New Developments in Breast Cancer and Their Impact on Daily Practice in Pathology

Xiaoxian Li, MD, PhD; Gabriela M. Oprea-Ilies, MD; Uma Krishnamurti, MD, PhD

Advances in research have transformed our understanding of breast cancers and have altered the daily practice of pathology. Theranostic evaluations performed by pathologists are now critical in triaging the patients into appropriate treatment groups, as are new guidelines that were recently established for the evaluation of HER2/neu gene amplification. Emerging molecular classifications of breast cancers bring novel perspectives to the assessment of individual cases, and opportunities for better treatments. Molecular studies have particularly shed light on distinct biological subsets of triple-negative breast cancers, for which new targeted therapies are being developed. The prognostic and therapeutic utility of new histopathologic parameters, such as tumor-infiltrating lymphocytes, are also being elucidated, and new protocols have been devised for the pathologic evaluation of breast specimens that have undergone neoadjuvant treatment. Novel clinical practices, such as radioactive seed localization, also affect the way breast specimens are processed and evaluated. In this brief review, we highlight the developments that are most relevant to pathology and are changing or could potentially impact our daily practice.


Breast carcinoma is the most commonly diagnosed cancer in women. It is estimated that approximately 15% of women will develop breast cancer during their lifetime. In the past few years, significant developments have taken place in our understanding and classification of breast cancer, some of which are incorporated into the most recent American Society of Clinical Oncology (ASCO) recommendations. These recent developments, which have profound implications in breast cancer diagnosis and treatments and are rapidly being translated into daily practice, will be discussed in this review.

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MOLECULAR AND IMMUNOPHENOTYPIC CLASSIFICATION OF BREAST CARCINOMA

The seminal studies by Perou et al1 and Sorlie et al2 classified breast carcinoma into at least 4 distinct intrinsic subtypes by molecular phenotype: luminal A, luminal B, HER2/neu enriched, and basal-like. Luminal A and B breast cancers are estrogen receptor (ER) or progesterone receptor (PR) positive, while the luminal B subtype is positive for HER2/neu gene amplification or shows a high proliferative index.3,4 The HER2/neu-enriched subtype is negative for ER and PR expression and positive for HER2/neu gene amplification. Most breast carcinomas fall into these 3 groups, for which specific targeted therapies are available.

The basal-like subtype is characterized by high expression of keratins 5, 6, and 17, which are usually found in breast myoepithelial cells (and the basal epithelial cells of other normal tissues).5,6,11 This subtype is associated with a higher frequency of p53 mutation, higher proliferative index, higher tumor grade, and worse prognosis, and it occurs more frequently in African Americans.1,3,5–10,12–17 Most BRCA-mutated breast carcinomas fall into this subtype.1,18,19

In clinical practice, the breast carcinomas that are negative for ER, PR, and HER2/neu are referred to as triple-negative breast carcinomas (TNBCs). Most basal-like carcinomas are TNBCs.5–8 Studies have shown that most TNBCs with positive cytokeratin 5/6 and epithelial differentiation factor receptor (EGFR) expression correspond to the basal-like subtype.5,6,6 It should be noted, however, that although there is great overlap between basal-like carcinoma and TNBC, these 2 entities are not exactly the same: the basal-like subtype is a molecular classification with a distinct gene signature, while TNBC is a clinical classification defined by negative ER, PR, and HER2/neu expression. Approximately 50% to 80% of TNBCs are basal-like, but 10% to 30% are HER2/neu enriched and a small number are luminal.1,2,20

Triple-negative breast carcinoma is also characterized by loss of various markers that are otherwise commonly expressed in low-grade breast cancers and used in daily diagnostic practice, including GATA-3 expression.21 Recent studies revealed the existence of another subtype, the claudin-low subtype,22 characterized by down-regulation of tight junction proteins including E-cadherin, occludin, and some claudins, and by high expression of genes associated with epithelial-mesenchymal transition (EMT), immune response, and the breast cancer stem-cell phenotype.22,23 The claudin-low breast carcinoma is generally triple negative and this subtype includes most of the spindle cell (sarcomatoid) metaplastic carcinomas.24,25 The
enhanced expression of EMT and breast cancer stem cell
tively, are similar to the claudin-low subtype in showing
chymal
mesen-prognosis. The fourth and fifth categories, termed
comprises medullary carcinoma, which has a good
by expression of immune-related genes; this group also
like subtype and are associated with
and some BL2 breast cancers belong to the intrinsic basal-
features such as upregulation of TP63 and CD10. Most BL1
for growth factor pathways and shows basal/myoepithelial
genes. The basal-like–2 (BL2) group, by contrast, is enriched
higher expression of proliferative and DNA damage repair
classification, the basal-like–1 (BL1) group is defined by
TNBC as well as a seventh, unstable subtype. In this
apies,26 so it is not surprising that the spindle cell
breast cancer stem cells.23,25 Cancer stem cells are generally
claudin-low carcinoma shares similar gene signature with
breast cancer stem cells.23,25 Cancer stem cells are generally
considered to be more resistant to traditional chemother-
ies,26 so it is not surprising that the spindle cell
metaplastic carcinoma of the breast does not respond to
conventional triple-negative invasive carcinoma.27,28
Molecular classification of breast carcinomas is rapidly
joining immunohistochemical studies as part of the routine
pathologic evaluation. Estrogen receptor, PR, and HER2/neu
expression has been an integral part of the pathology report
for years, and the criteria for assessing those markers are
constantly being refined. Molecular studies are now
elucidating the finding that carcinoma types such as spindle
cell metaplastic carcinoma not only are morphologically
distinct entities with different behavior, but also have a
molecular profile that (not surprisingly) makes them a target
for different therapeutic protocols.

**MOLECULAR CHARACTERIZATION OF TRIPLE-NEGATIVE BREAST CANCERS**

Triple-negative breast carcinoma remains highly chal-
lenging in terms of diagnosis and treatment. The main tasks
are to predict the behavior of individual tumors in this
pathologic complete response rates (52%, 0%, and 10%,
respectively) when treated with neoadjuvant chemotherapy;
however, despite having a low pathologic complete response
rate, the LAR subtype had the best overall survival.
Genomic studies on TNBC have identified many target-
able pathways. Shah et al33 identified mutations in
PIK3CA, EGFR, RB1, PTEN, and in other genes including the newly
identified deletions of the PARK2 tumor suppressor gene
in TNBC. Other groups29,30,34,35 also found other targetable
pathways in TNBCs, such as FGFR2 gene amplification.
These classification schemes illustrate that the TNBCs are
heterogeneous, comprising several theranostically distinct
subsets. These classifications will likely become important in
better management of affected patients in the near future,
even if they have not yet taken a specific role in
pathologists’ daily practice.

**EVOLVING TARGETED THERAPIES IN TRIPLE-NEGATIVE BREAST CANCER**

The following is a brief overview of the most salient recent
discoveries of the pathways with targetable agents in
TNBCs. Although there are no established guidelines yet
as to their incorporation to daily practice, it is safe to assume
that at least some will become a part of routine evaluation of
breast carcinomas in the near future.

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**Approximate Correlation Among 3 Molecular Classifications (Lehmann, Burstein, Perou) of the Triple-Negative Breast Cancer**

<table>
<thead>
<tr>
<th>Lehmann31</th>
<th>Burstein30</th>
<th>Perou1</th>
<th>Gene Signature</th>
<th>Possible Targets</th>
</tr>
</thead>
<tbody>
<tr>
<td>LAR</td>
<td>LAR</td>
<td>Luminal</td>
<td>Enriched hormone-regulated pathway</td>
<td>AR</td>
</tr>
<tr>
<td>BL1</td>
<td>BLIA, BLIS</td>
<td>Basal-like</td>
<td>Enriched proliferative and DNA-damaging repair genes (BL1); upregulation (BLIA) and down-regulation (BLIS) of immune-regulating pathway</td>
<td>Platinum-based therapy, PARP</td>
</tr>
<tr>
<td>BL2</td>
<td>BLIA</td>
<td>Basal-like</td>
<td>Enriched growth factor pathway (BL2); upregulation of immune-regulating pathway (BLIA)</td>
<td>Growth factor pathways</td>
</tr>
<tr>
<td>IM</td>
<td>MES, BLIA</td>
<td>Basal-like and unclassified</td>
<td>Upregulation of immune-related pathway (IM, BLIA); upregulation of cell cycle, DNA-damaging repair, and growth factor pathways (MES)</td>
<td>Immune-related pathway</td>
</tr>
<tr>
<td>M</td>
<td>BLIS</td>
<td>Basal-like and claudin-low</td>
<td>Enriched EMT and breast cancer stem cell genes (M); down-regulation of immune-regulating pathway (BLIS)</td>
<td>Cancer stem cell pathway; PI3K pathway</td>
</tr>
<tr>
<td>MSL</td>
<td>MES</td>
<td>Basal-like and claudin-low</td>
<td>Enriched EMT, breast cancer stem cell genes, and growth factor pathways (MSL); upregulation of cell cycle, DNA-damaging repair, and growth factor pathways (MES)</td>
<td>Cancer stem cell pathway; PI3K pathway</td>
</tr>
</tbody>
</table>

Abbreviations: AR, androgen receptor inhibitor; BL1, basal-like–1; BL2, basal-like–2; BLIA, basal-like immune activated; BLIS, basal-like immunsuppressed; EMT, epithelial-mesenchymal transition; IM, immunomodulatory; LAR, luminal androgen receptor; M, mesenchymal; MES, mesenchymal; MSL, mesenchymal stem-like; PARP, poly-ADP ribose polymerase.

claudin-low carcinoma shares similar gene signature with breast cancer stem cells.23,25 Cancer stem cells are generally considered to be more resistant to traditional chemother-
ies,26 so it is not surprising that the spindle cell
metaplastic carcinoma of the breast does not respond to
conventional triple-negative invasive carcinoma.27,28

Approximate Correlation Among 3 Molecular Classifications (Lehmann, Burstein, Perou) of the Triple-Negative Breast Cancer
PI3K/AKT/mTOR Pathway

The phosphatidylinositol-3-kinase (PI3K) pathway activates a variety of downstream proteins including the mechanistic target of rapamycin (mTOR) complex. The latter complex regulates cell survival and synthesis of various regulatory proteins, including cyclin D1 and hypoxia-inducible factor–1A (HIF-1A), which help to regulate cell proliferation and angiogenesis, respectively. In breast cancers, mutations that activate PIK3CA occur frequently in ER- and HER2/neu-positive cancers and may account for treatment resistance in these tumors. On the other hand, while PIK3CA mutations are infrequent in TNBCs, they have been reported in up to 47% of metaplastic carcinomas of the breast. Thus, it is important to recognize and classify metaplastic carcinomas accurately, rather than designating them merely as poorly differentiated carcinomas. Several trials are underway to determine the role of mTOR and PI3K pathway inhibitors in breast cancer.

Androgen Receptor

A significant number of TNBCs show AR overexpression. In vitro studies showed sensitivity of LAR cell lines and of cell-line–derived xenografts to the AR inhibitor bicalutamide. A phase II trial showed a good safety profile of bicalutamide and a 19% benefit rate in patients with advanced AR-positive, ER/PR-negative breast cancer. If AR inhibition eventually proves to be an effective therapy, theranostic evaluation of AR expression will likely become a part of routine practice, on a par with ER, PR, and HER2/neu.

Platinum-Based Chemotherapy and Poly-ADP Ribose Polymerase Inhibitor

Platinum and poly-ADP ribose polymerase (PARP) inhibitors are agents that disrupt chromosomal DNA integrity and might be useful in treating tumors with DNA repair deficiency. Platinum-based therapy has been used in clinical trials to treat TNBC and has shown benefits in patients with BRCA1 germline mutations or low BRCA1 expression associated with promoter methylation. Several clinical trials also examined the safety and efficacy of PARP inhibitors in TNBC. A subset of TNBCs with DNA repair deficiency, such as the Lehmann BL1 and BL2 subtypes, or TNBC with BRCA mutations, may also potentially benefit from these reagents.

p53 Pathway

TP53 is the most frequently mutated gene in cancer, and its product, p53, is an important tumor suppressor protein. Abnormalities of p53 lead to tumor initiation and progression. Shah et al showed that 62% of basal-like and 43% of non–basal-like TNBCs had TP53 mutations. Several clinical trials are now examining the antitumor function of small molecules that target the p53 pathway.

Growth Factor Pathways

Molecular studies have revealed alterations of several growth factor pathways in TNBC. The Lehmann BL2 and MSL subtypes are enriched in growth factor pathway–related gene expression. Epidermal growth factor receptor (EGFR) is frequently expressed in TNBC. Anti-EGFR antibodies have been tested in early clinical trials in metastatic TNBC. Antagonists of the vascular endothelial growth factor receptor and fibroblast growth factor receptor are also under investigation. While none of these markers is currently tested routinely, it is conceivable that in the near future, some of these markers will be used to better select TNBC treatments.

Immune Checkpoint Inhibitors

The programmed cell death protein 1 (PD-1) is an immune checkpoint protein that is expressed on immune cells. When PD-1 binds to its ligand (PD-L1), PD-1 suppresses T-cell immune functions. Anti–PD-1 pathway antibodies have been approved by the US Food and Drug Administration (FDA) to treat various cancers. Platinumbased therapy has been used in clinical trials to treat TNBC, and some of these are already becoming used in daily practice, such as the platinum-based agents. Accurate morphologic classification, supplemented by immunohistochemical and molecular studies, is crucial in directing patients into the most appropriate treatment protocols. We, as pathologists, have to embrace these new developments and be prepared to incorporate the new biomarkers, as data warrant, into our morphologic evaluation of breast cancers.

Updated Approach to the Evaluation of HER2/neu

Evaluation of HER2/neu expression, along with ER/PR, is crucial in prognostication and therapeutic stratification of breast cancers. ASCO/College of American Pathologists (CAP) guidelines mandate routine testing of HER2/neu, along with ER and PR, in every new, recurrent, invasive, and metastatic breast carcinoma. The guidelines were revised in 2013 to improve the testing sensitivity and accuracy, since inaccuracy in HER2/neu testing was found to be as high as 20%. Misinterpretation of HER2/neu expression can lead to very expensive medical treatments as well as exposure of the patient to unnecessary treatment with the associated risk on one hand, or missed opportunity to potentially cure a patient on the other. The new guidelines emphasize sensitivity over specificity, especially after pertuzumab received FDA approval for the neoadjuvant treatment of patients with HER2/neu+ breast cancer, and as optimizing treatment of HER2/neu-positive metastatic breast cancer.

The 2013 HER2/neu scoring criteria by IHC are summarized as follows.

- Score 0: No staining observed or membrane staining that is incomplete and faint/barely perceptible and within 10% or less of the invasive tumor cells. Score 0 is negative for HER2/neu overexpression.
- Score 1+: Incomplete membrane staining that is faint/barely perceptible and within more than 10% of invasive tumor cells. Score 1+ is negative for HER2/neu overexpression.
Score 2+: Circumferential membrane staining that is incomplete and/or weak/moderate and within more than 10% of the invasive tumor cells, or complete and circumferential membrane staining that is intense and within 10% or less of the invasive tumor cells. Score 2+ is equivocal and requires reflex testing by in situ hybridization for HER2/neu amplification.

Score 3+: Complete intense circumferential membrane staining in more than 10% of the invasive tumor cells. Score 3+ is positive for HER2/neu overexpression.

Three important points about these scoring criteria need to be emphasized: (1) To render a 3+ score, completely circumferential and very strong membranous staining is required (Figure 1, A). In our consultation practice, we see examples with strong but granular cytoplasmic staining that were initially overcalled as 3+ only to prove negative by fluorescence in situ hybridization (FISH) analysis. For similar reasons, some of the automated systems also tend to overcall these 2+ cases as 3+ (Figure 1, B), which creates unwarranted treatment dilemma. (2) It was realized that using the terms circumferential and incomplete together in defining score 2+ was confusing, resulting in large numbers of cases being submitted for reflex in situ hybridization testing. Such testing would increase the cost of the test and be a resource issue for many laboratories. Therefore, the 2013 guidelines are being updated. The definition for HER2/neu IHC 2+ will be "weak to moderate complete membrane staining that is observed in more than 10% of tumor cells." (3) The 2013 guidelines stated that, "If the initial HER2 test in a core needle biopsy specimen of a primary breast cancer is negative, a new HER2 test may be ordered on the excision specimen." These revisions are expected to be published shortly.

For HER2/neu FISH testing using a dual-color system, criteria for positivity for HER2/neu amplification are as follows: HER2/neu/CEP17 ratio of 2.0 or greater, or average HER2/neu of at least 6 copies per cell; criteria for negativity are as follows: HER2/neu/CEP17 ratio less than 2.0 with average HER2/neu of fewer than 4.0 copies per cell. All other results are considered equivocal for HER2/neu amplification.

Following the 2013 guidelines, centers have reported increased rates of overall HER2/neu positivity (by ~2%) and of equivocal cases (~4%–5%). The increase in equivocal cases results in delay of definitive diagnoses of HER2/neu status. Most of these cases have increased CEP17 copy numbers (3–4/cell nucleus). Previous studies have suggested that tumors with increased HER2/neu copy number respond to anti-HER2/neu treatment, independent of HER2/neu/CEP ratio and even when HER2/neu copy number is in the equivocal range. The equivocal group defined by the 2013 criteria may be enriched for patients who could benefit from anti-HER2/neu therapy. This is in addition to patients whose condition is shifted from equivocal to positive by 2013 criteria. However, the clinical significance of HER2/neu equivocal cases is uncertain. Long et al reported that there is an increased request for additional testing using alternate chromosome 17 probes and even polymerase chain reaction assays for breast cancers with both IHC 2+ and equivocal FISH results. Additional testing will increase costs but with uncertain clinical benefit. Until further studies demonstrate how HER2/neu equivocal cases respond to therapy, pathologists will be revised as follows: “If the initial HER2 testing result in a core needle biopsy specimen of a primary breast cancer is negative, a new HER2 test may be ordered on the excision specimen.” These revisions are expected to be published shortly.

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should apply these updated guidelines when reporting HER2/neu in breast carcinoma.

NEW HISTOPATHOLOGIC THERANOSTIC MARKERS: TUMOR-INFILTRATING LYMPHOCYTES

There is mounting evidence that tumor-infiltrating lymphocytes (TILs) are important immunologic biomarkers in breast carcinoma, as in many other cancers. The immune system is constantly engaged in immune surveillance. Immune responses may control nascent tumors and influence patient outcomes. The specific mechanisms involved are still being debated. Chemotherapy and radiotherapy may trigger immunologic memory and help to control residual disease. The role and importance of TILs appear to vary significantly among different subtypes of breast cancer. For example, TILs were found to be a positive prognostic biomarker in TNBC but not in the luminal breast cancers. High levels of TILs were associated with good prognosis in HER2/neu-positive carcinomas treated with chemotherapy and HER2/neu-targeted therapy in an adjuvant setting. Mao et al found that higher numbers of TILs in the pretreatment biopsy specimen correlated with better pathologic complete response in HER2/neu+ and TNBC but not in ER+ breast cancer. While the specific meaning of TILs in any given case is still under scrutiny, it is clear that the analysis of the TIL amount and composition is likely to become an integral part of pathologic evaluation. In fact, for this purpose, an international working group has proposed guidelines for standardized evaluation of TILs in breast cancer for daily clinical and research practice.

Some of the salient points of the consensus guidelines in the evaluation of TILs are as follows: Stromal TILs are the immune cells in the stromal tissue, excluding the tumor cells. Intratumoral TILs are the immune cells within the tumor that are in direct contact with malignant cells. Tertiary lymphoid structures are located in the area surrounding the tumor and are defined as consisting of a T-cell zone next to a B-cell follicle that often has germinal centers. These are difficult to distinguish from lymphoid aggregates and are not recommended for clinical assessments.

Stromal TIL assessment has been found to be easier, superior, and more reproducible than intratumoral TIL assessment. Stromal TILs have been found to be predictive of increased response to adjuvant and neoadjuvant therapy. In scoring for TILs, all mononuclear lymphoid cells (including lymphocytes and plasma cells) are counted, but polymorphonuclear leukocytes are excluded. Average TILs in the tumor area should be assessed without focusing on hot spots. Lymphocyte-predominant breast cancer is defined as those cancers with at least 50% to 60% of the stromal area occupied by TILs.

Evaluation of TILs in colon cancer is already listed as optional in the CAP cancer protocol checklist. It may be only a matter of time before evaluation of TILs is added to the breast cancer protocol checklist as well.

THE ROLE OF PATHOLOGISTS IN ASSESSING CASES WITH NEOADJUVANT THERAPY

Neoadjuvant systemic therapy (ie, therapy rendered before surgery) is now widely used for a significant proportion of breast cancers including locally advanced disease and inflammatory breast cancer, and is also increasingly used for patients with early-stage breast cancer. Pathologic complete response (pCR) is defined as the absence of residual invasive carcinoma in the breast and lymph nodes at the time of surgery and is an excellent prognostic indicator. Thus, pCR was approved by the FDA as a surrogate endpoint for clinical trials and drug approval. The strongest correlation between pCR and outcomes is found in HER2/neu+ cancer and TNBC. Houssami et al reported that pCR occurred in about 9% of hormonal receptor (HR)+/HER2/neu−, 19% of HR+/HER2/neu+, and 39% of HR−/HER2/neu+ cancers, and 31% of TNBCs. If pCR is not achieved, residual cancer burden in the breast and nodes is associated with increased regional recurrence and decreased survival. Therefore, accurate assessment of pCR or residual cancer burden is crucial.

To ensure a standard approach to evaluate tumor responses to neoadjuvant therapies, a multidisciplinary international working group convened by the Breast International Group–North American Breast Cancer Group leadership developed recommendations for the pathologic assessment of residual cancer burden. While these recommendations are intended for clinical trials but not routine practice, it is becoming increasingly used as a part of routine practice in tertiary care institutions. We refer readers to the original publication for detailed recommendations. The key elements for pathologists, which we follow in our institution, are listed below:

1. The specimen is evaluated in the context of pretreatment clinical and imaging findings. Screening mammography and improved imaging technology have made detection of nonpalpable breast lesions possible, and currently about a third of radiologically suspicious breast lesions are clinically occult. Image-directed localization of nonpalpable breast lesions is necessary to perform breast-conserving procedures. The most commonly used method for the surgical excision of nonpalpable breast lesions is wire-guided localization (WGL). This method has many inherent problems. The
entry site of the wire in a nonuniform specimen may result in asymmetric surgical margins,123 which could lead to false-positive margins requiring unnecessary re-excision.124–126 Disadvantages also include wire transection or displacement,127,128 retained metallic fragments, and failed localization due to the "accordion" effect from breast tissue decompression, which could cause removal of excessive tissue or even failure to excise the targeted lesion.129,130 In addition, with the need for close coordination among radiologists, operating room staff, and the surgeon for same-day procedures, WGL may represent a logistical challenge.

To overcome some of those challenges, radio-guided localization techniques have been developed. Currently, there are 2 main techniques: radio-guided occult lesion localization and radioactive seed localization (RSL). Radio-guided occult lesion localization uses colloidal human serum albumin particles labeled with radioactive technetium (99mTc) that is inoculated directly into the lesion during mammographic or ultrasound procedure.131 More recently, RSL was introduced and a pilot study found it to be a safe means of localization with 100% pathologic confirmation of lesion removal.124,132,133 Radioactive seed localization is now being used in multiple institutions.

Increased patient comfort is one of many advantages of RSL. Patients with RSL rated it less painful while causing the same level of anxiety as compared with WGL.134 Radioactive seed localization saves the patient from being transported between departments with a wire protruding out of the skin, which can dislodge, fracture, or produce pain with movement. Radioactive seed localization can be done ahead of time, greatly simplifying operating room schedules, improving turnaround time, and minimizing patient inconvenience.135 Radioactive seed localization may also offer the surgeon continuous real-time acoustic orientation resulting in a more uniform specimen centered around the radioactive seed. The long half-life of the radioactive seed, iodine 125, allows for RSL placement before neoadjuvant chemotherapy. The cost of the procedure was reported to be comparable to that of WGL, especially if a large volume of cases is performed.137,138

In the RSL procedure, the radioactive seed is introduced with an 18-gauge needle during standard ultrasound or mammographic exam. Sentinel lymph node mapping and dissection is possible during the RSL procedure by using different radioactive materials. The gamma-probe can confirm the presence of the seed in the specimen, which can be further confirmed by specimen radiography. The gamma-probe also helps the pathologist retrieve the seed during intraoperative examination. In our department, the specimen is delivered to the pathology frozen section room where gross examination and inking of surgical margins are performed. The probe helps to identify the area of maximum activity. The seed is retrieved and placed in a dedicated container for return to the radiology department staff. All these steps are carefully documented in the electronic chart. The specimen should be handled with care, as cutting the seed may lead to the theoretical risk of radioactive iodine becoming airborne. However, this is a remote possibility, as iodine 125 is covalently bound in a halide silver wire or an exchange resin encased in a titanium shell.132

Performance of these procedures requires proper licensing, which is rigorous.123 The RSL licensing program requires routine and emergency training of all persons involved in handling the radioactive seeds. The receipt, storage, implantation by radiologists, surgical excision by surgeons, retrieval by pathologists, and return of seeds to the radiology department and decay of the seeds should be carefully documented according to the protocol developed by each institution.135 Failure to do so may result in temporary suspension of RSL procedures until a corrective protocol is put in place.138

References


