Surgery

CARE AND SUPPORT OF PATIENTS UNDERGOING RADIATION THERAPY

INTRODUCTION:

The care and support of patients undergoing radiation therapy is a complex task. Patients and physicians must be vigilant towards the potential complications resulting from treatment. Appropriate follow-up is critical to ensure best future treatment.

OBJECTIVES:

After reading the web materials and attending the seminar, students will be able to…

1. Understand the basic cellular effects of radiation.
2. Understand the basic difference in response to radiation between normal tissue and tumour.
3. Anticipate and manage acute radiation effects.
4. Anticipate and manage late radiation effects.
5. Understand the rationale and issues relating to follow-up of patients after therapy.

The following objectives will be covered specifically by the seminar:

1. Understand what are the various ways that patients can be referred to the cancer center.
2. Understand what is the experience of a patient new to the cancer center.
3. Understand the various ways of delivering radiotherapy.
4. Understand the planning process for patients undergoing radiation therapy.

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BACKGROUND:

BIOLOGICAL BASIS OF RADIATION THERAPY

Radiation damages DNA, either by direct interaction with DNA molecules or indirectly via free radicals created by radiation splitting water. Radiation effects at the cellular level are random and can cause detriment to the reproductive integrity of the cell leading to necrosis, apoptosis, accelerated senescence, or terminal differentiation.

FOUR R'S AND FRACTIONATION

Modern radiotherapy exploits **fractionation** - the administration of a course of radiation in a planned series of treatment sessions to the total dose, in order to exploit key differences between tumor and normal tissue. Normal and tumor tissues differ in terms of four R's: *repair* of sublethal injury, *regeneration* , *redistribution* within the cell cycle, and *reoxygenation* . Rapidly proliferating cells, like those in tumors and some epithelial layers, display an early response to radiation (cell damage evident in hours to weeks). Slowly proliferating cells, like those in spinal cord, lung, kidney, liver, and heart, show a late response to radiation (cell damage evident only after months to years).

REPAIR

This is the ability of a cell to heal sublethal intracellular injury. Slower responding tissues (normal tissue) have a greater repair capacity than rapidly responding tissues such as many tumors. A given decrease in dose per fraction gives a bigger survival benefit to late responding tissues than to tumors, thus hyperfractionation (using lower than standard doses) may increase the tumoricidal effect of radiotherapy whilst relatively sparing normal tissue ("therapeutic index").

REGENERATION

Regeneration or repopulation is the ability of a cell population to continue (or increase) division and to replace dying and dead cells. Protracting the overall duration of the treatment course allows rapidly responding tissues to regenerate. Treatment must balance acute mucosal reactions (made worse by rapid treatment) with tumor regeneration (controlled best by rapid treatment) by treating the patient as rapidly as feasible and taking as few breaks as possible.

REDISTRIBUTION

Cells vary in radiosensitivity at different stages of the cell cycle. Cells are most sensitive to radiation during G2 to M phases and least sensitive during late S phase. A dose of radiation therefore tends to synchronise cells to a more resistant phase in the cell cycle. Proliferating cells, especially tumors, display a wide range of cell cycle speeds, thus, after a dose these cells quickly develop asynchrony and more cells progress to more sensitive stages quicker in a process known as self-sensitization. Late responding normal tissues do not display self-sensitization. Fractionation exploits self-sensitization of tumors to increase the therapeutic index.

REOXYGENATION

Markedly hypoxic cancer cells are 2.5 to 3.0 times less radiosensitive than well-oxygenated cells. Oxygen distribution in tumors is heterogeneous, some areas are hypoxic and others are oxic. A single dose of radiation kills

the radiosensitive cells in the oxic areas leaving the supply of oxygen to be used by the previously hypoxic cells, rendering them radiosensitive. This process of sensitization is called reoxygenation. Fractionation exploits this mechanism to increase the therapeutic index.

RADIATION EFFECTS

The ultimate severity of radiation effects depends on the extent to which a tissue's stem cell population is depleted. The rate of development of injury to a tissue depends on the pattern and rate of terminal differentiation of the progeny of stem cells as well as the rate of proliferation of the stem cells.

ACUTE RESPONSE

More rapidly dividing tissues are lost more quickly by radiotherapy than more slowly dividing tissues and thus display adverse effects more quickly. Acute effects of radiotherapy usually present after about two weeks of therapy and may peak at 4-5 weeks. Because of the ability of rapidly dividing tissues to regenerate, severe early side effects may necessitate adjusting the dose schedule.

LATE RESPONSE

Slowly dividing tissues respond slowly to radiotherapy and therefore display side effects much later. Late toxicity occurs long after completion of treatment and thus cannot be used to adjust dosage on an individual level. However, on a population level late responses can be used to set treatment parameters.

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ASSESSMENT AND MANAGEMENT:

The location of the tumor and thus the location of the radiotherapy being delivered determine the extent and type of side effects. The following is an incomplete list to allow the student to understand basic principles and examples only.

MISCELLANEOUS EFFECTS

- Fatigue – most common complaint of patients undergoing radiotherapy, occurs early in course of RT but for small volume treatments to cure this is usually mild; management is directed to underlying symptomatic causes, emphasizing psychosocial support, exercise, adequate nutrition and hydration.

SKIN

Acute Effects – occur within two weeks of start of radiotherapy (RT)

- **Erythema** : skin may become erythematous, warm, edematous; blood vessels in the upper dermis become dilated; inflammatory cell presence
- **Moist or dry desquamation** : eruption of the epidermal layer

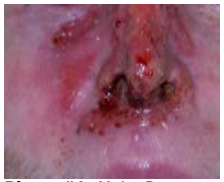

Photo #1: Moist Desquamation in Radiotherapy Patient

Management

- Avoid perfume, alcohol, astringents, deodorants and adhesives
- Avoid chlorinated pools, extremes of hot or cold, direct sunlight and wind
- Apply moisturizer **or** powder
- Wear loose cotton clothing, wash with tepid water and mild soap
- Apply hydrocortisone cream as prescribed in areas of inflammation
- With moist desquamation use saline soaks or silver sulfadiazine cream to avoid secondary infection

Late Effects >6 mo post RT

- **Atrophic epidermis** : prone to injury

- **Increased interstitial fibrosis**
- **Hyperpigmentation of irradiated skin**
- **Telangiectasia**

Management

- Gentle treatment of skin
- Manual massage, physical therapy, and oral or topical triiodothyronine for subcutaneous fibrosis
- Hyperpigmentation will fade gradually

CENTRAL NERVOUS SYSTEM

Acute Effects

- Increased intracranial pressure from reactive edema: signs and symptoms include lethargy, nausea, vomiting, headache, dizziness

Sub-Acute Effects – 1-3 mo post RT

- Lhermitte's sign: paresthesia with neck flexion due to transient demyelination of spinal cord
- Mild encephalopathy and focal neurological changes may occur after radiation treatment to cranium

Late Effects – 6-36 mo post RT

- Brain necrosis (is rare)
- Leukoencephalopathy (necrotizing reaction): may occur with treatment combination of Methotrexate and cranial irradiation
- Transverse myelitis: high dose spinal radiotherapy may lead to progressive and irreversible leg weakness and loss of bladder function

Management

- Minimize exposure. Manage symptoms
- Acute effects: use oral steroids to reduce CNS edema

LUNG

Radiation Effects

- **Pneumonitis** : found in patients receiving high-dose radiotherapy for lung cancer treatment and breast cancer treatment when tangents clip the anterior lung; symptoms usually occur 2-3 months post RT, (rarely within first month or after 6 months post RT); cardinal symptom is dyspnea, also may have cough and fever – most patients develop gradual progressive fibrosis over 6-24 months
- **Bronchiolitis obliterans with organizing pneumonia (BOOP)** : may occur in patients receiving radiotherapy to breast; cardinal symptoms are cough and fever

Management

- CXR (ground glass opacification, diffuse haziness, alveolar infiltrates) can confirm the clinical suspicion of pneumonitis
- Pneumonitis is treated with corticosteroids, antibiotics, and anticoagulants; late changes may be unresponsive
- BOOP is treated with corticosteroids (taper very slowly)

GASTROINTESTINAL

Radiation induced damage to epithelium occurs quickly, submucosa becomes edematous and capillaries dilate. Later pathologies include fibrosis and rarely fistula formation.

Acute Effects – begin almost immediately or within 2-3 weeks of start of RT

- **Acute gastritis** : symptoms include anorexia, nausea and emesis; decreased gastric acidity may occur; aggravated by chemotherapy (e.g. 5-flourouracil)
- **Acute enteropathy** : symptoms include nausea, emesis, diarrhea, and cramping pain

Chronic Effects – 6 mo to 5 years post RT

- Enteropathy: symptoms same as acute enteropathy plus malabsorption and obstruction
- Fibrosis, perforation, fistula formation, stenosis

Management

- Nausea and vomiting often respond to prochlorperazine but ondansetron may be required
- Gastritis responds to a regimen of bland diet, antacids, sedatives, and antispasmodics

BLADDER

Acute Effects – begin 3-6 weeks after start of RT

- **Acute Cystitis** : symptoms include increased urinary frequency and dysuria
- **Prostate swelling** can also lead to obstructive complaints

Late Effects

- Interstitial fibrosis, telangiectasia, ulceration and painless hematuria

Management

- Rule out infection, manage symptoms e.g. flavoxate hydrochloride, phenazopyridine hydrochloride, terazosin

HEAD AND NECK

The soft tissues of the oral cavity and pharynx are quite sensitive to radiation as well as environmental insult (such as smoking and alcohol) and infectious agents.

Acute Effects – subtle changes begin within first week, pseudomembrane by the last weeks of RT

- **Mucositis** : inflammation and injury to oral mucosal membranes; progresses from asymptomatic redness through tender desquamative patches to acutely painful pseudomembranes; symptoms include pain, dysphagia, and decreased oral intake
- **Xerostomia** : dry mouth from salivary dysfunction and dry mucous membranes

Late Effects

- **Osteoradionecrosis** : non-healing, acellular, avascular bone, may be clinically silent for months or years

Management

- Avoid spicy foods, alcohol and smoking
- Mucositis prevention: chlorhexidine gluconate, saline rinses, sodium bicarbonate rinses, acyclovir, amphotericin and ice. Mucositis treatment: lidocaine, magnesium-based antacids, diphenhydramine (Benadryl), nystatin, or sucralfate – as mouthwashes. Severe mucositis may necessitate hospitalization,

parenteral nutrition and use of narcotics.
- Xerostomia: physically and psychologically stimulatory diet, maintain excellent oral hygiene, monitor and maintain adequate vitamin A and nicotinic acid levels, spray mister before and during meals
- Osteoradionecrosis requires surgical excision, hyperbaric oxygen and prophylactic IV antibiotics

GONADS
TESTIS

- **Oligospermia** : doses between 0.15 Gy and 0.5 Gy may diminish sperm count beginning 6 weeks after start of RT, with a Nadir at 4-6 months, and recovery at 10 to 18 months
- **Azoospermia** : duration is dose dependent - less than 1 Gy requires 1 year, 2 Gy requires 2-3.5 years, greater than 2.5 Gy results in prolonged or permanent azoospermia
- **Decreased testosterone levels** – seen with high doses (>20 Gy)

OVARIES

- **Ovarian failure** : dose and age dependent - older women more sensitive; 4-5 Gy induces amenorrhea and menopause in almost all women >35 years old

Management

- Shield gonads when possible and keep dosage to minimum required

FOLLOW-UP

The primary goal of follow-up is to detect potentially curable, new or recurrent disease. A secondary goal is to assess treatment outcome. Follow-up schedules and protocols are specific to the type of cancer being monitored and the intent of treatment. Potentially curative cases responding to salvage therapy include local failure of prostate and breast cancer, nodal failure of seminoma and head and neck cancer, systemic failure of lymphoma and germ cell tumors, and new primaries of testicular and head and neck cancer. If the patient is inappropriate for curative therapy, then follow-up should be palliative, with an aim to prolonging survival, delaying or alleviating symptoms, relieving pain and improving quality of life. Both GP's and specialists, with specialists providing diagnostic tests, treatment plans, and management of certain complications (e.g. chronic radiation complications) conduct follow-up.

For specific follow-up schedules and protocols please refer to the BCCA web site via the links posted below (if links are broken find protocols under specific tumor types under cancer management guidelines). You are not responsible for specific details but should be familiar with the overall follow up approach to common cancers.

BCCA Follow-up Guidelines:

Lung Cancer

Breast Cancer

Prostate Cancer

Colorectal Cancer

Skin Cancer – Melanoma

Skin Cancer – Non Melanoma

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CASES:

Case #1

Mr T, a 76-year-old man is referred to the BCCA with a 3cm-diameter preauricular mass (photo #2 below). A histological examination of the biopsy specimen reveals a poorly differentiated squamous cell carcinoma, and the history reveals that it is growing rapidly.

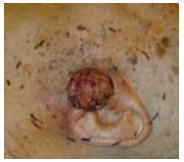

Photo #2: Squamous cell carcinoma in elderly male.

1. What treatment would you recommend, and how would you deliver it?
2. What side effects would you anticipate from this therapy and how would you manage them?
3. What follow up would be appropriate for this patient and what would be the purpose of this follow up?

Epilogue

Mr. T undergoes radiation therapy to the zone demarcated by the black pen markings in Photo #2. He receives a total dose of 50 Gy fractionated into 15 sessions over 3 weeks.

Within a week of starting RT Mr. T notices some redness and heat in the area which is receiving radiation. A week later he notices that this same area of skin is beginning to erupt and desquamate, though he feels that the area is dry. His oncologist recommends that he avoid harsh soaps, astringents, direct sunlight, and wind. Mr. T is instructed to keep the area clean with tepid water and mild soap and to apply unscented moisturizer.

After more than two weeks of treatment Mr. T begins to feel pain when swallowing and has difficulty masticating his food. His oncologist examines his mouth and makes a diagnosis of mucositis upon seeing redness and desquamative patches in the oropharynx. Mr. T is subsequently given a mouthwash containing a mix of Benadryl, viscous lidocaine, and Maalox to be used four to six times a day. Mr. T's xerostomia is likely due to direct RT damage to his parotid gland (in tumor treatment area).

Five months after the start of RT Mr. T's primary carcinoma is well resolved. See Photo #3.

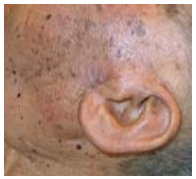

Photo #3: Mr. T 5 months after start of radiotherapy.

Mr. T's squamous cell carcinoma was a rapidly growing lesion by history and poorly differentiated by histology. Thus he is at high risk for recurrence and should have the treatment site and regional lymph nodes examined every two to three months for the first year, decreasing in steps to annually after 5 years.

He should have his sun-exposed skin examined at each follow-up visit and even after five years, examined at least yearly for new actinic keratosis or skin cancers.

At Mr. T's third follow up visit (six months post RT) his oncologist notices palpable mid-jugular lymphadenopathy. Mr. T undergoes radical neck dissection. The pathologist finds poorly differentiated squamous cell carcinoma in one 1.5 cm enlarged node.

Case #2

Mr P, a 76-year-old otherwise healthy male is referred to the BCCA by his family physician for treatment of prostate cancer. Mr. P has a PSA of 9 and palpable nodules in the right and left lobes. Transrectal ultrasound guided needle biopsy of his prostate reveals his tumor to be confined to his prostate and involving both lobes T2c with a Gleason score of 6/10. CT of pelvis and bone scan are negative for metastasis.

After consultation with his oncologist Mr. P decides to undergo radical external beam radiotherapy. This is delivered by a four-beam radiotherapy plan (see Photo 4) designed to concentrate the dosage on the prostate (aquamarine outline) and a thin margin of surrounding tissue (outlined in purple).

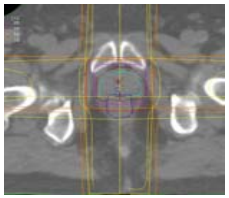

Photo #4 : Radiotherapy Treatment Planning

1. What potential side effects of radiotherapy to the prostate would you advise Mr. P about?

Epilogue

Mr. P undergoes five treatments a week for 7 weeks. His radiation oncologist advises Mr. P that he may experience urgency, diarrhoea, urinary frequency or the passage of small amounts of blood or mucus from the rectum or bladder during and for a few weeks following RT. In about 90% of patients these side effects clear up within 6 weeks of RT completion. Incontinence following RT is very rare. 30-50% of men will lose their ability to have an erection within five years of RT. Two years post RT Mr. P is disease free and is enjoying an active sex life with his partner.

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RESOURCES:

1. DeVita, V.T., Hellman, S., & Rosenberg , S.A. (Eds.). (2001). *CANCER: Principles & Practice of Oncology* . Philadelphia , PA : Lippincott Williams &Wilkins. Chapter 55: Adverse Effects of treatment
2. Perez , C.A. , Brady, L.W. (Eds.). (3 rd ed.). (1998). *Principles and Practice of Radiation Oncology* . Philadelphia , PA : Lippincott - Raven Company. Chapter 2: Biologic Basis of Radiation Therapy, Chapter 85: Supportive Care in Radiation Oncology
3. BC Cancer Agency Web Site : Links to cancer management guidelines, prevention, support, follow-up and information for patients.
4. Harrison 's Principles of Internal Medicine. (15 th ed.). (2001). New York : McGraw-Hill Chapter 394: Radiation Injury

This web document was written and produced by George Yearsley , medical student, 2003. Please direct any comments and corrections to Dr Graeme Duncan , Coordinator Undergraduate Education for Radiation Oncology at gduncan@bccancer.bc.ca

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