VETERINARY SPECIALTY HOSPITAL

# Surgical Considerations in the Radiation Therapy Patient

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This topic is important as most patients have already had surgical excisions of their tumors by the time they are presented for radiation therapy. While surgery is often the most important aspect of these patients' treatments, this poses several potential complications for the radiation oncologist when deciding upon the proper course of treatment and appropriate doses and beam field sizes. The most important and obvious complication is that without seeing the tumor before surgery and knowing the full extent of the mass, it can be difficult to know where to direct the radiation treatment on the patient. Furthermore, surgical manipulation can result in tumor seeding and disruption of tissue planes that are not obvious on examination or advanced imaging, further complicating the process. This talk will outline several principles of combination therapy with radiation and surgery and will offer examples of methods that can be used by surgeons to improve outcome with radiation therapy.

## Pre-Operative vs Post-Operative Radiation Therapy

In veterinary medicine, most patients are presented for radiation therapy after definitive surgery. Reasons for this include necessity of debulking the tumor to alleviate discomfort, inflammation, or infection, the chance of obtaining a complete removal negating the need for further therapy, lesser cost of surgery versus combined radiation therapy and surgery, avoidance of surgical complications in irradiated tissue, historical scarcity of radiation therapy facilities, and alleviation of stress and worry on the part of the owner by removing the mass.

In contrast, many human tumors are dealt with by administering radiation therapy first or as the sole modality. While there are notable exceptions (i.e., breast cancers and lung cancers), the order of treatments is often quite different from what is seen in veterinary medicine. Reasons for this include the acceptance that radiation therapy is necessary for tumor control in humans, ready access to radiation facilities for most communities, less concern about overall cost of treatment, and a medical understanding of proven benefits of pre-operative irradiation.

While it is unlikely that radiation will become the treatment of first resort in veterinary patients, it is important to understand the principles behind pre-operative irradiation in order to better understand the benefits and consequences of post-operative radiation.

## Advantages of Pre-Operative Radiation Therapy

### Known Geographic Target

Simply put, if you can see it, you can more accurately define its location and treat it. When a tumor has been debulked, especially if no diagnostic images have been made prior to removal, it is impossible to know exactly where the tumor was located along the scar line. This may lead to a geographic miss or to a lesser dose of radiation being given to an area that needs a higher dose.

### Smaller Field Size – Fewer Normal Tissue Complications

Radiation treatments, regardless of the size of the fields involved, necessarily involve normal tissue surrounding the gross tumor. In most definitive treatments, a margin must be established around the identifiable gross disease in order to treat any microscopic extensions. Even highly conformed Intensity-Modulated Radiation Therapy (IMRT) requires margins, although they are much smaller than for other radiation techniques.

The typical margin established around a tumor for a definitive treatment is from 2-3 cm. This is the same margin that is often used in surgery. If a gross tumor is irradiated, a volume of tissue greater than that of the tumor alone must be irradiated to account for these margins. If a surgery with 2-3 cm margins is performed prior to radiation therapy, the resulting radiation field must establish margins of 2-3 cm around the surgical field. This effectively increases the volume of tissue receiving a clinically significant dose of radiation and can exacerbate normal tissue complications.

### Blood Supply is not Altered – Decreased Hypoxia in the Tumor Bed

Tumor vasculature is highly unstable. Foci of transient and chronic hypoxia have been identified in all evaluated tumor types and contribute to radioresistance. Oxygen is required for “fixation” of DNA damage caused by radiation; areas of low oxygen tension result in damage that can be repaired, hence greater resistance to treatment. These foci of hypoxia are typically located in the bulky portion of the tumor while the reactive zone and normal tissue around the mass are unaltered. The goal of most radiation treatments is to sterilize the microscopic extensions in the reactive zone and normal tissue and to reduce the bulk of the tumor as best as possible. If a complete remission is not achieved, surgery is performed to remove the remaining bulky component.

Surgery disrupts tissue planes and the vascular supply of the tumor and normal tissue. Pockets of hypoxia have been identified in examined suture lines and scar tissue due to these disruptions. Therefore, if radiation is given after surgery, the previously normoxic environment will have been altered and hypoxic foci will have been created. These foci may contain tumor cells that will be more resistant to irradiation than they would have been if undisturbed. These cells can survive radiation therapy and eventually repopulate the tumor. This is thought to be the major cause of tumor recurrence along a scar or within a radiation field.

### No Delay in Radiation Therapy

If radiation is begun right away, it may be possible to sterilize peripheral tumor cells and metastatic clonogens in the bulky portion that would otherwise contribute to dissemination of the tumor.

### Decreased Risk of Tumor Dissemination During Surgery

Surgical manipulation of the tumor typically results in large numbers of tumor cells entering circulation and the lymphatic drainage. This increase in circulating neoplastic cells may result in a higher risk of distant metastasis. Irradiation of the tumor prior to surgery would presumably sterilize the cells so even if they gained access to distant sites and implanted, they would be dead from a reproductive standpoint, decreasing the likelihood of distant metastasis.

### Extent of Surgery Potentially Less

Radiation therapy may be used to significantly decrease the extent of a tumor in order to reduce the size and scope of any subsequent surgical procedure. This could be of particular value for large, invasive head-and-neck tumors where an extensive surgery could result in high morbidity or loss of function.

## Disadvantages of Pre-Operative Radiation Therapy

### Potential for Poor Wound Healing

There is no question that irradiated tissue has a reduced ability to heal following surgery or accidental wounding. Most of this reduction is caused by damage to fibroblasts resulting in decreased or aberrant collagen production. Surgical wounds in irradiated tissue have a higher likelihood of breaking down under tension, dehiscence, delayed granulation, and poor scar formation. This alteration in healing can persist for years after irradiation. Chronic effects of radiation result from the initial abnormalities in collagen formation as well as late alterations in vasculature.

## Advantages of Post-Operative Radiation Therapy

### No Delay in Surgery

This is especially important for tumors that are infected or inflamed or that ae causing pain or functional derangements by impinging on local tissues. Smaller tumors may be dealt with effectively by early surgery, prior to invasion or metastasis.

### More Complete Staging of the Cancer

Surgery prior to radiation can yield a more complete sample for histopathology. Margins and actual tumor size may be identified and local lymph nodes could be excised to present for evaluation. Irradiation results in tumor necrosis and other changes to the surrounding stroma that can make histological evaluation difficult or impossible.

### Normal Tissue Healing

Aggressive oncologic surgery has the same prognosis for adequate healing that any other surgery would offer. Properly apposed normal tissue margins will undergo healing as expected and irradiation following the inflammatory and proliferative phases of healing will not have an adverse effect. Most radiation oncologists advise waiting two weeks before initiating radiation therapy to avoid complications in healing.

## Disadvantages of Post-Operative Radiation Therapy

**Larger Radiation Field Size**
**Increased Risk of Tumor Dissemination**
**Altered Blood Supply – Hypoxic Regions in Suture Line**

All three of these are addressed as advantages for pre-operative radiation therapy.

### Tumor Repopulation Before Irradiation

While a delay between surgery and radiation therapy is recommended, this does open to the possibility of tumor regrowth prior to irradiation. Should this occur, radiation would be theoretically less effective than if applied to microscopic disease. Radiation kills a proportion of cells each time it is applied, so better results are typically seen when the starting number of cells is smaller.

### Improving the Effectiveness of Post-Operative Radiation Therapy

While most evidence points to pre-operative radiation therapy as a more effective means of treatment, the reality is that veterinary patients will more often be treated with surgery first with radiation as an optional adjuvant. Because of the greater number of potential problems arising from post-operative radiation therapy, it is important to maximize the effectiveness of surgery and to minimize the potential complications. The reduction of complications is the responsibility mainly of the radiation oncologist but this job is made easier if certain surgical principles are observed.

The following principles are important for any oncologic surgery but are especially important for patients who are likely to receive radiation therapy.

**Placement of Biopsy or Aspirate Site**

Any biopsy or needle aspirate, regardless of method, should be taken from a location that will fall within the normal excisional margins. The reason for this is simply that any extension beyond these margins requires that the radiation field be extended to include it due to the risk of tumor seeding. Needle tracks are impossible to discern and needle core biopsies or incisional biopsies that tunnel under skin may be difficult to find, as well.

**Pre-Operative Imaging**

Pre-operative images can be invaluable to the radiation oncologist as they can show exactly where the tumor was located prior to surgery. Simple photographs can be all that is necessary to help determine where the tumor was situated in relationship to the resulting scar. Radiographs of a site can also be helpful, especially on limbs, even if no bone involvement is noted. These films can be compared to the port films that are obtained for positioning during treatment and can help delineate the proper treatment volume. Pre-operative advanced imaging, such as CT scans or MRI, is extremely helpful for tumors in body cavities. The “before surgery” images can be compared to “after surgery” images obtained for therapy planning to ensure a sufficient margin is placed around the tumor site.

**Incision Placement**

The location and length of an incision can have a major impact on radiation therapy, particularly where normal tissue side effects are concerned. Location is particularly important for tumors on the limbs. Whenever possible, radiation fields are planned in such a way as to avoid irradiating the entire circumference of a limb. This is to avoid inflammation and fibrosis of draining lymphatics that could result in pitting edema distal to the site. Incisions on the limbs should run longitudinally and preferably to one side of a plane. That is, the incision should be limited to one plane (cranial aspect or lateral aspect or caudal aspect only, etc.) and should be toward the “edge” of that plane. This will allow the best chance to treat the scar and underlying tumor bed while sparing a strip of skin and avoiding unnecessary tissue complications. Diagonal or transverse incisions should be avoided as they cross over more than one plane and make it impossible to avoid circumferential irradiation.

Incision length is also of concern for several reasons. While it is desirable to obtain aggressive margins (~ 3 cm) for most tumors, it is important not to take excessive margins that become difficult to treat with radiation.

Most incomplete resections occur at the deep margin, not at the periphery. Therefore, excessive superficial margins may result in an incomplete excision at the deep margin with the possibility of tumor seeding along the resulting scar. This requires the radiation oncologist to treat the entire scar and underlying tissue to account for the possibility of occult surgical metastases.

Very long scars result in large volumes of normal tissue receiving substantial radiation dose. They also pose the problem of requiring overlapping fields to treat them adequately. Overlapping fields of radiation result in hot and cold spots where they meet and can cause an over or underdose of normal tissue and tumor, respectively. This problem can be overcome by changing the location of the overlap each day, but this complicates treatment and invites error.

In cases where a large tumor exists and the resulting scar and tumor bed may be very large, pre-operative radiation may be a better course of treatment to avoid excessive dose to normal tissue and difficulties with radiation delivery.

**Depth of Biopsy or Aspirate**

Care should be taken to ensure that biopsies and aspirates do not plunge deeper into normal tissue than is necessary to obtain an adequate sample. Aggressive use of a dermal punch biopsy instrument or repeated passages of a fine needle through a tumor into deeper tissue planes can spread a tumor beyond its original extent. While any radiation field will have a margin built into it to encompass disease beyond the obvious gross tumor, it is possible that some tumor cells may be spread beyond the anticipated radiation margins by aggressive biopsy technique.

**Placement of Hemoclips or Other Radio-opaque Markers**

Traditionally, radiation fields have been planned off of the scar post-surgery. That is, a margin was delineated around the scar and fields were designed to treat the volume within those margins. Recent studies have indicated that the underlying surgical field is often much more extensive than indicated by the scar and that radiation fields based only on that scar are likely to miss residual tumor. Steps should be taken to label the margins of the surgical field so they can be identified by radiography or special imaging and result in better radiation field coverage.

The easiest method of identifying the margins of the surgical field is to place hemoclips within the field before closing. These clips are not used for hemostasis but to delineate the greatest extent of the surgical site in five planes: cranial, caudal, medial, lateral, and deep. The superficial margin is marked, of course, by the scar. These hemoclips are easily identified by a simple radiograph and can provide better guidance for the radiation oncologist when planning the treatment fields.

Care should be taken to place the clips at fixed locations, otherwise they will all come together when the tissue planes are closed and their information is lost.

### Tumor Marking

Tumor marking is of great importance because it can identify which margins require the most attention from the radiation oncologist. This is particularly important in head-and-neck cancers where the radiation fields impinge of sensitive normal tissues such as the eyes and oral cavity. It is important to know which margins are incomplete in order to avoid excessive dose to normal tissues adjoining histologically clean margins. Without such information, large margins must be placed on all borders and the result is an increase of dose to normal tissue.

The use of suture to mark one or two margins on resected tissue is a common practice but it is not foolproof. The sutures are often removed when the tissues are "cut in" for fixation and the pathologist may never see them. Most technicians will take care to review the submitter's notes prior to preparing the tissue and will mark the cassettes appropriately, but confusion can occur here, as well.

The most effective method of tumor marking is to use indelible inks. India ink is often used to demarcate on or more margins, but this is often not enough to give a complete reference for all margins. Commercial tumor marking dyes, such as the Davidson Tumor Marking System™, are widely available and are straightforward to use. These dyes are painted onto the cut surfaces of the tumor before placement in formalin and can identify all margins for the pathologist.

## Summary

Many advantages exist for radiation therapy given prior to surgical intervention but the reality of the veterinary field is that post-operative radiation therapy will be the most commonly seen practice.

The biological disadvantages of post-operative radiation therapy (tumor hypoxia, increased tumor dissemination, tumor repopulation, increased dose to normal tissues) cannot be avoided, however their consequences can be reduced by observing several techniques.  Once a patient has been identified as a candidate for post-operative surgery, surgery may proceed with these techniques in mind.

The most important considerations for surgeon sending a patient to radiation therapy include careful recording of tumor location and extent, appropriate incision placement and surgical field size, adequate marking of the extent of surgery, and providing adequate information regarding margins and tumor orientation.  All of these factors are of great help to the radiation oncologist in establishing the best treatment plan for the patient and reducing the chances of a geographic miss or severe side effects.

Together, surgery and radiation can provide the best chance for long term control or cure for many cancers and careful planning of both can greatly improve the patient’s quality of life and tumor-free survival.