How will radiogenomics improve breast cancer management?

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Adjuvant radiotherapy following breast-conserving surgery represents an acceptable alternative to mastectomy [1], resulting in 5-year relative survival rates for women with either local- or regional-stage breast cancer approaching 100 and 90%, respectively [2]. In addition, postmastectomy radiotherapy (PMRT) has been shown to decrease local recurrence and improve survival for women with locally advanced breast cancer [3]. Thus, for the large number of women who live long periods following treatment for local/regional disease, a concern arises associated with complications resulting from exposure to the high doses of radiation necessary for effective radiotherapy. Although every effort is routinely made to limit the toxicity of treatment through improvements in dosimetric parameters, which are now feasible with the sophisticated technology available to deliver radiotherapy that spares normal tissues and organs, many women still experience radiation-induced injuries. The possible chronic adverse outcomes following breast cancer radiotherapy include fibrosis, induration, chest wall pain, edema and telangiectasia in addition to erythema and desquamation that are generally manifested during treatment [4].

With the substantial advances in genetics and genomics that have been achieved over the past 30 years, the hypothesis was put forward that genomic alterations could influence susceptibility for the development of adverse effects resulting from radiotherapy [5]. This resulted in creation of the field of radiogenomics whose aim is to identify the genomic factors that account for the range of responses observed in individuals following cancer treatment with radiation. Although it is likely that genomic characteristics also impact tumor responses to radiation, the emphasis of research in radiogenomics has been on the identification of biomarkers that influence susceptibility for development of radiation-induced normal tissue and organ injuries. The overall goal of radiogenomics is the development of assays to predict which patients are most likely to develop complications from radiotherapy. Research in this field has greatly benefited from creation of the Radiogenomics Consortium, a National Cancer Institute (NCI)-supported cancer epidemiology consortium [6], which currently consists of 225 member investigators at 131 institutions in 32 countries [7]. The common aim of the Radiogenomics Consortium membership is to share biospecimens and data so as to achieve large-scale studies with increased statistical power to enable identification of relevant genomic biomarkers.

For a woman faced with a diagnosis of breast cancer, her choice is to either have limited breast-conserving surgery followed by radiotherapy or to undergo mastectomy. This may be a difficult decision that can be influenced by a variety of medical, psychological and sociologic factors. Certainly one important factor when considering radiotherapy is the concern about developing complications as a result of treatment with high doses of radiation. These radiation toxicities may either be uncomfortable to painful or cause poor cosmesis that can impact upon the quality of life for breast cancer patients and result in negative psychological outcomes. Therefore, a test that could predict the probability for developing radiation damage would be of benefit as it would help women diagnosed with breast cancer and their physicians to determine the most appropriate treatment on an individual basis. It

is also important to keep in mind that while radiotherapy is generally curative for early stage breast cancer, the adverse effects resulting from treatment can place a financial burden on both individuals as well as the healthcare system [8]. In addition, for patients who undergo mastectomy, caution as to postmastectomy radiotherapy (PMRT) may be advisable for those women predicted to be at high risk for complications resulting radiation exposure. This would be a particular concern for these putatively radiosensitive women since the damage caused by PMRT could jeopardize the ability to perform a successful breast reconstruction [9].

Research in radiogenomics has focused primarily on the identification of single nucleotide polymorphisms (SNPs) that are associated with an altered susceptibility for development of adverse responses to radiotherapy. SNPs represent a major source of genetic variation between individuals as approximately once every 1000 nucleotides more than 5% of people have an alternate base pair at a particular nucleotide, although the frequency of specific SNPs depends on ethnic, racial and geographic location [10]. It should also be noted that epigenetic and other panomic factors likely play a role influencing susceptibility for development of complications from radiotherapy. Progress in radiogenomics has been made toward the discovery and validation of biomarkers associated with normal tissue toxicities following breast cancer radiotherapy. One large study involved more than 2000 breast cancer patients from four cohorts treated with radiotherapy that were genotyped for SNPs related to the TGF β pathway and associations reported for several outcomes, including breast induration, telangiectasia and overall toxicity [11]. Significant and replicated associations with adverse outcomes were discovered for the *TNF α* SNP rs1800629 and rs2857595, which is located 25.7 kb from rs1800629 and resides in the intergenic region between *NCR3* and *AIF1*. Another validated study identified SNP rs1139793 in *TXNRD2* associated with subcutaneous fibrosis [12]. *TXNRD2* encodes the mitochondrial selenoprotein thioredoxin reductase 2, which plays a central role preventing oxidative damage. Therefore, alteration of the protein encoded by this gene could impact upon reactive oxygen species produced through irradiation and thus influence the risk for fibrosis development following radiotherapy. An additional study used a two-stage design to investigate associations between SNPs in genes whose products are involved with responses to oxidative stress with toxicities following radiation treatment of approximately 2600 women diagnosed with breast cancer [13]. The rs2682585 SNP in *XRCC1* was found to be associated with risk for skin toxicities. The protein encoded by *XRCC1* plays a role in base excision repair of oxidative damage produced by radiation. A genome-wide association study was performed in which more than 1500 patients were examined for SNPs associated with adverse effects [14]. The quantile–quantile plots from this study revealed a larger number of associations at the $p < 5 \times 10^{-7}$ level than would be expected by chance. This result provides evidence that common genetic variants are associated with risk for development of adverse effects following breast cancer radiotherapy. In addition, a study of more than 5000 patients treated for either breast or prostate cancer reported an association between the rs1801516 SNP in the *ATM* gene with both acute and late radiation toxicity [15].

It is also important to note that several large projects are currently in progress to extend radiogenomic research focused on breast cancer patients. This work includes roughly 6200 women treated for breast cancer with radiotherapy in which biospecimens as well as detailed clinical, dosimetric and longitudinal outcomes data are available for approximately: 1000 women treated as part of RTOG 1005, a trial examining the use of a hypofractionated protocol with a concurrent boost [16]; 2000 women enrolled into the REQUITE study [17]; 1100 subjects from a series of clinical protocols performed at New York University School of Medicine [18,19]; 900 subjects enrolled through the RAPPER (Radiogenomics: Assessment of Polymorphisms for Predicting the Effects of Radiotherapy) study [20]; and 1200 women treated at Aarhus University Hospital. It is likely that the results of these projects in radiogenomics will result in the discovery of new SNPs and the validation of previously identified genomic genetic markers.

In summary, progress in radiogenomic research has been achieved toward the identification of genomic biomarkers associated with adverse effects resulting from breast cancer radiotherapy. It is expected that the results of this research will lead to the creation of a test predictive of susceptibility for the development of toxicities resulting from treatment of breast cancer with radiation that could be used in routine breast cancer care. It is anticipated that clinical implementation of a predictive instrument will enhance the ability for each individual woman diagnosed with breast cancer to select the most appropriate treatment and thereby improve outcomes for breast cancer patients.

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