells with the phenotype CD44(+)CD24(−/low) Lineage(−) were able to form tumors in mice, whereas tens of thousands of cells with alternate phenotypes failed to form tumors. The tumorigenic subpopulation was able to generate new tumors containing additional CD44(+)CD24(−/low)Lineage(−) tumorigenic cells as well as the phenotypically diverse mixed populations of nontumorigenic cells present in the initial tumor.

The cancer stem cell population is believed to be a distinct minority, comprising only 0.1% to 1% of tumor cells. The relatively small number of these cells and their inherent resistance to systemic therapy mediated by multidrug and ABC transporters, has been proposed as a possible explanation for the failure of existing therapies to cure advanced cancer.[89-91] Although some therapies are successful in achieving remarkable remissions by eradicating the bulk of the disease, relapse is ultimately inevitable, due to the regeneration of the tumor by the stem cells. Experiments demonstrating the ability to undergo more than 30 cycles of androgen deprivation with subsequent regeneration on reintroduction of androgens, suggested the existence of prostatic stem cells (PSC) with the ability of replication, quiescence, self-renewal and multilineage differentiation, and ultimately tissue regeneration. Prostatic subpopulations capable of regeneration of the organ in transplantation experiments confirm this hypothesis.[92]

PSC are traditionally thought to be located in the basal cell layer of the prostate, where they divide to give rise to the highly proliferative transit-amplifying cells (TACs) that in turn differentiate to produce neuroendocrine cells and terminal, secretory luminal cells.[93] Whereas the stem cells are androgen independent, the TAC are androgen responsive (require androgens for proliferation but not for survival) and the luminal cells are androgen dependent.[94] This finding bears striking resemblance to subpopulations identified in breast cancer cells with the basal cell carcinoma identified by hormone receptor negativity and dismal prognosis[6,7] and the luminal subset, predominantly hormone responsive, with a generally better clinical outcome.[25]

The Tumor Microenvironment: A New Target

The recognition of cancer stem cells as the true target of anticancer therapy has led to research into understanding the regulation of stem cell proliferation. While in the embryonic period the stem cells give rise to multilineage differentiated cells and are highly proliferative; in the adult, stem cells are quiescent and tightly regulated, but retain their full proliferating and differentiation potentials. This regulation is exerted through interaction with insoluble extracellular matrix (ECM) proteins, soluble growth factors, and other factors secreted by the adjacent stroma.[95] The most studied to date is the transforming growth factor beta (TGF-β) signaling pathway.[96] TGF-β secreted by adjacent fibroblasts modulates the growth and oncogenesis of the nearby epithelia. Conditional inactivation of this inhibitory pathway in mice fibroblasts led to the development of intraepithelial neoplasia in the prostate and invasive squamous cell carcinoma of the forestomach.

In parallel, mammary developmental research led to the discovery of the importance of the microenvironment—the "niche," a necessary complement to both normal and neoplastic stem cells. Preclinical models of breast neoplasias consistently required the introduction of human fibroblasts to support growth of human mammary epithelium.[97] In addition, experiments in the humanized mammary gland demonstrated that the malignant transformation of susceptible epithelium was mediated by TGF-β or hepatocyte growth factor (HGF) produced by fibroblasts.[98] Other studies demonstrated that by exposing the stromal fibroblasts to carcinogens such as N-methylnitrosourea or to ionizing radiation the subsequently added epithelial component developed tumors, suggesting a promoting effect of the irradiated stroma to the development of tumors originating from initiated epithelial cells.[99,100]

A possible role of the tumor microenvironment in preventing tumor progression and even inducing tumor reversion was suggested by experiments disrupting tumor cell interaction with the ECM, by using integrin-blocking antibodies.[101] Under the antibody treatment, the aggressive, disorganized malignant breast cancer cells reverted to organized cells forming "acini-like" structures. The clinical relevance of such intervention cannot be overestimated, should it be reproducible in vivo.

Chemoprevention studies also support the concept that the microenvironment can be manipulated to inhibit mammary tumor progression.[102] Chemoprevention with difluoromethylornithine and retinoids inhibited progression of chemically induced rat mammary tumors. These

agents disrupted epithelial cell-ECM interactions, leading to epithelial apoptosis and protection from tumor progression.

In the prostate, the stroma surrounding the tumor is enriched by myofibroblasts, whereas in the normal prostatic tissue, the main cell type is the smooth muscle cell.[102] The myofibroblasts show increased ECM protein production and increased local vascular density due to the secretion of the ps20 protein.[103] Similar to what was experimentally observed in breast cancer, prostate stromal cells are required to successfully grow prostate cancer cell lines in nude mice.[104] Both luminal cells and stromal smooth muscle cells secrete vascular endothelial growth factor (VEGF), but most angiogenesis is attributed to the latter, because the luminal cells secrete VEGF apically, in the glandular lumen.[105] The stromal cells also secrete a variety of fibroblast growth factors, all of which are found at increased levels in prostate cancer.[106] Activation of the respective receptors in the epithelial cells leads to signal transduction in multiple pathways involved in cancer progression, namely enhanced proliferation, resistance to cell death, increased motility and invasiveness, increased angiogenesis, enhanced metastasis, resistance to chemotherapy and radiation, and androgen independence. These pathways offer appealing therapeutic approaches similar to those tested in other solid cancers, such as receptor-blocking antibodies or small molecules binding to the intracellular tyrosine kinases family of receptors.

Conclusions

Breast and prostate cancer bear many similarities. Their management, which is characteristically interdisciplinary, is rapidly evolving as a result of the translation of laboratory findings to the clinic. In both diseases, the progress in genomics and cancer molecular biology is drastically modifying the understanding of the disease and gradually influencing its classification and management. Particularly, the identification of cancer stem cells and their dependency on the tumor microenvironment offer the hope to find a cure for either disease. Until recently most preclinical work was conducted on cell lines and tumor xenograft models, inevitably missing the biology of the stem cells. Drugs and radiation were screened in models that could not adequately recapitulate the biology of the disease. It has now become clear that true progress can be predicted only by understanding the biology of the cancer stem cell and its capacity for latency and recurrence after resisting the initial treatment.

The public health impact of such progress is particularly relevant in view of a growing population of aging men and women who are highly susceptible to either disease. ■

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Main Points

- Breast and prostate cancer bear many similarities and their management is rapidly evolving as a result of the translation of laboratory findings to the clinic.
- The identification of cancer stem cells and their dependency on the tumor microenvironment offer hope to find a cure for either disease.
- By understanding the biology of the cancer stem cell and its capacity for latency and recurrence after resisting the initial treatment, true progress can be predicted.

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