Surgical margins for soft tissue sarcoma

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Local recurrence after surgical removal of a soft tissue sarcoma is believed to occur because microscopic tumor tissue is left. When such tumor tissue grows into a macroscopic tumor, a local recurrence (or local regrowth) becomes clinically apparent. Other explanations for local recurrence have been suggested, such as reseeding in the wound of systemically circulating tumor cells. However, the close association between the extent of surgery and the local recurrence rate clearly indicates that persistent tumor is responsible. To estimate the risk of local recurrence after surgery, some classification of surgical margins is necessary; the better the margin the less the risk of recurrence.

Historical perspective

In the past, soft tissue sarcomas of the extremities were treated by local excision, often followed by local recurrence or amputation. In 1958, Bowden and Bower reported techniques for limb-sparing procedures, with a low local recurrence risk. They emphasized that soft tissue sarcomas grow infiltratively. This explains the high local recurrence risk after shelling-out of the tumor, which leaves microscopic tumor tissue. In their opinion, "the criterion for the choice of surgical procedure should be the *gross anatomic setting of the tumor.* An extensive resection of soft tissue should be carried out for a sarcoma, regardless of histogenesis, when complete removal of the tumor and its surrounding muscles, fascia, and skin can be readily accomplished" (Bowden and Booher 1958).

The same surgical principles were reported by Stener et al. (1958) in the same year. Stener too stressed the infiltrative manner of sarcoma growth and he also realized that the width of the margin of tissue required all around the tumor depended on its *quality*:

> "The quality of the margin decides how wide it must be. A tumor originating in a muscle tends to get an elongated shape growing as it does preferentially in the direction of the muscle fibers. Therefore, in the longitudinal planes of the muscle, the margin must be very wide, which often means the removal of the whole muscle. In the transverse planes, the margin need not be as wide providing the preformed fascial boundary of the tumor-bearing region is included in the specimen." (Stener 1979).

Sarcomas tend to respect preformed fibrous barriers (muscle fascia and aponeurosis, deep fascia and intermuscular septae) until a very late stage; an unengaged fascia, even if in contact with the gross tumor, is an adequate margin. In contrast, several centimeters of surrounding subcutaneous fat, muscle tissue or the loose areolar tissue between muscles is required for a wide margin. To not violate preformed fibrous barriers, Stener refrained from open biopsy. In most cases, he based his preoperative diagnosis on the history, the findings in the physical examination and angiography, later on also on CT. If information from these examinations was not sufficient, a fine-needle aspiration was also performed. Berlin et al (1990) described Stener's results in a series of 89 patients with soft tissue sarcomas of the extremities who had been referred before surgery. More than four fifths of the tumors were high-grade malignant and larger than 5 cm. The follow-up was between 6 and 26 years. All patients were operated on but no adjunvant therapy was given. Thus, *no local radiotherapy was used.* 13 patients underwent amputation. 37 patients had a "function-preserving operation"—a wide local excision—without biopsy (clinical diagnosis only), 1 patient had a local recurrence. After the same surgical procedure, 3/16 patients had a local recurrence if a diagnostic fine-needle aspiration had been performed, and 6/22 patients had a local recurrence if the definitive operation was preceeded by an open biopsy.

The Enneking classification

I have cited Bowden and Booher and Stener because their principles form the basis of the next great step as regards the definition of surgical principles for sarcoma—that of Enneking (1980, 1981, 1983). Enneking's description of tumor growth and classification of surgical margins can be summarized as follows:

When a tumor grows, the normal connective tissue surrounding the tumor is compressed and forms a capsule of fibrous tissue. A growing lesion also causes a reaction in the adjacent normal tissue; a reactive zone forms between the capsule and surrounding normal tissue. This zone is composed of proliferating mesenchymal cells, neovascularization and inflammatory cells. Malignant tumors, even low-grade, destroy and grow through the capsule into the reactive zone and also form small, isolated islands of tumor cells lacking continuity with the main tumor. Enneking called these nodules "satellites". The reactive zone and remnants of the capsule form a pseudocapsule. A low-grade tumor does not grow outside the reactive zone. High-grade tumors totally destroy the capsule and the reactive zone is more prominent than it is around a low-grade tumor. A high-grade tumor also gives rise to satellites (isolated skip nodules or skip metastases) in normal tissue far beyond the reactive zone. These skips are presumably intravascular micrometastases. Skips are seldom found beyond natural barriers to local tumor extension; for intracompartmental tumors the skips are usually confined within the compartment.

Based on these observations, Enneking formulated the concept of compartmentalization and surgical margins. A compartment is an anatomic structure or space bounded by natural barriers to tumor extension, e.g., major fasciae for soft tissue tumors; a functional muscle group bounded by major fascial septae is a compartment. Thus, the soft tissues of the thigh form 3 compartments: the anterolateral (quadriceps), the medial (adductors) and the posterior (which includes the sciatic nerve). Subcutaneous tumors were classified as intracompartmental although there are no longitudinal barriers in the subcutaneous tissue. One reason for this classification may be the observation that a subcutaneous sarcoma removed en bloc by a 5-cm margin in the subcutaneous fat and inclusion of the overlying skin and the deep fascia beneath the tumor gave a low local recurrence risk, as low as the risk after radical (compartmentectomy) removal of a deep-seated intracompartmental tumor.

Surgical margins

Enneking classified surgical margins as intracapsular, marginal, wide and radical:

> "An *intracapsular* margin means that the lesion has been removed from within the (pseudo)capsule and that gross tumor is seen at the wound margin. Left in the wound are portions of the lesion, the reactive zone containing satellites, and skips in the surrounding normal tissues.
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> A *marginal* margin means that the lesion has been removed en bloc, that the plane of dissection has been extracapsular, either between the (pseudo) capsule and the reactive zone or within the reactive zone, and that the margin of the wound is composed of reactive tissue. Remaining in the wound are portions of the reactive zone containing satellites and skips in the surrounding normal tissue of the compartment.
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> A *wide* surgical margin means that the lesion has been removed en bloc, and that the plane of dissection has been peripheral to the reactive zone through normal tissue but has taken place within the compartment of origin. No natural barrier is between the lesion and the margin. Left in the wound are the skips in the remaining normal intracompartmental tissues. If the lesion is extracompartmental, the dissection takes place in normal tissue beyond the reactive zone but between the reactive zone and the boundaries of the adjacent compartment.
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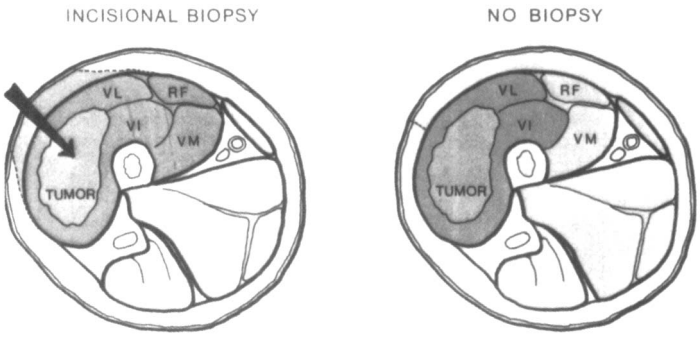
> A *radical* margin means that the lesion and the entire compartment(s) which it involved have been removed en bloc. The plane of dissection has taken place peripheral to the boundaries of the compartment in the transverse sense and proximal and distal to the longitudinal extent of the compartment. There must be a natural barrier(s) between the margin of the wound and the lesion in all dimensions. If a lesion is extracompartmental, a radical margin is achieved only when the dissection takes place peripheral to the barrier of the adjacent compartment(s) in the tranverse sense and proximal and distal to the longitudinal extent of the adjacent compartment(s)" (Enneking 1983).

Correlation of margin and local recurrence

Sarcomas were graded in low- and high-malignant tumors and Enneking described local recurrence risks (without adjuvant therapy) for all combinations of surgical margins, compartmentalization and malignancy-grade: a marginal excision of a low (high) grade sarcoma was followed by local recurrence in 70 (90)%, irrespective of compartmentalization. A wide margin for a low-grade, intracompartmental sarcoma resulted in a local recurrence in 10%, whereas the same margin for a high-grade intra(extra)compartmental sarcoma resulted in a local recurrence in 50 (70)% of the cases. There were no recurrences after a radical resection of low-grade sarcoma, but 10 (20)% after the same margin for a high-grade, intra(extra)-compartmental tumor.

Stener used the same definition of compartment but included also a single muscle(s) provided no open biopsy had been performed. For example, a tumor in the rectus femoris muscle is intracompartmental so long as no open biopsy has been performed, a tumor in the vastus lateralis is intracompartmental, the compartment is formed by the vastus lateralis and vastus intermedius muscles. Enneking's definition of compartment may be based on experience with patients referred after open biopsy, or still worse, after marginal



Sarcoma posterolateral in the quadriceps muscle. Dark fields indicate loss of muscles after incisional biopsy and radical resection (left) and after no open biopsy and primary myectomy. After incisional biopsy, the total quadriceps compartment (as defined by Enneking), bounded by the deep fascia, intermuscular septa, and periosteum, is removed because of possible spread of tumor in the compartment by the biopsy. If an open biopsy has not been done, the vastus lateralis muscle and the vastus intermedius muscle alone are removed from their origin to the insertion with the surrounding muscle fascia and adjacent deep facia and periosteum. According to the Enneking classification the margin in the first case is called radical whereas the margin in the latter case is wide (wide-F). Reprinted with permission from Stener (1979).

excision or local recurrence. The use of preformed fibrous barriers to define surgical margins is important; the quality of the margin, and not its physical distance, influences the risk of local recurrence. Kawaguchi et al. (1995) suggested a new classification of surgical margins: a so-called curative wide margin required a margin more than 5 cm outside the reactive zone. This is impossible to achieve without amputation. Azzarelli (1993) pointed out that a margin even larger than 2 cm all around the tumor required resection of bone or major nerves or vessels. also in the largest muscular region, the thigh.

There are difficulties with the Enneking system as regards the margins for an extracompartmental tumor; the difference between a wide and radical margin for these tumors is not clear-cut. Taking this into account and the fact that the type of tissue which constitutes the margin is of importance and accepting that a muscle(s) may constitute a compartment (provided no open biopsy has been performed), we introduced a slight modification of the Enneking system (Rydholm and Rööser 1987).

A marginal margin was defined according to Enneking. A wide-S margin (**s**ubcutaneous) was achieved when a subcutaneous tumor was excised en bloc with a cuff of subcutaneous tissue (and often skin) and with the deep fascia beneath the tumor included. A wide-F margin (**f**ascia) was obtained when a deep tumor was removed with the specimen bounded by uninvolved and unopened fascia in all directions (primary myectomy without removal of the total compartment, as defined by Enneking). A wide-AM margin (**a**reolar, **m**uscle) was achieved when a deep tumor was excised by a wide margin where some or all boundaries were not fascia but muscle tissue and/or the loose areolar tissue found between muscles. A radical margin for an intracompartmental tumor required removal of the total compartment, as defined by Enneking (Figure). The local recurrence rate for the wide-S and wide-F margins (81 extremity or trunk wall sarcomas, 72 high-grade malignant, no adjuvant therapy, cumulative 5-year data) was the same and less than 10%. A local recurrence occurred in 30 % after a wide-AM margin.

In a randomized trial, by the Scandinavian Sarcoma Group, of adjuvant doxorubicin after wide or radical surgery of high-grade soft tissue sarcomas in the extremities, a local recurrence occurred in 7/84 patients after a wide local excision and minimum 10-year follow-up. Half of the patients received doxorubicin, but the local recurrence rate did not differ between patients with or without chemotherapy. The definition of a wide margin was according to Enneking. Of these 84 tumors, 32 were diagnosed without open biopsy (Alho et al. 1989, updated). Karakousis et al. (1995) also reported a local recurrence rate of 10% for primary soft tissue sarcomas in the extremities after wide excision, without adjuvant radiotherapy. In a population-based series, the local recurrence rate was 60% for high-grade tumors and 30 % for low-grade tumors after marginal excision without adjuvant therapy, (southern Swedish sarcoma database, median 7 (2–30) years follow-up, unpublished data).

Thus, the correlation between the Enneking margins and the local recurrence rates has been confirmed. However, the exact rates vary. One explana-

tion of these different local recurrence rates, after wide and compartmental margins, may be local tumor spread because of open biopsy. Several of the tumors in the Scandinavian series (Rydholm and Rööser 1987, Alho et al. 1989, Berlin et al. 1990, southern Swedish database) were operated on without open biopsy and in the other cases open biopsy was commonly performed by experts at a treatment center. The variation in rates after marginal excision may be explained by referral bias; patients who suffer a local recurrence are more often referred than patients who do not have a recurrence. Enneking's data are based on patients seen at a tumor center, our data are population-based; patients not referred are also included.

The Enneking classification system for surgical margins was rapidly accepted by the orthopedic oncology community and soon became the gold standard. One scientific journal even obliged all authors to use this system, otherwise articles were not accepted. The system was of great importance for a rational approach in treating sarcomas and reporting results after different treatments. So great was the impact that researchers have felt obliged to apply the classification in the wrong way; a margin known to give a low local recurrence risk has been called wide for that reason and not because of the margin itself. A well-known example is the decreasing margin now used for osteosarcoma after effective chemotherapy. For example, osteosarcomas with a large soft tissue tumor component in the popliteal fossa dislocating the nerve and the vessels are operated on by excision of the distal femur but with preservation of the nerve and vessels and the margin is called "wide" because the surgeon knows that the risk of local recurrence is small. It would have been better to stick to Enneking's definition of surgical margins, but one should accept that a marginal margin in special circumstances may be followed by a low incidence of local recurrence even in high- grade tumors.

The fact that all high-grade malignant tumors do not recur locally after a wide excision, or not even after a marginal excision, implies that the Enneking description of tumor growth does not apply to all tumors. There seem to be subsets of sarcomas which do not grow infiltratively and do not cause satellites or skips. However, surprisingly little has been published as regards the interaction between sarcomas and surrounding normal tissue. Akpinar Basdemir (1997) studied multiple samples of the tumor border in 36 musculoskeletal tumors, most of them highly malignant, and found that a reactive zone was an exception rather than the rule. These observations, of course, do not exclude the use of Enneking's classification of surgical margins but they obviate the need for further studies and classification of local tumor growth. It seems not correct to assume that most high-grade malignant tumors form satellites and skips. The pattern of local tumor growth should be combined with the Enneking margins to allow for a still better prognostication of the local recurrence risk.

Are new definitions of margins required?

It is not clear why for several years past, a "new" classification of margins for soft tissue sarcoma has been increasingly common. Enneking's classification is not used but margins are classified as positive or negative (see, for example, Bell et al. 1989, Tanabe et al. 1993, Singer et al. 1995, Pisters et al. 1996, Heslin et al. 1996). According to Pisters et al. (1996), in a report on over 1000 patients from the Memorial Sloan-Kettering Cancer Center, "A positive surgical margin was defined as tumor present within less than one half of a 10 X microscopic field (1 mm) from the inked margin". In another report from the same center (Heslin et al. 1996) "the pathologic margin was defined as positive when the tumor was identified to be at a margin of resection. " In both reports there was a correlation between the type of margin and the local recurrence rate; 10-20% of patients with negative margins had a local recurrence, 40% of the others had. A substantial number of the patients had had radiotherapy. Tanabe et al. (1993), in a study of 95 preoperatively irradiated soft tissue sarcomas of the extremities, graded surgical margins "as positive, if the final pathology report identified tumor cells at or close to the cut edge of the specimen". 6/71 patients with negative margins had a local recurrence, compared to 8/24 with postive margins. At surgery, "Although careful attempts were always made to achieve tumor-free surgical margins, no attempts were made to excise entire muscle compartments" (Tanabe et al. 1993). This is the common, vague description of surgery, often called "conservative surgery", applied in connection with radiotherapy. Common to all these studies, using positive/negative margins as a description of surgery is that surgery has been combined with radiotherapy, as in almost all series reported the last 10 years. However, it is hard for me to understand why the classification of margins, as described by Enneking, could not be used in combination with radiotherapy. One may suspect that the good results, as regards local recurrence, that have been reported with adjuvant radiotherapy, have diminished the interest in a strict classification of surgical margins. This is a retrograde step which will not solve today's problem with uncontrolled radiotherapy—i.e., surgery combined with radiotherapy in *all* patients, see also pages 117–119.

The positive/negative margin classification violates the Enneking concept of tumor growth. A negative margin, of course, says nothing about the situation in the tissue outside the resection border, it may very well contain satellites or skips. This is evident from the findings in the above-mentioned studies; local recurrences also occurred in patients with negative margins.

Summary

The Enneking classification of surgical margins is the only one which shows a resonable correlation between the type of margin and the risk of local recurrence. However, it can be improved by a complementary definition of compartments and a better investigation of local tumor growth. Thus, if no open biopsy has been performed, a single muscle or a group of muscles, may constitute a compartment. Secondly, tumor growth at the border between the gross tumor and surrounding tissues should be better studied and classified. If preoperative radiotherapy is preferred, hopefully, growth patterns can be correlated with preoperative MR-findings to select patients who would benefit from radiotherapy combined with surgery. If postoperative radiotherapy is preferred, the operative specimen should be used for a microscopic classification of the tumor growth at the border, to make it possible to select only patients who need postoperative radiotherapy. Thus, it may be possible to combine Enneking's margins with a classification of tumor growth at the border, which permits a still better prognostication of local recurrence.

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