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EDITORIAL

Has Placement of Surgical Clips in the Lumpectomy Bed Fallen Out of Favor?

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Surgical clips were originally developed in the early 1900s, and initially utilized for hemostasis in intracranial operations.[1,2] Since then, the clinical applications of surgical clips have broadened to include procedures across all surgical disciplines. In oncologic procedures, surgeons may place clips in the cavity of a tumor bed for a myriad of reasons, with the most common being to control hemostasis; other uses include placement to mark extent of dissection, denote anatomic location during a future operation or for accuracy of postoperative imaging.[3] Another value of surgical clips is technical efficiency, which may allow for decreased operative time. In reality, appreciation for surgical clip application extends beyond the surgical theater. Just as surgeons rely on percutaneously placed clips to target a nonpalpable lesion for wire localization, radiation oncologists rely on clips in the tumor bed to accurately delineate the surgical cavity, as postoperative changes on computed tomography (CT) scans may be difficult to visualize.

Typically, surgical clips are made of titanium or steel, both of which are radio opaque and can be visualized on plain film or CT scans. In early-stage breast cancer, clips placed in the surgical bed at time of definitive surgical resection have traditionally been used by radiation oncologists to direct the boost treatment after whole-breast irradiation.[4,5] More recently, however, with the advent of accelerated partial-breast irradiation (APBI) using external-beam radiation therapy, detection and delineation of the surgical cavity are of even greater importance, given the large radiotherapy fraction doses delivered over a short period of time.

Accurate delineation of lumpectomy cavity target volumes by relying on seroma formation or location of lumpectomy incision has been shown to be largely inaccurate.[6–9] The seroma is a postoperative serous fluid accumulation and is sometimes used to estimate the lumpectomy cavity borders when no metallic marker is present. Seroma formation after lumpectomy, however, is variable, making it difficult to assess the true cavity borders accurately. The lumpectomy incision scar has also been used in an effort to define lumpectomy borders, but accuracy in this technique has also been unsuccessful.[6,8] In a small, prospective series by Krawczyk and colleagues, measurement from lumpectomy scar to breast tissue border was found to be an inadequate prediction tool for radiation planning.[6] In fact, relying on the lumpectomy scar may result in a significant risk of underdosing of the lumpectomy cavity.

From a radiation oncologist perspective, it may be best for clips to be placed along all margins of a cavity to improve targeted radiation therapy. In fact, published data from our group suggest that directed placement of fiducial markers on the walls of the surgical cavity allowed for improved interphysician accuracy in delineation of the lumpectomy cavity.[10] However, in many centers, including ours, surgical clip placement is left to surgeon discretion. To our knowledge, no standard recommendation for clip placement exists, and patterns of variation have prompted discussion amongst radiation oncologist and breast surgical oncologist at our institution.

Multiple studies over the past 10–20 years have evaluated the clinical importance of surgical clip placement in radiotherapy planning.[6,11–14] In 2008, Coles et al. performed an audit of titanium clip placement utilized in the

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UK IMPORT LOW (Intensity Modulated Partial Organ Radiotherapy) Trial and found clips to be essential for tumor bed localization in 73% of their cohort.[15] Directed clip insertion was performed using six titanium clips placed in a specific, uniform fashion in all study patients: (1) medial, lateral, superior, and inferior: half-way between skin and fascia; (2) deep/posterior: mid-point, usually the pectoralis fascia; and (3) anterior: close to the suture line. In only 27% of their cohort could the seroma cavity be localized without placed surgical clips on CT.

Observed inconsistency in placement of surgical clips was recently studied at our institution.[15,16] A review of 131 consecutively treated patients in the Department of Radiation Oncology at the Cancer Institute of New Jersey (B.H and S.G.) revealed that only 58 (44%) of the seroma cavities had at least 1 surgical clip; of these 66% had 1–5 clips, 22% had 6–10 clips, and 12% had >10 clips present (mean 5, median 4, range 1–16). Our group currently is enrolling subjects to a phase I clinical trial investigating the improvement in accuracy in patients receiving accelerated partial-breast irradiation after directed fiducial marker placement. Fiducials are intrinsically or extrinsically placed markers utilized clinically to identify an anatomic landmark and serve as a reference point for medical imaging.[17] Compared with metallic surgical clips, fiducials are thought to produce less scatter on CT planning and treatment scans.

Another challenge in accelerated partial-breast irradiation is the dynamic seroma cavity, seen if the lumpectomy cavity is left open at the time of surgery, or the lack of a seroma cavity altogether, which is often seen when a lumpectomy cavity is closed intraoperatively. The open cavity approach entails only approximating superficial tissue, leaving deeper dermal tissue unapproximated, thus allowing for seroma formation, while closing the cavity consists of reapproximating the breast tissue prior to skin closure.[18] Many surgeons feel that leaving the cavity open allows for a better cosmetic outcome because seroma presence may allow improved breast contour, although not necessarily in a permanent fashion. However, some surgeons prefer closing the breast parenchyma surrounding the tumor bed, also in an attempt to improve cosmesis and decrease seroma formation. Indelicato and colleagues reported a higher rate of infection in the immediate postoperative period in the presence of a seroma (11.7 vs. 5.2%).[19] The technique of combing plastic surgery principles in the setting of breast lumpectomy, often referred to as oncoplastic surgery, is commonly used in France and is growing in popularity in the USA.[3]

Data regarding surgical clip placement and radiation planning in lumpectomy cavities are emerging, and evidence suggests a benefit with directed placement of surgical clips in the surgical bed. At our institution, a study published by Shaikh et al. evaluated patients undergoing placement of gold fiducial markers sutured to the superior, inferior, medial, lateral, and posterior walls of the surgical cavity at time of lumpectomy.[10] Three radiation oncologists who specialize in breast cancer then delineated the lumpectomy cavities for APBI purposes in patients with gold markers, and a group of patients without gold markers which served as a control. The presence of gold fiducial markers in the surgical bed improved interphysician identification and delineation of the seroma cavity, and radiotherapy target volumes. Another study from the Institut Gustave Roussy, where lumpectomy cavity closure was performed, recently reported on the significance of placing surgical clips in improving accuracy of three-dimensional (3D) accelerated partial-breast irradiation planning.[20] Four breast surgeons placed surgical clips at four cardinal points after breast remodeling was performed to reapproximate the lumpectomy cavity into a closed space. The clips were placed at the upper, inner, outer, and lower lumpectomy cavity margins. Their findings revealed that a conformity index of tumor bed delineation was significantly improved by having surgical clips within the lumpectomy cavity. In particular, placing clips at the four cardinal points of the lumpectomy cavity reflected favorably on target contouring accuracy**.** It should be noted that there are no data to support the notion that more accurate tumor bed delineation will lead to improvement in local control; however, it may improve cosmetic outcomes in patients receiving whole-breast and partial-breast irradiation given modern radiotherapy techniques such as 3D conformal radiation therapy and intensity-modulated radiation therapy (IMRT).[21–23]

Currently, the National Surgical Adjuvant Breast and Bowel Project (NSABP) and the Radiation Therapy Oncology Group (RTOG) are randomizing patients with early-stage breast cancer to whole-breast irradiation (WBI) versus APBI. The NSABP B-39/RTOG 0413 protocol bases their three-dimensional conformal external-beam radiotherapy (3D-CRT) target volumes on the postoperative seroma cavity as defined on the planning CT scan. The surgical cavity is defined on CT scan, and an expansion of 1.5 cm is added to form the clinical target volume (CTV). The CTV is then restricted to within the lung–chest wall interface and 5 mm of the skin surface; an additional 1.0-cm margin is provided to form the planning target volume (PTV). With the standard regimen of APBI, 385 cGy is delivered twice daily over the course of 5 days, and when using such a hypofractionated regimen, necessary precautions must be taken into account to prevent unnecessary radiation being delivered to organs at risk while ensuring delivery of radiotherapy to those areas at risk for microscopic disease. Thus, accurate estimation and delineation of the postoperative seroma cavity is crucial given that subsequent target volumes are exponentially expanded off

this original volume; improper delineation of this structure may ultimately result in critical differences in the expanded CTV and PTV structures. For example, the volume of a sphere (e.g., seroma cavity) is $4/3\pi r^3$, where r is the radius of the seroma cavity. Thus, when a 1.5-cm margin is added to the seroma cavity to form the CTV, this expanded volume may be exponentially affected by any variation in the "true" radius of the seroma cavity.

The authors acknowledge that surgical clip placement may not be warranted in patients selected preoperatively for APBI using balloon-catheter brachytherapy, such as MammoSite® or Contura®. It is presumed that the presence of surgical clips in the lumpectomy cavity may pose a risk of increased balloon rupture, although this has not yet been confirmed. However, patients treated with balloon-catheter brachytherapy on the NSABP B-39/RTOG 0413 APBI protocol account for less than 25% of the treated population, and may affect the decision to place clips in those patients selected to undergo APBI using balloon-catheter brachytherapy.

While studies confirm that surgical clip placement into the tumor bed at time of lumpectomy results in improved accuracy of radiation planning, practically speaking, however, many surgeons do not clip the tumor bed, and reasons as to why are only speculative. Perhaps the importance of cavity clipping is not shared amongst all surgeons. One possibility is that some surgeons may place surgical clips in the lumpectomy cavity for hemostasis and feel that evidence of any clip adequately indicates tumor bed location. Although placement of even a single clip is probably preferred to none at all, studies suggest that clip placement along the defined margins is significantly better for radiation planning.[15,16] Another reason that a lumpectomy cavity may be left without clips is the surgeon inadvertently failing to recall intention to place clips as the last step in tumor bed evaluation prior to closing. Also, placement of clips may be related to the preferences of the radiation oncologists who work with the surgeons. The reasons for lack of surgical clip placement are varied, but evidence supporting their clinical utility in improving the accuracy of delivering radiotherapy treatments in patients undergoing breast-conserving surgery for breast cancer is not. Ideally, a standardized pattern of directed clip placement would be adopted amongst surgeons, allowing for improved, uniform radiation treatment planning for all breast cancer patients.

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