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TOTAL DOSE RELATED TO TUMOR VOLUME AND TOXICITY RISK CORRELATION IN MODERN RADIOTHERAPY

BY

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Abstract. Radiotherapy is a critical and inseparable component of comprehensive cancer treatment and care. It is estimated that about 70% of cancer patients would benefit from radiotherapy for treatment of localized disease, local control, and palliation. Yet, in planning and building treatment capacity for cancer, radiotherapy is frequently the last resource to be considered.

Keywords: radiotherapy; tumor volume; dose; radiation toxicity.

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1. Introduction

Managing cancer requires both effective preventive measures to reduce future burden of disease, and health-care systems that provide accurate diagnose and high-quality multimodality treatment. Such multimodality treatment should include radiotherapy, surgery, drugs, and access to palliative and supportive care. Radiotherapy is perceived as a complex treatment. Estimation of the exact proportion of new cancer cases that will need radiotherapy is complex, in view of the variable patterns of cancer presentation and limited information on the current proportion of patients receiving radiotherapy. During the past 20 years, several investigators have developed evidence-based estimates of desirable radiotherapy use on the basis of the indication for radiotherapy in clinical practice guidelines and the distribution of cancer and different stages of disease at presentation. These estimates suggest that 60-70% of all patients with cancer will need radiotherapy. Radiation therapy acts both on tumor cells and normal tissue making the therapeutic benefit both toxicities and complications caused by acute and delayed treatment. Maintaining the balance between local tumor control and minimize side effects and complications remains a challenge for radiotherapy. Unfortunately, despite significant technological advances of the past three decades, more than 100 years of experience in radiotherapy, indicates that data on the effects of radiation are beneficial and detrimental in many cases.

In historical perspective the first comments on the biological effects of radiation from the late IXX century belong to Gassmann (1898), which depicts two histological types of ray-induced chronic ulcer. The first study analyzing tolerances healthy tissues to radiation therapy has been published by Rubbin and Casarett treaty “Radiation Clinical Pathology” (1968). The paper presents a set of pictures taken during irradiation, highlighting the progression of lesions radiomucositis and described the evolution from acute to chronic and tardive. 80-90 years of the twentieth century have made significant progress by introducing radiotherapy CT simulators, computer systems dosimetry of collimator and multi optimizations that allowed the transition to three-dimensional radiotherapy volumes enabling evaluation of receiving certain doses. There were also introduced unique criteria for assessing the level of toxic effects of radiation in the form of scales, the LENT-SOMA being used and CTCAE (Dobbs *et al*., 2009).

The first database, with correlations between organ volume receiving a given dose risk of complications is offered by prestigious study Emami (1991). It proposes dividing the organ on the basis of volumetric three recommendations restrictions being given doses 1/3, 2/3 and full organ. Original work, known as Emami Guide, was, despite its limitations, a review of medical literature until 1991. It is only for severe complications. 3D techniques, IMRT, VMAT were nonexistent at the time, so was used only conventional

fractionation (2Gy/fraction). In the 25 years since the publication of his work Emami, the practice has been completely revolutionized radiotherapy (Bortfeld *et al*., 2006; Van der Kogel and Joiner, 2009):

- multi-disciplinary cancer treatment become standard;
- end-points in the complications have changed;
- 3D-CRT and "inverse planning" totally replaced the 2D radiation therapy;
- CT simulation images using CT, MRI and PET-CT become standard

As a result, the dose distribution has become increasingly more complex and more recently, was placed 4-dimension (time). It became necessary to introduce new updated models correlation dose-volume-complications. The Quantec work, resulting a collective effort by 57 experts, appears to support ASTRO (American Association of Radiotherapy) and AAPM (American Association of Medical Physics), and is published in the Supplement to the journal "*International Journal of Radiation Oncology, Biology, Physics*" (the Red Journal), Vol. 76, No. 3, 2010 (Nishimura and Komaki, 2015). This gives the review last 2 decades radiotherapy putting in relationships, in a detailed way, the parameters dose/volume with clinical complications. It also provides a simple set of data grouped into 16 radiosensitive organs in order to provide a useful and easily accessible to validate plans carried out jointly by the radiotherapists, physicians and medical physicists (Van der Kogel and Joiner, 2009; Nishimura and Komaki, 2015).

In an era of personalized medicine, progress means that radiotherapy beams can be shaped and modulated to conform to the exact shape of tumors, maximizing radiation dose deposition in the cancer while sparing normal tissues from high doses, those most likely to evoke normal tissue toxic effects. Radiotherapy is also a powerful instrument in palliation of symptoms associated with cancer. According to the survey noted, factors affecting normal tissues to radiation tolerance are:

- patient condition (age, comorbidities, Karnofsky score, pathogens, response to therapy);
- organ radio sensibility variations;
- serial dose-response organization (spinal cord);
- organization of parallel volume effect (liver, lung);
- serial and parallel mixed organization (kidney);
- natural history of the tumor;
- radio therapeutic treatment: dose value (maximum, medium, minimum dose), dose, overall treatment time, energy, irradiated volume;
- non-radio therapeutic treatment: chemotherapy, surgery, *i.e*.

In the context of the plurality of data from the medical literature, it aims to develop predictive models based on the dose-volume, which will act as a guide only and may not substitute medical experience.

With the development of mathematical models and radiobiological, more and more authors use conversion dose/fraction, at a dose equivalent biological dosimetry to compare different parameters. Izo-effect formula (1) based on the linear quadratic model and the index α/β is calculated from survival curves cell tumor model extrapolated to five.

$$BED = \frac{E}{\alpha} = D\left(1 + \frac{d}{(\alpha+\beta)}\right) \quad (1)$$

Failure assessment values α/β in human tumor tissue makes use of radiobiological model, with more than indicative value, cannot be recommended as routine practice. Applying value BED (2) or 2Gy equalization formula should be implemented taking into account the limits of the model

$$EQD_2 = D\left(1 + \frac{d+(\propto/\beta)}{2Gy+(\propto/\beta)}\right) \quad (2)$$

and certain physical and biological parameters that were taken into account in the work underlying the guidelines dosimetric (Van der Kogel and Joiner, 2009):

- dose/fraction has a significant impact in the acute and late complications;
- 1.8 or 2Gy/fraction /5 fractions/ week is considered standard fractionation;
- most publications of the last two decades considered the report of α/β = 2 for CNS;
- BED Quantec publications calculated using a value of α/β = 3 for CNS;
- IMRT technology allows the use of any fractional (integrated boost) that makes it difficult to evaluate existing plans after recommendations.

With broad deployment IMRT and VMAT techniques, Niemierko proposed a biological model for assessing treatment plans that would be applicable to non-uniform dose distributions. At its core are the parameters EUD (equivalent uniform dose transmitted tissue would produce the same effect on cell populations) and NTCP (healthy tissue likelihood of developing complication) (Schwartz *et al*., 2005; Rubin *et al*., 2014). NTCP use in clinical practice is recommended only as a guide, new studies are needed to validate this parameter as a predictor of toxicities.

A. Central Nervous System (CNS) & Sensorial Organs

1. Brain tissue. Brain tissue radiation toxicity is the neurocognitive impairment and cerebral radionecrosis. This generally occurs between three months and several years (average 1-2) from irradiation (Hayes and Kruger, 2007).

Volume	Dose	Risk of Radionecrosis
1/3cerebral volume	D < 60Gy	5% (Emami *et al*., 1991)
	D max < 60Gy	3%
	D max = 70Gy	5%
	D max = 90Gy	10%
$\alpha/\beta = 3$ BED	D = 120Gy	5%
SRT	D > 12Gy	20%
children	D total (WBRT) > 18Gy	Neurocognitive modifications
Re-irradiation $\alpha/\beta = 2$ (2Gy equivalent)	D total < 100Gy	

Risk Factors (Bentzen *et al*., 2010; Marks, 2010a; Marks, 2010b):

- old age / young (children);
- female gender;
- NF-1 mutation;
- extensive surgery;
- diabetes;
- hydrocephalus;
- chemotherapy (especially with methotrexate);
- dose/fractionation/volume;
- a low index of conformity;
- location of the target volume.

2. Brainstem. Induced toxicity on the brainstem can be debilitating and potentially lethal due to its origin at this level of the 12 pairs of cranial nerves:

Volume	Dose	Toxicity risk (%)
100% brainstem	< 50Gy	5% (Emami *et al*., 1991)
100% brainstem	< 54Gy	5%
V < 1-10 cm^3	< 59Gy	< 5%
V < 1 cm^3	< 64Gy	< 5%
SRT	D max > 12.5Gy	

Risk Factors (Bentzen *et al*., 2010; Lawrence *et al*., 2010):

- hypertension;
- diabetes;
- number surgery;
- target volume in proximity;
- MRI imaging for a lack of planning.

3. Spinal cord. Bone marrow toxicity of radiation is rare but severe consequences (paralysis, sensory deficit, pain, urinary incontinence). Toxicities were evaluated doses of 2-9Gy /fraction, calculating the equivalent dose of 26Gy to a value $\alpha/\beta = 0.87$ (Dawson *et al*., 2010; Emami, 2013).

Risk factors (Bentzen *et al*., 2010; Mayo *et al*., 2010a; Mayo *et al*., 2010b):

- neurotoxic chemotherapy;
- segment irradiated bone marrow (cervical bone is more sensitive than chest probably the components of cranial nerves - IX, X, XI, XII);
- young age (children).

Volume	Dose	Risk for myelopathy (%)
	D max = 50Gy	0.2%
	D max = 60Gy	6%
	D max = 69.6%	50%
SRT – unique dose	D max = 13Gy	1%
SRT – hyper fractions	D max = 20.6Gy	1%
Re-irradiation	25% dose “forgotten” after 6 months	

4. Optic nerves & optic chiasma. Optic neuropathy is rare and is manifested by rapid and painless loss of vision (Van der Kogel and Joiner, 2009; Kirkpatrick *et al*., 2010).

Volume	Dose	Risk for Optic neuropathy (%)
Whole volume organ	D < 50Gy	
	D max = 54Gy	< 3%
	D max = 55-60Gy	> 3-7%
	D max = 60Gy	> 7-20%

Risk Factors (Bentzen *et al*., 2010; Kirkpatrick *et al*., 2010):

- age;
- diabetes;
- hypertension;
- chemotherapy(anticancer agent - Bevacizumab has a protective effect);
- re-irradiation (dose fraction within the first irradiation).

5. Retina. Radiation induced retinopathy is a decrease in visual acuity similarly to diabetic retinopathy. There were reported rarely retinopathy radiation induced at doses below 50Gy, but for doses < 45Gy received by posterior pole, it is practically non-existent (Dobbs *et al*., 2009; Van der Kogeland Joiner, 2009).

Risk Factors (Bentzen *et al*., 2010; Bhandare *et al*., 2010):

- hypertension;
- diabetes;
- dose/volume/fractionation (to 3-fold decrease in the risk of retinopathy by hyper fraction).

6. Cochlea. Damage of cochlea consists in neurosensorial hearing loss. High frequency hearing impairment is more common than at low frequencies. Age and high acuity hearing before treatment and chemotherapy with Cisplatin are factors that significantly affect toxicity. Occurrence of otitis media after radiotherapy is considered a significant factor (Bentzen *et al*., 2010; Deasy *et al*., 2010).

Volume	Dose	Neurosensorial risk (%)
concomitant with cisplatin	D < 45Gy	< 30%
	D med < 47Gy	< 15%
SRT	D max < 14Gy	< 25%

Risk factors (Dobbs *et al*., 2009; Bentzen *et al*., 2010; Deasy *et al*., 2010):

- total dose of irradiation;
- age;
- positioning a target volume;
- dose of cisplatin
- hearing aid existing pathologies and subsequent irradiation.

B. Head & Neck

1. Parotids, submandibular and sublingual salivary glands. Impaired secretion of salivary glands (xerostomia) is common for cephalic extremity irradiation and can be a cause of deteriorating quality of life patient for a period of up to 2 years after completion of radiotherapy. Xerostomia is to reduce salivary flow and significantly reduces its risk by reducing the dose from a single submandibular gland (recommended doses < 35Gy). Xerostomia grade IV (decrease by more than 75% of salivary volume) was the threshold for who proposed building dosimetry and is a risk factor for oral bacterial and fungal superinfections after radiotherapy (Dobbs *et al*., 2009; Rancati *et al*., 2010).

Volume	Dose	Risk for Xerostomia (%)
Bilateral parotids	D med < 25Gy	< 20%
Unilateral parotid	D med < 20Gy	< 20%

Risk Factors (Bentzen *et al*., 2010; Marks *et al*., 2010a; Marks *et al*., 2010b):

- drugs that interferes with salivation;
- eating disorders;
- rheumatologic diseases;
- smoking.

2. Mandible. Rates of osteonecrosis of the jaw has dropped considerably with the introduction of IMRT and VMAT techniques (Dobbs *et al*., 2010; Marks *et al*., 2010a; Marks *et al*., 2010b).

Dose	Risk for Osteonecrosis (%)
D max < 70Gy	< 5%

Risk Factors (Bentzen *et al*., 2010):

- radiation dose;
- chemotherapy;
- dental hygiene;
- tumor site;
- oro-maxillo-facial surgery history.

3. Pharyngeal constrictors muscles. Dose escalation irradiation for head and neck cancers has increased the rate of late toxicities (dysphagia and aspiration) on swallowing mechanisms. Some studies have associated toxicity with the dose received by superior and medium pharyngeal constrictor muscles, others studies considered relevant only the dose received by inferior pharyngeal constrictor muscle (Kavanagh *et al*., 2010).

Dose	Toxicity risk (%)
D_{medie} < 50Gy	20%
D_{max} < 70Gy	< 5% (compulsory PEG, aspiration)

Risk Factors (Bentzen *et al*., 2010; Marks *et al*., 2010a; Marks *et al*., 2010b):

- local advanced neoplasms;
- concomitant chemotherapy (hazard of swelling and dysphagia).

4. Larynx. Radiation toxicity affecting the larynx include laryngeal edema formation and (especially glottis). Radionecrosis laryngeal cartilages risk is low in the context of using modern techniques, but remains present in particular as a consequence the long term (Marks *et al*., 2010a; Marks *et al*., 2010b).

	Dose	Toxicity risk (%)
RTE +CHT	D_{max} < 66Gy	< 20% (dyspnea)
RTE +CHT	D_{max} < 50Gy	< 30% (aspiration risk)
	D_{medie} < 44Gy	< 20% (edema)

Risk factors (Dobbs *et al*., 2009; Bentzen *et al*., 2010; Marks *et al*., 2010a; Marks *et al*., 2010b; Michalski *et al*., 2010; Pan *et al*., 2010):

- concurrent chemotherapy;
- staging (except T1, larynx glottis → low risk of impaired phonation);
- concomitance with EGFR inhibitors (cetuximab) → mucositis/infections.

C. Thorax

1. Brahial plexus. Brachial plexopathy may be manifested by pain, paresthesia or upper limb motor deficit. Muscular atrophy and edema are occasional complications. Toxicity can signal and after 5 years of the end of radiotherapy (Dobbs *et al*., 2009; Van der Kogel and Joiner, 2009; Roach *et al*., 2010; Viswanathan *et al*., 2010).

Volume	Dose	Risk of plexopathy (%)
Whole brachial plexus	D max < 60Gy	< 5%

Risk Factors (Bentzen *et al*., 2010):

- hyper fractionated regimes;
- Lymphadenectomy;
- obesity;
- hypertension;
- diabetes
- valvulopathy.

2. Lungs. Radice pneumonitis is one of the most common toxicities in patients receiving radiation for lung neoplasms: breast, esophagus and mediastinal lymphadenopathy. The risk of developing pneumonitis radice limited dosage used in treating these malignancies (Van der Kogel and Joiner, 2009; Gagliardi *et al*., 2010; Werner-Wasik *et al*., 2010).

Volume	Dose	Pneumonitis radice risk (%)
V_5 < 42%	D med = 7Gy	5%
V_{20} < 22%	D med < 13Gy	10%
V_{20} < 31%	D med < 20Gy	20%
V_{20} < 40%	D med < 24Gy	30%
	D med < 26Gy	40%

Risk factors (Bentzen *et al*., 2010; Gagliardi *et al*., 2010):

- chemotherapy with taxanes, gemcitabine;
- concomitant therapy with TKI inhibitor (erlotinib);
- pre-existing lung diseases

3. Heart and pericardium. Pericarditis and cardiac mortality in the long run are two of the most common toxicities. Increase in survival for patients with breast cancer and lymphoma requires revaluation heart of the doses received and their correlation with late mortality.

	Volume	Dose	Toxicity risk (%)
RTE +Adriamicina	3/3 heart $V_{25} < 10\%$	D < 15Gy	1% risk 15 years after the end of irradiation
RTE +Adriamicina	3/3 heart $V_{30} < 46\%$	D < 30Gy	Risk < 15% (pericarditis)

Risk factors:

- age;
- sex;
- diabetes;
- hypertension;
- high levels of cholesterol;
- smoking;
- family history of heart.

4. Esophagus. Radice esophagitis is constant during irradiation of thoracic tumors, and is manifested by dysphagia, swallowing and may adversely affect the patient's condition causing discontinuation of treatment.

Volume	Dose	Risk of radice esophagitis (%)
$V_{35} < 50\%$	D med < 34Gy	Grd III = 5-20%
$V_{50} < 40\%$		Grd II < 20%
$V_{70} < 20\ \%$		

Risk factors:

- aged > 70 years;
- hyper fractionated regimes;
- concomitant boost;
- concurrent chemo-radiotherapy;
- large number of hotspots in the treatment plan.

D. Abdomen

1. Liver. Radio-induced hepatitis usually occurs between 2 weeks and 3 months after completion of radiation therapy, the radiation dose limiting complication of biliary tumors and upper digestive tract. Subacute form of hepatitis is usually manifested by fatigue, abdominal pain, hepatomegaly, ascites anicteric, increased alkaline phosphatase and liver enzymes.

Volume	Dose	Hepatitis risk (%)
Liver cancer with preexisting disease	D med < 30Gy D med < 28Gy	5%
Whole organ	≤ 30Gy (2Gy/fr) ≤ 21Gy (3Gy/fr) < 28Gy (2Gy/fr) < 21Gy (3Gy/fr)	5%
	D med < 42Gy	
Liver metastasis	D med < 13Gy (3fr) D med < 18Gy (6fr)	< 5%

Risk factors:

- hepatocarcinoma > metastases;
- hepatitis B and C;
- portal thrombosis;
- chemotherapy;
- chemoembolization;
- tumor stage;
- male gender;
- score Child - Pugh.

2. Stomach. Late toxicity manifests as gastric ulceration and dyspepsia. Loss of appetite, feeding behavior and disturbances in fluid intake can lead to malnutrition and cachexia, exacerbating the patient's condition.

	Volume	Dose	Risk of gastric toxicity (%)
	3/3 stomach	D < 50Gy	
SRT	V 22.5 < 4% / 5 cm^3	D max < 30Gy (3Gy/fr)	5-7%

3. Small intestine. Gastro-intestinal toxicity is significantly increased in case of concurrent chemotherapy or previous abdominal surgery. Decrease of absorption, diarrhea, impaired intestinal flora and pathogens are frequent

complications during irradiation for abdominal and pelvic tumors. New studies show that large volumes of small intestine receiving relatively low doses are correlated with acute toxicity. If the individual emerges intestines, the most representative volume predictor of toxicity is V15. Late toxicity consists of obstructions, perforations and is commonly associated with abdominal wall surgery.

Organ	Volume	Dose	Risk of enteric toxicity (%)
Intestinal coils	$V_{15} < 150$ cm^3	D < 50Gy	10%
Peritoneal cavity	$V_{45} < 195$ cm^3	D < 50Gy	10%
1/3 small intestine	$V_{50} < 51\%$	D < 50Gy	
SRT	$V_{12.5} < 30$ cm^3	D max < 30Gy (3-5Gy/fr)	10%

Risk factors:

- anatomical conformation (large intestines in the field of radiation);
- abdominal surgery;
- cardiovascular pathologies;
- diabetes;
- chemotherapy (adriamycin, 5-FU);

E. Pelvis

1. Rectum. Improving regimens irradiation in prostate cancer with the decrease of late post-radiotherapy rectal toxicity has made many of these patients as long term survivors. Dose escalation, by moving from 2D and 3D techniques to IMRT required the assessment of dosimetric parameters correlated with late proctopathia.

Volume	Toxicity risk grd II (%)	Toxicity risk grd III (%)
$V_{50} < 50\%$	15%	10%
$V_{60} < 35\%$	15%	10%
$V_{70} < 20\%$	15%	10%
$V_{75} < 15\%$	15%	10%

Risk factors:

- diabetes;
- inflammatory digestive diseases;
- hemorrhoids;
- age;
- treatment with anti-androgens;
- size rectum;
- abdominal surgery.

2. Bladder elasticity makes difficult a performing dosimetric analysis with predictive toxicity. Affecting the entire body may be manifested by dysuria, urinary frequency, bladder spasm, reducing the flow urinary incontinence. Damage is focal manifestations: hematuria, fistula, obstruction, ulceration and necrosis.

Risk factors:

- hormone therapy;
- chemotherapy (cyclophosphamide);
- TUR-V&TUR-P;
- underlying genitourinary pathology;
- hysterectomy;
- obesity;
- smoking;
- black race;
- age;
- diabetes.

3. Kidney. Renal dysfunction after radiotherapy can cause symptoms and biochemical and radiological changes form. High latency ranges are as renal toxicity late to be undervalued. Most studies have evaluated serum creatinine clearance decreased in relation to the dose received by both kidneys.

Risk factors:

- renal failure;
- diabetes;
- cardiac pathologies;
- smoking.

4. Penile bulb. Erectile dysfunction can be a cause of discomfort for patients with prostate cancer. The dose received by the penile bulb is considered a predictor.

Volume	Dose	Toxicity risk (%)
V_{60}-V_{70} < 70Gy	D med < 52Gy	< 55%
V_{90} < 50Gy	D med 95% din gland < 50Gy	< 35%

Risk factors:

- age;
- diabetes;
- treatment with anti-androgens;
- hypertension;
- smoking

F. Other Radiosensitive Organs

Radio-sensitive organs outside Quantec included in the guide, benefit the records of the toxic and other parts of the body. Keeping average dose associated with various complications, below the various studies, may help optimize quality of life. In clinical practice, to assess the dose equivalent hypo-fractionated regimes use the value ratio α/β = 10Gy to the tumor tissue and α/β = 3Gy for late toxic effects. For a more precise risk assessment of the possibility of toxic and tumor control is recommended in the report izo-equivalent formula α/β correlated with each organ specific toxicities

Legend

D max – maximum dose received by an organ;

D medium – average dose received by an organ;

Vx – The volume of the organ receiving the higher dose of "x" Gray;

Dy – minimum dose received by the 'y'% of an organ;

SRT – Stereotactic Radiotherapy;

WBRT – "Whole brain" Palliative Radiotherapy;

PEG – percutaneous gastrostomy;

IMRT – intensity modulated radiotherapy external;

VMAT – intensity modulated radiotherapy external volume (with continuous irradiation Rotational);

Anti - EGFR – epidermal growth factor inhibitor;

TKI – tyrozin kinase inhibitor;

5FU – 5-Fluorouracil;

ACE – inhibitor of angiotensin converting enzyme;

CT – computed tomography;

MRI (MRI) – magnetic resonance imaging;

REVERSE PLANNING – planimetric technique is proposed the conformation bundles computer after dosimetry constriction introduced by physicist;

Quantec – Quantitative Analyses of Normal Tissue Effects in the Clinic;

PET-CT – Positron emission tomography;

E – biological effect;

α/β – The ratio of intrinsic cellular radiosensitivity and cell fraction which completely repaired lesions in 6 hours or more;

EUD – equivalent uniform dose transmitted tissue would produce the same effect on cell populations;

NTCP – Probability healthy tissue of developing complications;

EQD2 – 2Gy fractionated dose equivalent that would produce the same biological effect as prescribed.

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DOZA TOTALĂ CORELATĂ CU VOLUMUL TUMORAL ŞI RISCUL DE TOXICITATE ÎN RADIOTERAPIA MODERNĂ

(Rezumat)

Radioterapia este o componentă esențială și inseparabilă în contextul tratamentului multidisciplinar al cancerului. Se estimează că aproximativ 70% dintre pacienții cu cancer ar putea beneficia de radioterapie pentru tratamentul bolii localizate, controlul local și paliativ. Cu toate acestea, în planificarea și implementarea secvențelor terapeutice oncologice, radioterapia este frecvent ultima resursă care se ia în considerare.