Evaluation of Surgical Margins in Anatomic Pathology: Technical, Conceptual, and Clinical Considerations

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• Virtually all anatomic pathologists are involved in the assessment of tissue margins in surgical procedures that are performed for malignant diseases. The natural tendency to view this process as uncomplicated has, in recent years, been countered by a body of literature on the biological milieu of the marginal zone. Moreover, empirical clinical information has shown that "negative" and "positive" marginal status has an imperfect correlation with risk of recurrent disease in several organ systems and in reference to various tumor types. Problems also remain regarding the optimal techniques for pathologic sampling of margins; the possible roles, if any, of adjuvant (eg, immunohistologic and "molecular") procedures for margin evaluation, and reporting motifs for selected surgical resections. This review considers conceptual data now available on surgical margins, provides a working approach to the generic assessment of marginal surfaces, and presents organ- and tumor- specific information pertaining to this area of practice.

INDEX WORDS: Surgical margins, immunohistologic margin evaluation, molecular margins, tumor markers

THROUGHOUT the evolution of surgical oncology, one of the most troublesome problems encountered by surgeons has been the local recurrence of malignant neoplasms after apparently adequate excision. On the other hand, it is now widely known that incomplete removal of some lesions does not necessarily predict their regrowth at the surgical site. The implementation of frozen section examinations was a seminal event in general surgical practice, to ascertain in "real time" whether or not a tumor was present at the margins of a resection specimen.[1] Indeed, this is still the procedure by which the marginal status is generally determined. The following overview will examine the current status of this practice, both in general and in relation to several selected organ systems. It will also address several biologically oriented topics that influence the pathologist's ability to evaluate surgical margins in a meaningful manner.

RESOURCES AND METHODS FOR INTRAOPERATIVE EVALUATION OF SURGICAL MARGINS

The most commonly used and well-validated technique for microscopic assessment of surgical margins continues to be the preparation of histologic sections with a cryostat.[2-6] This instrument has gone through several iterations and improvements over time, such that modern versions now provide good temperature control, consistency in thin tissue sectioning, and various attachments to minimize or eliminate "roll" artifact. Indeed, in good hands, the overall quality of cryostat preparations may approximate that of some permanent sections. The main drawback in the use of the cryostat is the time required for completion; even an experienced operator under ideal conditions cannot produce a good final (stained) product with this device in much less than 15 minutes after a specimen is received in the laboratory. This problem is compounded by the expense of adequate quality cryostats; they cost at least $5,000 apiece and may be more than $25,000 each. The cost factor, together with the space required for operation of the machines, makes it generally impractical for most hospitals to have a large number of them in operation at the same time in the same place. Therefore, if several specimens are received in the laboratory simultaneously, a significant period of time may elapse before all of them can be sectioned properly on the available cryostat(s). Such considerations, together with the cost of "dead time" in the operating room, account for the escalating costs of frozen sections in modern hospital practice.

Partially in response to these problems, but also as a viable procedure in its own right, intraoperative cytologic analysis of surgical margins has also gained popularity over the past 20 years.[7-12] In this method, en face margin surfaces are touched or scraped onto glass slides and stained with hematoxylin & eosin (H&E), Romanowsky dyes, or the Papanicolaou technique, in or-

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der to determine whether malignant cells are present thereon. Advantages of the procedure are its rapidity and ease, such that many surfaces can be sampled in a relatively short time. The principle disadvantage is the inability to tell exactly where a "positive" result originated. Probably the best application of marginal cytological analyses is to obtain them together with frozen sections[8,9,11]; for example, a positive cytologic preparation can be followed by a cryostat section on the same portion of the main specimen.

In recent times, additional adjunctive methods have been tested with regard to their abilities to detect tumor "positivity" in tissue margins that appeared to be uninvolved by conventional morphologic assessment. These have included immunostaining studies using antibodies to tumor-selective markers,[13-28] and "molecular" evaluations centered on the presence of specific gene aberrations or microsatellite alterations.[29-37] The latter of these techniques has generally applied the polymerase chain reaction (PCR) together with specific nucleic acid primers designed to detect the abnormalities in question. Examples of immunohistochemical studies in this area of assessment include those for eukaryotic initiating factor 4E (eIF4E)[14,18,19] and mutant p53 protein[15-17,19,20] in squamous carcinomas of the upper airway; HMB45 antigen in mucosal and cutaneous melanomas[24]; S202 glycoprotein in gastric carcinoma[28]; CD34 in dermatofibrosarcoma protuberans[26,27]; and cytokeratin-7, carcinoembryonic antigen, or epithelial membrane antigen in extramammary cutaneous Paget's disease.[21-23,25] In the realm of molecular (i.e., PCR) evaluation, several nucleotide sequences have been studied in specific reference to surgical margins for various malignancies. For instance, these have encompassed genes encoding the tumor-selective E48 antigen in squamous cell carcinomas[16]; specific mutant forms of p53 in lesions of assorted anatomic locations[23,35,37]; prostate-specific antigen and prostate-specific membrane antigen in prostatic adenocarcinomas[31,33,34]; and telomerase or instable microsatellites in neoplasms of the head and neck, bladder, prostate, colon, and lung.[29,30,32,36] The relative merits and drawbacks of these procedures will be addressed subsequently.

There are several more banal but nonetheless important considerations that should also be mentioned in the context of this discussion on the technical aspects of surgical margin analysis. First, several publications have shown that false negativity in frozen section assessments is related to spatial sampling limitations in 30% to 45% of cases where intraoperative and final diagnostic conclusions are different.[5-6] It should be understood that although these figures might be improved somewhat in the future, there will be an irreducible residuum of "missed" intraoperative margins; this fact has its origins in the practical reality that the entire margin often cannot be sampled by the pathologist. If the specimen concerned is very large, or very complicated anatomically, or both, the marginal surface area will be sizable. Hence, procedural constraints prohibit submitting it in its entirety for microscopic examination.

An allied topic is the common surgical practice of attempting "complete" marginal sampling in the operating room. In this process, which is most often pursued in procedures on the head and neck, the surgeon submits many separate specimens that are supposed to represent the entire marginal surface. The pathologist is then expected to validate that assumption by examining the resected tissue thereafter. Realistically, this is again unfeasible in most instances because one cannot easily match intraoperative margin biopsies to the resection specimen, especially without the help of the surgeon in the grossing room. Similar comments apply to any other sizable surgical excision in which many margins have been sampled intraoperatively; hence, in the end, there may be considerable ambiguity in the pathologist's mind regarding whether a tumor has or has not been removed with total tumor "clearance." Still another allied subject concerns requests by surgeons to place a pre-inked marginal surface on the cryostat chuck so that it is "away" from the chuck. This practice assumes that if the first cryostat sections prepared in such a manner are free of tumor, the lesion has been removed adequately even if subsequent serial preparations from the same block do show the presence of the neoplasm. In our judgment, one is falsely confident if one is satisfied clinically with a margin that is measured only in microns.

The spectrum of reagents and techniques that have been touted as adjunctive tools for detecting occult marginal tumor deposits is not available to all pathologists. Most diagnostic laboratories prefer to limit immunohistochemical testing to those analytes that have been validated extensively in the published pathology literature, and which can be done with commercially available reagents. Thus, antibodies to eIF4E,[14,18,19] S202 protein,[28] and other markers[13,21-27] in the developmental clinical literature on tumor margins are not part of this repertoire. Even more restrictive comments apply to the current in-house availability of molecular testing in most medical centers, even academic ones. Finally, there have been no formal cost-effectiveness or

clinical outcomes analyses to prove the practical worth of changes in the way tissue margins are presently analyzed pathologically. Until those data appear, there will be no compelling reason to alter the procedures, especially in the judgment of financial analysts at health care organizations.

The Surgical Margin: Uniform and Static Environment or Complicated Milieu?

Both pathologists and surgeons have a natural tendency to view surgical margins as static "snapshots" of tissue. The basic question posed by each party at the time of resection of a malignant neoplasm concerns the presence or absence of tumor at the line of mechanical transection. The assumption is, of course, that positive margins will equate with local recurrence of the lesion, or, at least, with the inevitable presence of residual tumor in a re-excision specimen. Conversely, it is presupposed that the absence of neoplastic tissue at all margins will preclude the reappearance of tumor at the surgical site. A related issue has to do with the amount of tumor-free parenchymal tissue that separates malignant neoplasms from the actual margin: recommendations for optimal marginal widths may be organ- and tumor- specific, but they have usually been based on empirical information rather than objectively-verified precepts. In mind of the foregoing comments, the following discussion examines selected biological underpinnings of topics that are relevant to the histological assessment of surgical margins.

The Healing Response and Its Possible Effects on Tumor Growth

It is perhaps best-realized by dermatologists that incomplete excision of selected malignant cutaneous neoplasms (eg, "usual" forms of basal cell carcinoma) is not inevitably followed by regrowth of those lesions at the same anatomic location, even if they are not treated by additional surgical methods.[38-44] The same statement applies to tumors in other organ sites as well, such as invasive mammary ductal adenocarcinoma,[45-48] and primary pulmonary squamous cell carcinoma.[49] These scenarios obviously contradict the dogma that all positive margins must be acted upon immediately by the surgeon, and the underlying mechanisms relate to the relatively complex interplay between tumor and host in such situations.

Immediately after the mechanical insult of surgical intervention, a healing response is obviously stimulated. As outlined in basic reference sources,[50,51] hemostasis is the initial event in this cascade. In that phase, thrombogenic moieties are generated which in turn influence the subsequent proliferation of several tissue components. Interestingly, some of the molecular participants in the healing process are potential promoters of tumor growth, whereas others inhibit neoplastic proliferation.[52-56] Ultimately, the balance between those factors, as well as native attributes of the tumor cells themselves, will determine whether or not the neoplasm survives and recurs or is obliterated by the reparative sequence.

Possible "pro"- tumor elements in healing scars principally include platelet-related cytokines such as platelet-derived growth factor, platelet-derived endothelial cell growth factor, fibroblast growth factors, and transforming growth factor-beta (TGF-β) [50,51]; likewise, the fibronectin-associated generation of procollagenous peptides provides the possible substrate for a tumor matrix, together with the maturation of granulation tissue formed under the influence of TGF-β and macrophage/monocyte-derived growth factors. "Anti-" tumor participants in the repair process may include the direct effects of enzymatic lysis and cytokine release by acute and chronic inflammatory cells, proteolytic remodeling of cellular matrices by collagenases, elastase, and various metalloproteinases, and alterations in the expression of various proteoglycans and integrins by tumor cells.[50-56] Ultimately, the overall biological vigor of a specific tumor cell type, the volume of neoplastic tissue escaping surgical removal, the capacity for tumor multifocality or satellitism, and various constitutional characteristics of the individual host organism will be the determinants of whether a residual tumor survives in the healing tissue milieu, or is destroyed by the process. Obviously, neither the necessary information nor the technological tools are currently available to be able to predict those outcomes in any given case.

The Width of Surgical Margins: How Much is Enough?

In the authors' opinion, much arbitrariness exists in the clinical literature on "optimal" surgical margins for some neoplasms. For example, right hemicolectomies are still performed routinely for invasive adenocarcinomas arising in the cecum and ascending colon, regardless of the grades, sizes, or histologic types of such tumors. Similarly, pulmonary lobectomies are de rigueur for peripheral carcinomas of the lung in suitable operative candidates, again with little consideration for the pathologic details of the lesions in individual cases. One could argue that there is usually sufficient remaining physiological function in the remaining tissue in

those limitations to make this issue moot. Nonetheless, that is not always true, as exemplified by patients with severe abnormalities of gas exchange who also develop lung cancer.

The most objectively studied tumor margins have been those pertaining to carcinomas of the skin, breast, uterine cervix, and prostate, as well as cutaneous melanomas. In reference to basal cell carcinomas and most squamous cell carcinomas of the skin, "narrow" margins of only 1 to 2 mm are generally regarded as adequate to prevent recurrence; indeed, that premise underlies the entire discipline of Mohs' chemosurgery.[57,58] Similar comments apply to common histologic variants of invasive breast carcinoma.[59-61] In regard to selected cases of prostatic carcinoma with low- to mid- Gleason scores, "ordinary" types of cutaneous basal cell carcinoma, and uterine cervical in-situ squamous cell carcinomas (cervical intraepithelial neoplasia, grade III), this paradigm may extend even further to include frank involvement of the margins by tumor. Several analyses have shown that recurrence does not reproducibly accompany an overtly positive margin in those settings.[40,41,13,62-66]

Over the past 15 years, a remarkable transformation has developed in the treatment of melanoma. In the 1980s, many surgeons were still performing extremely "wide" excisions of deep melanomas, including removal of subjacent fascia and striated muscle.[67,68] Prospective trials were then initiated to study the advisability of more conservative resections, and those supported the current practice of using more limited margins for deep melanocytic malignancies.[69,70] There was no excess of local recurrence when this approach was compared with older, much more aggressive surgical procedures, and morbidity was greatly improved.

Distillation of the foregoing information should make it apparent that the behavioral features of different tumors are dissimilar in various organs and with surgical margins of variable widths. Hence, although it is certainly desirable to achieve complete excisions whenever possible, the pathologist and the surgeon must together consider the specifics of any particular case to decide whether a positive margin must be acted upon, and if so, how.

"Field Effect" and Assessment of Marginal Status

Another important consideration in the assessment of any given surgical site is the likely tissue environment in which it resides. In certain anatomic locales, such as the oropharyngeal mucosa and the prostatic glandular parenchyma, it is a virtual certainty that a clinically obvious mass will be surrounded by multifocal microscopic neoplastic proliferations of the same general histological type.[14-20,30,32,37,71] The latter lesions may be in situ or microinvasive, and they may represent additional neoplastic clones or share clonal identity with the principal invasive tumor. Comparable comments apply to selected cases of pulmonary adenocarcinoma, particularly of the bronchioloalveolar type.[72,73] In those circumstances, the submacroscopic abnormalities are most properly classified as manifestations of a "field effect," wherein synchronous or metachronous neoplasms develop in the same general tissue area in response to the same transformational stimuli. The practical meaning of these facts is that one cannot be at all certain in some cases whether a "positive" margin represents part of the main mass being resected, or a separate "satellite" lesion in a transformed field. In the setting of prostatic carcinoma, the "field" phenomenon has only academic importance inasmuch as total prostatectomy is performed pro forma. However, in the mucosal surfaces of the oropharynx or with reference to wedge resections of lung parenchyma, this issue has potentially important effects on the type and scope of the surgical procedure that is ultimately chosen. Moreover, there are no methods short of molecular clonality assays that can be applied to the resolution of this problem,[35-37,72,73] and gene-based analyses obviously cannot be done intraoperatively.

Considerations Regarding Marginal Status in Specific Tumor Types

With the foregoing information in mind, a discussion can now be undertaken of the literature on surgical margins in reference to specific organ sites. This topic is a work in progress, and therefore the list of tumors and tissue locations selected for consideration here is far from comprehensive.

Mucosal Squamous Cell Carcinoma of the Head and Neck

All practicing anatomic pathologists are well aware of the frequency with which otolaryngologists request intraoperative determinations of marginal status for squamous cell carcinoma (SCC) of the head and neck. Indeed, this is one of the most common scenarios seen in the frozen section (FS) laboratory. Despite that fact and the substantial experience that most pathologists have in this area, the "error" rate for cryostat sections is still relatively high for oropharyngeal SCC.[74] One study by Ord and Aisner (75) found that 20% of FS-"negative" cases manifested positive margins when all

permanent sections had been examined, although the actual accuracy of cryostat sectioning was 99%. In other words, the major reason for failure of the FS technique in this setting is sampling artifact, explained by the fact that many mucosal resections for SCC are sizable and cannot be sampled completely for cryostat examination.

Other FS-to-permanent section discrepancies in this setting are interpretative instead of technical in nature.[34] The distortion that is produced in freezing squamous mucosa accounts for part of this problem, but prior radiation therapy also has been employed in many cases and this further alters the microanatomy of the tissue.

These facts have more than passing interest, because they show that the FS determination of margins for oropharyngeal and hypopharyngeal SCC is accompanied by serious pitfalls. In that context, some recent publications that have used "molecular" techniques, in an attempt to better the situation, are also problematic. Several papers have described the immunohistochemical assessment of mucosal margins in the head and neck by detection of eIF4E, E48 antigen, or mutant p53 proteins.[34-39] Most of these communications have concluded that such adjuvant methods are desirable, with the implication that they detect tumor positivity in margins that are morphologically-negative. Returning to the points made above, however, one cannot actually be certain that the margins in question were tumor-free histologically because of the technical issues presented. Although adjuvant pathologic studies may indeed prove to have some worth in selected instances, it would seem more straightforward to concentrate on developing ways in which the morphologic features of the marginal tissue can be better preserved and techniques by which the margins can be sampled more completely yet efficiently (eg, by intraoperative cytology?). Similar comments apply to "molecular" analyses of p53 gene mutations and microsatellite instabilities in squamous mucosal surfaces.[30,32,35-37]

Indeed, another serious problem in using non-morphological methods to evaluate margins in the oral or pharyngeal mucosa is that those sites are notoriously prone to demonstrate "fields" of premalignant neoplasia. Moreover, the tissue in such fields commonly demonstrates molecular alterations that are identical to those seen in adjacent malignant neoplasms.[19] In this scenario, one is left with complete uncertainty as to which molecular aberrations reflect "positive margins" as opposed to contiguous (but not continuous) field effects. Thus, at the present time, the authors do not advocate the clinical application of immunohistochemical or molecular-genetic assessment of marginal status, with regard to oropharyngeal SCCs. Similarly, there are no recommendations that can be made on optimal widths of surgical margins for such lesions.

Cutaneous Malignancies

Probably because basal cell carcinoma (BCC) and squamous cell carcinoma of the skin are so ubiquitous in the general population, it has long been known that tumor-positive surgical margins do not necessarily predict the recurrence of those lesions.[38-40,41,43] In fact, BCC is often managed by curettage and electrodessication, with no attempt whatsoever to achieve histologically-negative tissue margins. Admittedly, this attitude of liberality must be tempered by the details of particular cases.[42,44] Overall, approximately 40% of margin-positive basal cell carcinomas do recur,[43] and particular variants such as sclerosing/desmoplastic/morpheaform BCC and superficial multifocal BCC are over represented in that group.[42,44] Accordingly, lesions with those histologic patterns should probably be re-excised if margins are involved by tumor. Because even banal SCC of the skin has aggressive potential that parallels its depth of invasion into the corium, margin-positive SCC that penetrates the deep reticular dermis also should be re-excised.[37,38] Various studies have shown that biologically aggressive epithelial tumors of the skin manifest alterations in their synthesis of syndecan-1 (a matrical proteoglycan), stromelysin-3 (a metalloproteinase), and beta-integrins (intercellular adhesion molecules), but these findings have not yet been applied to the clinical arena.[53,54,56]

Extramammary Paget's disease (EPD) is currently thought to be a glandular malignancy of the skin that originates in the epidermis.[21,22,25,76,77] It is usually multifocal in a regional sense, and therefore tumor-free surgical margins are often difficult to obtain. Indeed, several publications have suggested that staged excisions are prudent in reference to this neoplasm in order to assure its complete removal.[76,77] Marchesa et al[77] showed that tumor-free margins of $\geq$ 1 cm. were accompanied by significantly less risk of recurrence when compared with more narrow excisions. Several investigators have applied immunohistochemical studies (for cytokeratin-7, other low-molecular weight keratins, carcinoembryonic antigen, epithelial membrane antigen, and the CA-72 antigen) to marginal tissue in EPD to better identify the neoplastic cells.[71,77,25] Nevertheless, none of these studies has concluded that such

evaluations are necessary or superior to careful examination of conventionally stained tissue sections.

Because of its potential for lethality, cutaneous malignant melanoma has received the most attention of all skin tumors in regard to the definition of optimal surgical margins. In fact, the history of this topic has been an interesting one. It reflects the success of objective prospective clinical analyses, as well as the revolutions in practice that can be produced by such evaluations. As mentioned earlier in this discussion, large surgical resections of skin and soft tissue were commonplace for melanoma < 20 years ago, based on anecdotal teachings holding that such excisions were necessary to prevent local tumor recurrence.[67,68] In the mid-1980s, large trials were initiated that examined the feasibility of narrower margins for MM.[68-70] These supported the conclusion that even deep (> 4- mm thick), vertical-growth tumors could be managed successfully with only 2 to 2.5 cm margins.[78-87]

Selected publications have suggested that extremely narrow margins could be obtained in excisions of melanoma, using such techniques as Mohs' chemosurgery and adjunctive immunostaining for melanocytic markers such as HMB45.[24] Although this approach is indeed technically possible, it is very unwise from a biological perspective. Even in situ melanomas are usually associated with at least limited field effects in the surrounding skin, and invasive tumors show a propensity for satellitism.[81] That is a phenomenon wherein intralymphatic neoplastic deposits are present in the dermis within 5 cm. of the main lesion; satellitism differs from in-transit metastasis in that the latter term denotes intralymphatic tumor spread extending > 5 cm. laterally from the central mass. At first glance, such a distinction may seem arbitrary; however, melanomatous satellites correlate with a risk of local recurrence, whereas in-transit metastases predict a significant risk of distant spread outside the skin.[83] Returning to the information presented above on recommended marginal widths, one might expect that most satellites are usually detectable within 2 cm of an invasive melanoma, which is indeed true.[78-82]

As just alluded to, melanocytic malignancies do manifest an association with field changes in the adjacent integument. For that matter, so does EPD.[77] Thus, FS direction of surgical excision is predictably fraught with a high level of uncertainty and should not be attempted for these tumors.[76] It is much more logical to use punch biopsy-mediated "mapping" procedures to delineate the extent of these neoplasms before taking the patient to surgery.[76,77]

Another cutaneous tumor, dermatofibrosarcoma protuberans (DFSP), merits mention in this discussion, because adjunctive determination of surgical margins for it has been the subject of some attention in the published literature. DFSP is a "borderline" mesenchymal malignancy of the dermis characterized by immunostaining for CD34 (human hematopoietic progenitor cell antigen).[26,27] Again, some authors have suggested that Mohs' surgery should be utilized in the management of DFSP, and that CD34 could be used to distinguish tumoral tissue from adjacent non-neoplastic dermis.[27] A preference for chemosurgical treatment does indeed appear to be supported by the literature on this tumor.[84] Nonetheless, we have observed cases in which initial surgical removal of DFSPs was followed by re-excision and immunostaining for CD34. The latter technique may produce misleading false-positivity in this particular context, because CD34 appears to be an inducible protein in reparative benign dermal tissue. Hence, reliance on CD34-negativity to determine a final margin may result in significant over excision of non-neoplastic skin, and we do not advocate this procedure.

Uterine Cervical Intraepithelial Neoplasia

Cervical conization, either using "cold" technique or electrocauterization, has become increasingly common in the past 25 years as cytological screening for cervical intraepithelial neoplasia (CIN) has grown in scope. Various studies have examined the frequency with which conization is attended by surgical margins that are involved by CIN, as well as the biological significance of that finding.[66,85] In general, the likelihood of a positive margin is augmented by increasing grade of CIN, but this is a weak predictor of residual disease as judged by the results of further surgical procedures.[85] Moreover, the rate of recurrence shows a poor correlation with marginal status; only 14.5% of cases with positive margins demonstrated subsequent reappearance of CIN in a study by Bretelle et al.[66] These data suggest that the marginal status of this disease has only modest clinical significance; in light of that fact, there would seem to be no indication whatsoever for performing FS examinations of conization specimens for CIN, not to mention the technical difficulty that is encountered in trying to do so.

Goldstein and Mani[86] also evaluated conization margins in reference to cervical adenocarcinoma in situ. They likewise concluded that the presence of tumor at the line of surgical transection had little value with regard to predicting the existence of residual disease.

"Lumpectomy" for Invasive Adenocarcinomas of the Breast

Another area in which surgical practice has changed significantly in the past 2 decades is in the management of mammary carcinomas. Through the 1970s, the standard approach to these lesions was to perform an intraoperative biopsy with FS diagnosis, which, if interpreted as malignant, was followed immediately by a mastectomy. Now that sequence would be regarded as antediluvian. Current management dictates that a fine needle aspiration or core cutting biopsy be used for diagnosis, and every effort is typically expended to conserve the breast as much as possible for cosmetic purposes.[87] Lumpectomies are therefore much more common than mastectomies, and, after orientation by the surgeon, the margins of such partial excision specimens are typically covered with inks of different colors in the FS laboratory to designate their spatial identities (eg, lateral, medial).[88] Several articles have provided strong support for the contention that FS examination of lumpectomy margins—with immediate re-excision of positive ones—is the preferred succession of events.[89-92] Our own experience supports that conclusion; if re-excision is attempted at a later date, it is extremely doubtful that the operator will be able to match any given positive margin to the now contracted scar in the area of the former biopsy cavity. In many instances, margins around an invasive carcinoma can be adequately evaluated by gross examination if the surrounding tissue is virtually all adipose tissue. Frozen sections on such tissue are impossible to, at best, extremely difficult, and are invariably negative.

Other issues concern the use of "shave" (en face) versus standard marginal tissue sections in the evaluation of lumpectomy specimens, and alternatives to re-excision in cases where margins are found to be involved by tumor in "permanent" sections. In regard to the first topic, Guidi et al[93] showed that shave margins are not comparable to standard margin sections, and, for the time being, those authors appeared to recommend continued use of the latter. Additional studies by the same group of investigators,[47] and by Pittinger et al,[48] showed that "close" lumpectomy margins (with peripheral zones of uninvolved breast tissue < 1 mm) were acceptable with regard to clinical outcome, providing that the actual line of surgical excision was actually negative for tumor. That information further argues against the use of shave margins. Moreover, it also gives no support to the desirability of touch-imprint cytology of lumpectomy margins (which is roughly analogous to shave margin sectioning), as suggested by Klimberg et al.[90] The second topic of controversy, on how margin-positive lumpectomies should be managed subsequently, has received attention by Assersohn et al[95] and Papa et al.[96] Both of those groups of authors concluded that irradiation and chemoendocrine therapy were viable alternatives to further surgery, especially in cases where the tumor was ≤ 1 cm in maximum dimension.

Weber et al, found that approximately 5% of patients had local recurrences of their tumors after margin-negative lumpectomies had been performed.[91] At least in part, this observation undoubtedly reflects the tendency for breast cancers to be multifocal. Because of attendant sampling limitations, it also means that pathologists will, more than occasionally, fail to visualize residual tumor in the breast that is outside the topographic zone of any given invasive lesion; this is especially true of associated high-grade non-invasive (in situ) ductal carcinomas.[94] Owing to shared immunophenotypes for HER-2 and p53 protein, Horiguchi et al[53] concluded that "recurrent" tumors near previously excised lesions were always remnants of the initial neoplasms. Nevertheless, in light of the information just mentioned on field changes in the mammary epithelium, we believe that conclusion to be flawed.

Finally, the literature provides a general consensus for the conclusion that FS or intraoperative cytologic examination is unwarranted for excision specimens of in-situ carcinoma alone, with no evidence of an invasive breast tumor.[95-97] The influence of field changes is again a strong consideration in this specific context, and technical impediments to adequate pathologic evaluation are also substantial.

Resections for Carcinoma of the Lung

"Wedge" excision of peripheral pulmonary adenocarcinomas is now a well-established technique for the treatment of such tumors in patients with compromised respiratory reserve.[98,99] Available data indicate that this procedure is not quite as effective as lobectomy, vis-à-vis subsequent local recurrences of clinical stage I tumors,[99] but this may be true, at least in part, because wedge resections result in "understaging" of some cases due to lack of regional lymph node sampling.

On technical grounds, shave margins of wedge excisions of lung are the easiest to perform. This is also a circumstance where touch-imprint cytology is a comparable and expeditious alternative method of marginal evaluation. As mentioned earlier in this discussion, field changes do occur in the lung parenchyma around

adenocarcinomas, in analogy to those seen in the breast.[72,73] Accordingly, unexpected foci of tumor tissue may be seen at the line of surgical transection, which may represent separate primary neoplastic proliferations rather than microscopic extensions of the principal lesion in the specimen. Practically speaking, one cannot be certain of that interpretation intraoperatively, and it is therefore prudent to ask the surgeon to excise additional tissue when this situation is encountered. Subsequent growth of submacroscopic second primary tumors near wedge excision sites probably accounts for a proportion of so-called "local recurrences." However, it is unclear whether such adjuvant pathologic techniques as microsatellite analysis of wedge margins would be cost-effective in identifying this phenomenon.[36,100]

Interestingly, one analysis by Gebitekin et al[39] found that carcinoma-positive bronchial margins in lobectomy specimens were associated with no greater frequency of tumor recurrence than were negative margins, except for neoplasms that were stage III or above. This was true even though the majority of patients in that cohort did not receive adjuvant radiotherapy. Here again, there would appear to be little benefit in obtaining widely tumor-free margins at the expense of potentially greater short-term morbidity, and elaborate supplemental pathologic studies of marginal tissue would also seem misplaced in this context.

Prostatectomy for Adenocarcinoma

In analogy to other organ sites, a group of publications has appeared in recent years that tout the advisability of molecular studies in the evaluation of prostatectomy margins.[29,31,33,34] PCR for prostate specific antigen, prostate specific membrane antigen, and telomerase has been applied in this setting, and authors of these studies have claimed that such analyses were superior to morphologic assessment in predicting tumor recurrence.[31,34] In contrast, another cadre of papers has shown that up to 50% of patients with microscopically positive surgical margins for prostatic adenocarcinoma did not have reappearance of their tumors,[62-64] and Brannigan et al[17] further showed that touch-imprint cytology of marginal tissue was not predictive of recurrence.

Until this discrepancy is resolved, it would seem premature to apply molecular margin assessment in the clinical evaluation of prostatectomy specimens. Pending additional information, we suspect that the aforementioned differences can be ascribed to dissimilarities in surgical technique and pathologic sampling methods from one publication to another.

Resections for Enteric Adenocarcinomas

Because colorectal carcinoma is generally excised with a relatively generous margin of non-neoplastic tissue, there has been little activity focused thus far on the refinement of this procedure by adjunctive studies. On the other hand, gastric and esophageal malignancies are more challenging with respect to procurement of tumor-free surgical margins. Law et al[101] found that positive margins did not increase the rate of anastomotic recurrence of esophageal squamous cell carcinoma. Therefore, these authors did not stress the employment of special pathologic methods to evaluate the line of surgical transection. On the other hand, Yokota et al[28] used a monoclonal antibody ("S202") to a tumor-related glycoprotein for immunohistologic marginal analysis in the resection of gastric adenocarcinomas. They showed that immunostains with S202 were superior to conventional morphologic studies in delineating positive margins; nonetheless, only scanty follow-up information was provided in their communication, and it is uncertain whether final clinical results were actually affected by the use of immunohistochemistry. On empirical grounds, however, it is known that gastric carcinoma more often is linked to treatment failure because of the appearance of distant disease, rather than locoregional recurrence.

As with other tissue sites discussed above, the esophagogastrointestinal tract commonly manifests field changes in the mucosal epithelium.[13] Thus, this phenomenon must again be borne in mind when determining whether a microscopically-positive surgical margin represents extension of a clinically-apparent tumor, or the incidental proliferation of a second neoplastic clone in the region in question.

Excision of Soft Tissue Sarcomas

The accepted management of soft tissue sarcomas dictates that compartmental surgical excision should be done whenever possible, and less extensive margins are generally regarded as suboptimal.[102] Re-excision of marginal areas that are involved by tumor is commonplace, and FS examination is typically utilized to direct that process.[103] Nevertheless, there have been few prospective studies to compare surgery with other treatment modalities for positive margins, or establish objective guidelines for margin widths in reference to specific soft tissue sarcoma morphotypes. In that vein, a publication by Heslin et al[104] is intriguing. Those

authors suggested that re-excision of focally positive margins was probably unwarranted in cases of high-grade sarcoma, because therapeutic failures were usually ascribable to distant disease and additional aggressive resection had the risk of increasing overall morbidity substantially. Obviously, much more information will be needed in this area, and it will have to be tailored to particular tumor entities because of the broad biological spectrum of behavior that is seen among soft tissue malignancies.

"Metastatectomies"

Beginning in the 1970s, a model was established for the surgical treatment of selected metastatic tumors that are typically refractory to irradiation and chemotherapy. The first lesion to be managed by multiple "metastatectomies" was secondary osteosarcoma in the lungs,[105] and that approach was sometimes followed by long-term disease free survival. Surgical removal of other metastatic and slowly-growing sarcomas is now performed as well,[106] and excisions have become relatively common for solitary stable lesions of secondary colonic carcinoma in the liver, renal cell carcinoma in the lung, various metastatic carcinomas in the brain,[107-109] and secondary deposits of melanoma in selected organs.[110] This approach undoubtedly improves the quality of life for many patients, but most studies have shown only modest improvements in overall survival. Such an outcome is predictable, inasmuch as metastasis of any malignancy is a systemic process and surgery is conceptually unlikely to arrest its progress.

In this context, our opinion is that detailed margin examinations in metastatectomies have little clinical meaning. One is not concerned in this scenario with the local reappearance of a primary lesion, but rather the management of a disseminated neoplastic disorder. There is probably little to be lost by traditional inking of tissue margins in metastatectomies, but positivity of those margins should not necessarily prompt a pro forma re-excision. Furthermore, it would be an obvious misapplication of resources to undertake molecular assessment of marginal tissue in this setting.

SUMMARY

The topic of surgical margin analysis has changed from a seemingly straightforward one to a subject that is now increasingly recognized as organ and tumor-specific. Objective, prospectively obtained information on the optimization of margins is relatively scarce, and data from adjunctive morphological methods and molecular procedures are still relatively rudimentary. Over the next decade, it can be expected that much more detailed and targeted approaches to the surgical excision of various neoplasms will emerge, as an outgrowth of this line of inquiry.

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