DEFINITION OF SURGICAL MARGINS
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One of the most basic tenets of surgical oncology is determining the extent of tissue that must be removed about a mass to achieve effective local control. Since historic times, this simple question has challenged both human and veterinary surgeons. Surgical dogma has focused on finding the optimal “measured margin” about a mass as the solution to cancer control.\[1, 2\] However, despite extensive examination, the precise width of surgical margin necessary to completely eliminate recurrence has not been determined. It seems remarkable that, although complete resection of cancer is recognized as the most important goal of therapy, achievement of that goal is still largely influenced by a rudimentary application of an empirical surgical ruler, with the surgeon employing a ‘best guess’ to ensure sufficient tissue is removed about an individual tumour. Furthermore, the actual success of any surgery usually remains a mystery until the cancer is finally interrogated and the resected tissue examined. By then, the wound has been closed and the patient recovered from surgery.

What is a margin?
A tumour margin can mean many things to different people: to the surgeon, it will be the extent of normal tissue removed about the tumour at the time of surgery. To the pathologist, it will be the extent of tissue visible under a microscope surrounding the tumour. To the tumour, the margin may represent the section of the body that has been subjugated and influenced to support its ongoing survival. Despite its importance to the outcome of cancer, the ability to define “an adequate margin” is complicated and highly influenced by variations in individual tissue elasticity, tissue fixation, histological processing and interpretation.\[3, 4\] Almost from the moment the skin over a tumour is incised, there is disruption to the anatomical architecture of the surrounding tissues. The ability of a surgeon to maintain an appropriate boundary about the entire tumour circumference throughout the dissection is an important variable that may influence patient outcomes. This is a highly influential aspect of cancer surgery success but, surprisingly, has not been studied in any detail. In one veterinary study, an incomplete excision was significantly more likely when the tumour was excised by a surgical resident compared with a specialist surgeon.\[5\]

There are numerous technical factors that can influence the accuracy of margin evaluation. In studies where tissue specimens are measured throughout the various processing steps that occur after tumour resection, there is significant distortion of tissue dimensions following the first surgical incision. In various studies, the final measured histologic margin varied from 43-176% of the originally measured surgical margin.\[3, 4\] The extent of distortion was also found to differ for different tissues (e.g. skin, muscle, fat), based on their lipid content. Contraction of tissues will differ between tumour types, likely due to variances in stromal characteristics and microscopic infiltration about the tumour boundary. This can have a compounding effect on specimens composed of multiple tissue types (e.g. skin, subcutaneous, or musculoskeletal tumours). This work indicates that the histologic measurement of a tumour margin will likely underestimate the actual extent of the tumour-free margin, and the measured histologic tumour-free margin will likely be considerably smaller than the actual surgical margin obtained. However, extrapolating an optimal surgical resection margin from a desired histological tumour-free margin will likely be impossible, due to the variability in tissue shrinkage between patients, tissue and tumour types.
The importance of a clean resection

It is recognised that obtaining a histologically tumour-free resection about a tumour is important to achieve good local tumour control for most malignant cancers in most patients. For Patnaik Grade I and II mast cell tumours, 89-95% of dogs will experience successful long-term control following complete excision.[6] For STS, a similar proportion of dogs (88-92%) are reportedly cured after clean resection using wide excision of their tumour.[7, 8] However, for many of these tumour types, several recent publications have suggested that similar success could possibly have been achieved with less extensive surgery, leading to the suggestion that some patients have been over-treated for their disease.[9-11] However, the same data also suggests that a proportion of patients have been undertreated for their disease, suffering tumour recurrence or premature death due to local recurrence, despite an apparently clean resection.

The challenge to defining the success of a surgery is the awareness that defining a complete margin is not a binary state.[12-15] the width of normal tissue required about any tumour to prevent recurrence is ill-defined, and likely influenced by a variety of factors including tumour grade, size and other factors. There is, therefore, a transition between complete and incomplete where margins are considered “clean, but close” with “close” considered to be anything from 1mm of healthy tissue about the tumour to 5-10mm of healthy tissue.[12, 16, 17]

The literature provides conflicting advice on the management of patients with close or incomplete margins. For mast cell tumours, some authors have demonstrated significantly improved tumour control and survival following re-excision or radiotherapy in patients with incomplete or close margins.[18] However, other authors have not identified any difference in outcome between patients who are retreated and those that are not.[19, 20]

This lack of clarity creates a worrying situation for a client and patient with an incomplete or a close margin: was the surgery successful or was it not? Should more surgery be performed to be certain of success, or should additional therapies such as radiation or chemotherapy be administered? Not only does this additional treatment bring additional cost, morbidity and a disruption to life, there is also the potential risk of complications. In these situations, the clinician has to guide the client through a lottery of choices, balancing the risks of further intervention against the risk of tumour regrowth, with an awareness that this-regrowth may actually never occur.

The importance of a histologically tumour-free margin as an indicator of successful outcome is further muddied when it becomes apparent that even when a complete margin has been determined – to the best of our abilities – this is no guarantee that the cancer will not return. In dogs, recurrence rates of between 5-23% have been reported for mast cell tumours, and 8% for soft tissue sarcoma despite a clean resection being reported.[8] In human studies, rates of local recurrence rates ranging up to 30% have been reported for sarcoma, head and neck tumours, breast and various other tumour types despite ‘clean’ histological resections.[15]

Several reasons have been suggested to explain why recurrence of tumour may still occur when all of the original cancer has apparently removed. While technical limitations are a possible explanation, the phenomenon is common enough to suggest that some aspect of tumour biology plays a role.

Potential mechanisms that have been described include:

1. **Residual microscopic deposits of cells:**
   Migration of individual clusters of tumour cells beyond the tumour boundary has been recognised in human cancers for many years.[1, 21-23] Their occurrence may be of importance to tumour recurrence; in one study on human STS, tumour recurrence was almost 7-times more common when microscopic tumour foci were observed.[21] Tumour foci are not seen in every patient, but this characteristic was a common feature of higher grade tumours.

   However, while elimination of all grossly visibly tumour is an essential goal of cancer surgery, the extent of residual microscopic disease that must be removed to eliminate all risk of recurrence is unknown.
2. **Tumour microenvironment/stromal effects:**
A cancerous growth has become integrated into the host tissues. There is a dialogue occurring between the host and tumour from the combined output of cytokines, hormones and receptors generated from the dysregulated gene network of the cancer cell. This dialogue will vary both within an individual tumour and also for similar tumours in different patients, due to the unique evolutionary factors that have influenced its development. This will lead to different behaviors and growth patterns for an individual tumour.

3. **Cancer stem cells/Dormancy**
Following surgery, microscopic cellular deposits of tumour may remain in the tissues. Some of these clusters may not have the attributes to progress into a clinically relevant and recurrent tumour. Some clusters will remain dormant, or may be swept up by the patient's activated immune system. However, if appropriate environmental or genetic circumstances exist for continued tumourigenesis, then tumour recurrence will occur.

4. **Field cancerization effect**
Following removal of a gross tumour, stromal influences within the residual wound bed may continue to have an influence on any residual microscopic tumour cells that remain. An activated stroma may support immunomodulation and pro-angiogenic activities of any residual microscopic cellular deposits, or even enable the continued mutation of pre-cancerous cellular elements that had not been irreversibly transformed by the previous neoplasm (aka the field cancerization effect)

**How does this discussion influence our approach to surgical margins?**
Surgery remains the most effective treatment against successful local control of cancer. You may be surprised that in a discussion of surgical margins, there has been no focus on whether 1, 2 or 3cm (or more) margins are the ‘right’ dose for a particular tumour, or the role of anatomic resection of tumours and the influence of various tissue barriers on the success of surgery. This absence doesn't negate the importance of these issues. These are certainly important parallel issues, and undoubtedly influence the outcome for patients, but they are also reminiscent of conversations being held in the human oncology community 10, 20 and even 30 years ago.[1, 24-28] Until our decisions can be more precisely tailored to the individual biology of a mass, my suspicion is we will be continuing to have the exact same conversation in the future.

A continued focus on the demonstration of complete microscopic cellular margins should not remain our only determinant of outcome for patients with cancer. It seems likely that a purely cellular focus as an indicator of treatment success will provide an incomplete interpretation; a more holistic analysis of the cancer is required. If we are to move ahead from our current situation, and allow treatment plans to be more intelligently tailored to meet the requirements of each individual tumour, we need to improve our utilisation of techniques that provide a more comprehensive interrogation of tumour biology.

In coming years, we will need to become more intelligent in our surgical engagement with a tumour. For example, using information gained from a pre-operative interrogation of the tumour, we could more confidently identify which patients can be safely treated with a narrow cuff of healthy tissue, and those which demand a carefully planned anatomical resection, or multi-modal therapy. We need to discover the gene signature that correlates with important phenotypic attributes already known to be of relevance to recurrence, including the tumor profile and the propensity of cells to migrate beyond the tumor circumference. Finally, we need to use intraoperative or post-operative molecular analysis of shave margins to allow patients to be identified with a higher risk of recurrence, justifying the need for further intervention, but providing confidence of outcome for patients without such abnormalities.

This is not a unique desire; it is very much an idea of the moment. Similar themes are being expressed by our human colleagues who are experiencing the same challenges.[29-31] This coalescence of desire simply reflects the gap between the theoretical knowledge of cancer behavior and our ability to apply this in a practical setting. On completion of the human genome project in 2000, Dr Mike Stratton, head of the cancer genome project stated that "It would surprise me enormously if in 20 years the treatment of cancer
had not been transformed.” The veterinary oncology community is in a unique position to forge a new path in resolving this question. For our patients, routine incorporation of radiotherapy is unlikely to become commonplace, so surgery will likely remain the predominant weapon in the control of localized cancer. The known similarities in the biology of many of our common cancers provides a rich resource with which to understand the many complexities of this issue.

References


