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Radiotherapy in the combined treatment

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Tumor and normal tissue radiation side effects

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This paper presents the various side effects of radiation including tumor cure probability (TCP) accompanied with frequently severe but transient acute side effects in the surrounding normal (mainly epithelial) tissues and also the risk of late side effects in normal organs, confined to their partial or whole volumes. Besides the local side effects, unexpected exposure to low radiation doses results in the stochastic risk of mutagenic, teratogenic or cancerogenic side effects. In order to minimize the risk of various radiation side effects, some obligatory radiation protection constraints should be restrictively fulfilled.

Key words: TCP, acute and late side effects, teratogenesis, carcinogenesis

Particle and photon ionizing radiation produces various deterministic (both expected and unexpected) effects in malignant tumors and surrounding normal tissues (organs) in addition to undesirable stochastic effects in healthy people incidentally exposed to various types of radiation.

Tumor radiation effects (TRE)

Tumor response to the high energy of a single or fractionated dose of radiation (radiotherapy, brachytherapy) is usually beneficial due to cancer cells killed process. It is an obvious aim of radiotherapy (RT), and a probalistic event in its nature. At first glance, tumor response to radiation generally depends on their individual radiosensitivity. Lymphomas, seminomas as well as epithelial carcinomas, are classified as sensitive, whereas liposarcomas, neuro-, osteo- chondrosarcomas and parotid tumors are radioresistant in a larger or smaller degree. This latter group needs a significantly higher total radiation dose to achieve tumor cure probability (TCP) than the first one. This is often an obstacle to achieve with the use of RT only.

The major feature of the delivered fractionated dose is the random process of kill [1]. This means that some cells to be killed receive two or more hits of secondary electrons (or primary protons, neutrons), whereas other cells remain untouched. The probability of the TCP is an exponential function of the average number cells (e.g. survival of an average 0.1 cell/tumor results in the TCP = $e^{-0.1}$ = 0.9 (90%)), whereas an average 1 cell survived/tumor reduces TCP to $e^{-0.1}$ = 0.37. Such a "language of probability" does not satisfy patients who immediately raise the question: "Am I in the first (successfully treated) or in the second group (failures)?" Until now, there has been no reliable answer to such a question.

It is obvious that depending on the progression of the tumor size (stage), needs an increase in the higher fractionated total dose, however, only to a certain limit; above which a risk of severe late normal tissue complications outstrips the expected TCP [1, 2]. In such cases, radiotherapy loses its radical intent and becomes palliative in nature (fig. 1).

In order to intensify the radiation effects with regards to destroying cancer cells, some tests were performed, examining various altered dose fractionations and boost doses (brachytherapy), conformal techniques and concurrent chemoradiation, but only few of them have been successfully employed in the

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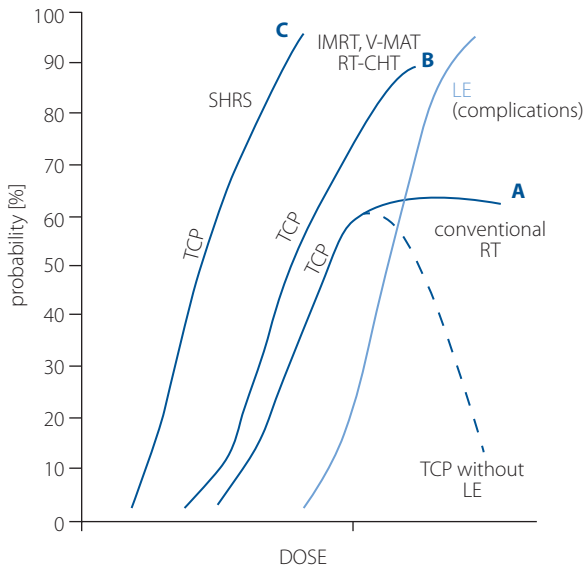


Figure 1. Dose-response (LTC, LE) as a function of dose (Gy) and dose intensity – DI (Gy/d) [TCP – tumor cure probability, LE – late effects (complications); (A) – TCP curve for conventionally fractionated, RT – effect *plateau* – further increase in the TD with extension time (OTT) does not result in higher TCP; (B) – LTC curve for conformal IMRT, V-MAT, chemo-radiotherapy; (C) – SHRS – stereotactic hypofractionated radiosurgery – high DI single dose or a few large fractions – very short OTT; dotted line – TCP without late complication]

daily practice [1, 3, 4, 5]. During the last 20–25 years it has been well documented that a single process – accelerated repopulation of the cancer cells which have survived consecutive dose fractions – significantly counterbalances cell kill effect [1 ,3, 4–6]. For example, at the end of the 6th week of fractionated RT, accelerated repopulation effectively neutralizes cell kill effect of as much as 1.4 Gy of the 2.0 Gy fraction delivered within the therapy. Thus, overall treatment time (OTT) has been recognized as a pronounced or even major factor determining the treatment outcome (TCP). Therefore, it became clear that radiotherapy (and other combined therapies) should be completed within overall treatment time (OTT) as short as possible. For this recommendation, some hope is seen in the stereotactic hypofractionated radiosurgery (SHRS) which allows to deliver a high single dose or a few large fractions (fig. 1) within a very short time (OTT) [7–10] resulting in unexpectedly high TCP (85–90%). On the other hand, this method is limited to a relatively small, primary or metastatic tumors, whilst the TCP only a local effect only, not necessarily equivalent to a patient's curability. Generally, tumor radiosensitivity has an influence on the position of the TCP curve on the dose coordinate. An increase of the dose above a certain level carries an unacceptably high risk of various late complications, depending on the volume of normal tissues (organs) involved, and therefore the rate of the TCP free from any complication decreases (fig. 1).

Normal tissue acute radiation side effects

Total dose, even if it is precisely focused within the tumor bounds, also partly affects the surrounding normal tissues (organs). Normal tissue side effects are generally classified as acute and/or late.

Acute radiation side effects (ARSE) are usually epithelial or hematopoietic in their etiology. Characteristic attribute of the ARSE is that their intensity progressively increases during daily irradiation, but is transient, and according to Fletcher [2], often heals at the end of irradiation (if dose/fraction is below 2.0 Gy) or within a few weeks thereafter.

The kinetics, severity, duration and healing of the ARSEs depend on various factors and parameters, such as patient's age, epithelial atrophy, concomitant diseases (e.g. diabetes), smoking, alcohol abuse, energy of radiation, irradiation techniques (e.g. conformal IMRT, IART, V-MAT), the area of the irradiated epithelium, the size and duration of dose accumulated per week, and the turn-over time of the epithelial cells (e.g. mitotic activity).

There is some lag period (a few days) before the radiation begins to induce epithelial damage, which is expressed morphologically and depends on cell kinetic characteristics. Short cellular turn-over leads to an early manifestation of the epithelial defects. The intensity of the epithelial cells repopulation is much higher than in the case of the cancer cells (about 1.8 Gy/day). A gradual depletion of the successive epithelial layers continues [11–14], and the first morphological EORTC grade is the redness, followed by erythema, spotted and finally confluent mucositis (grade IV). These morphological side effects (fig. 2A) trigger off progressive functional disorders (pain, oedema, dysphagia, odynophagia), which become much less tolerable by the patients than morphological defects. Sometimes they are so severe that a few days' break is needed within irradiation process to reduce the severity of the ARSE. Supportive care (parenteral nutrition, analgetics, steroid and non-steroid agents, antibiotics) has been recognized as very useful and effective, because it significantly reduces dysfunctional symptoms and therefore improves the patient's tolerance. DISCHE grading system (a wide scale ranging from 0 to 20) more precisely quantitates both morphological and functional disorders than narrow the EORTC 4-grade scale (which is, however, still used in practice). The ARSEs and their severity are generally more or less predictable. Early appearance of the erythema or spotted mucositis during the first few days of irradiation, is a pronounced sign to turn to supportive care immediately, especially when radiation therapy is concurrently combined with chemotherapy.

Sometimes confluent mucositis (CM) becomes very severe as the result of almost complete denudation of residual reserve of the basic epithelial cells (stem cells). It leads the CM to progress into the so-called consequential late effect (CLE), etiology of which is an acute defect but which manifests morphologically as a late reaction (necrosis, pathological fracture, severe fibrosis). The CLE is mainly the result of too intensive weekly accumulated doses (AD). The CLE risk steeply increases when the AD is higher than 15 Gy/week and is continued for

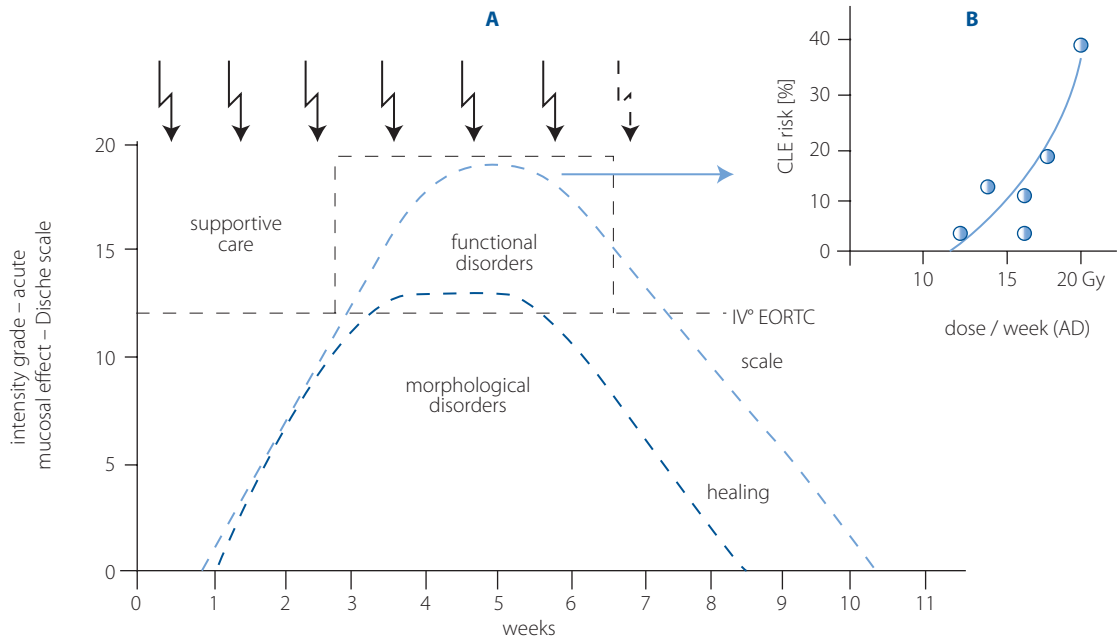
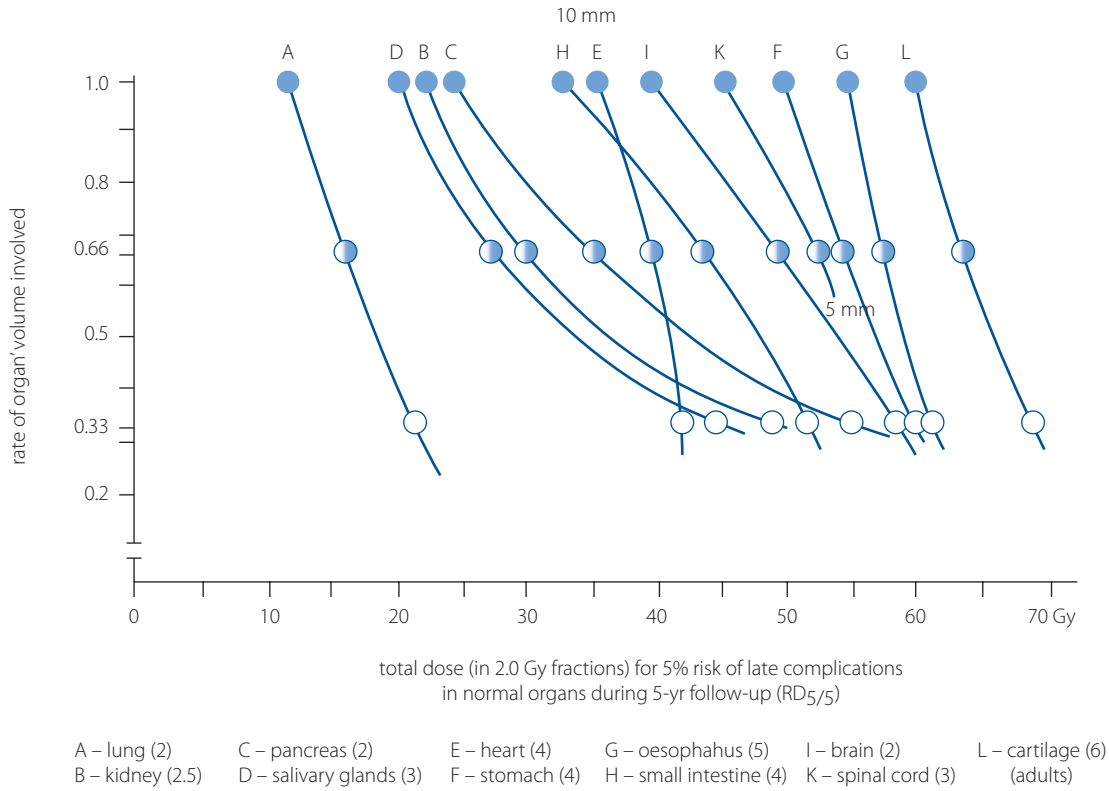


Figure 2. (A) Intensity and healing curves for acute mucosal reaction scored by Dische System as a function of treatment time (in weeks); (B) Risk of ◑ consequential late effect (CLE) as a function of dose accumulated per week – [AD in Gy/wk]



A – lung (2) C – pancreas (2) E – heart (4) G – oesophahus (5) I – brain (2) L – cartilage (6)
B – kidney (2.5) D – salivary glands (3) F – stomach (4) H – small intestine (4) K – spinal cord (3) (adults)

Figure 3. Risk curves for late post radiation effects (complications) for various normal organs as a function of conventional total dose (given in 2.0 Gy/fractions) [risk: ○ – acceptable, ◑ – too high, ● – unacceptable]

about 4–6 weeks. This definitively exceeds the limit of tolerance acceptable by the patients (fig. 2B, fig. 3).

Esophageal, gastrointestinal mucosa and hematopoietic tissues also demonstrate clinical signs of acute radiation damage. Although morphologically they remain similar to that occurred in the head and neck region but different functional disorders dominate (e.g. diarrhoea), especially when a large mucosal area is involved. In such cases supportive care plays substantial role.

Late radiation side effects

As opposed to the ARSEs, late side effects (complications – LRSE) are unpredictable a priori and they usually appear a few or even

more years after completing the RT. They develop in highly differentiated and specialized tissues and organs in type F (flexible), whose cells lost proliferative (mitotic) activity and accumulated potentially sublethal damage. Their metabolism and function, however, remain untouched until some environmental, microvascular and oxic conditions substantially worsen. Then sublethal damages lead to the cellular death. The LRSEs manifest clinically as a combination of many different pathological processes like atrophy, necrosis, atypia, dysplasia, aplasia, pathological structure, telangiectasia [1, 6, 11]. The risk of various LRSEs (constraints) which are generally acceptable are about 5% within 5 year follow-up ($RD_{5/5}$) but not more than 1% for spinal cord (paraplegia or hemiplegia). The range of the $RD_{5/5}$ doses is quite wide depending on type of the organ (tissue) and the irradiated area involved (fig. 3).

The weakness of the immune system reduces and lengthens the repair mechanisms in some of the normal organs and the LRSEs severity can progressively increase (avalanche effect). In case of the rare genetic disorders as ataxia telangiectasia, retinoblastoma, Fanconi anemia, Bloom, Sjogren, Nijmegen syndromes, progeria (progressive senility) normal tissues radiosensitivity is extraordinarily higher. In such rare mutations, fractionated dose deposited in the surrounding normal tissues should be much lower and very carefully planned [11].

A favorable feature of the stereotactic hyper-fractionated radiosurgery (SHRS) is that this high-tech method allows to focus many (over 100) pencil beams within the tumor volume (GTV), with the sharp-down dose gradient in the surrounding normal tissues. This property allows to deliver a much higher single or a few large fractional doses to the tumor. The tolerance dose consequently increases [7], but the current knowledge on the late SHRS side effects is not detailed enough and therefore these side effects are still rather guessed than precisely estimated because of inefficient clinical data available so far. Nevertheless, some of them listed in table I can provide some guideline for a daily practice.

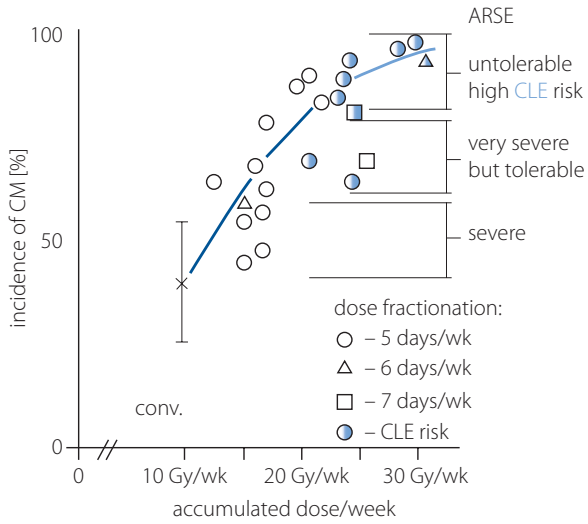


Figure 4. Incidence of acute confluent mucositis (CM) and the risk of CLE (consequential late effects) related to weekly accumulated dose (AD/wk) [red area within symbols corresponds with the CLE risk (based on ref. 15)]

Other than radiotherapy side effects

Radiotherapy which radiation effects are deterministic and depend on the dose threshold value below which no damage occurs. Stochastic radiation, in turn, damages display no threshold dose and even a very small dose of radiation may result in some events which are classified as induced cancers and/or hereditable genetic mutagenic side effects.

Induced cancers

After the exposure to even small doses of radiation practically all human organs can transform into a malignant lesion. In the past, medical staff (radiologists) exposed to small doses of the X-ray diagnostics frequently developed leukemia or severe skin necrosis, but this phenomenon was documented till 1930 only, when a new X-ray machines became fully protected against radiation.

Table I. Physical (TD) and biological equivalent dose (BED TD x [1 + di/α/β]) constraints for stereotactic hypo-fractionated radiosurgery (SHRS)

Organ	Dose constraints				Volume limits
	single		fractionated		
	physical (Gy)	BED (Gy α/β)	physical (Gy)	BED (Gy α/β)	
brain	10–13	≤98	3 x 8 Gy 5 x 6 Gy	≤120	≤1.0 cc
optic chiasm	8–10	<60	3 x 6.5 Gy 5 x 5 Gy	83–88	≤0.2 cc
spinal cord	10–13	≤98	3 x 7 Gy 5 x 5 Gy	≤70	≤0.35 cc
lung	9	48	3 x 5 Gy 5 x 3 Gy	50–55	≤4 cc
heart	22	131	3 x 10 Gy 5 x 7.5 Gy	110–116	≤15 cc
liver	12	58	3 x 6.6 Gy 5 x 4 Gy	56	≤170 cc
kidney	11	48	3 x 6.2 Gy 5 x 4.6 Gy	58	<200 cc

In 1984 and, later in 1991, the International Commission on Radiological Protection [16] has defined admissible dose limits of 20 mSv (Sievert) per year (100 mSv in 5 years) with an additional dose limit which should not exceed 50mSv within one year, and dose limits of 150 mSv for the lens of the eye and 500 mSv for hands. Nevertheless, it was quite well documented (in the case of nuclear disasters in Hiroshima, Nagasaki, Tschernobyl and also the exposure to unusually high natural radiation in Kerala (India), the Rocky Mountain (USA), China or Japan) that small doses can induce cancer development (hormesis). Bowel, lung, skin, breast, ovary, bladder, thyroid cancer and bone marrow dysplasia and atypia have been documented as the most frequent events induced by radiation. Their latent period takes on average 10 years, but only 2 years to develop leukemia. Even the dose of 0.5 cGy can induce chromosome damage in about a half of human lymphocytes.

Ionizing radiation and some other environmental (teratogenic) factors induce mutations (chromosome breaks, translocations, etc.) in germ cells depending on their phase of development. In the embryo during preimplantation period, blastogenesis is the most sensitive process, reacting to as little as 0.5 cGy. During organogenesis, after an exposure to low doses of radiation the risk of organs and growth deformities increases dramatically. Disorders within the central nervous system are the most prominent, and the risk of severe mental retardation is about 0.4%/1 cGy. The fetus in the utero is also very sensitive to radiation cancerogenesis. Although stochastic low-dose damage cancer or teratogenic effects do not appear early, the current reports document an increasing rate of the thyroid abnormalities and cancer.

Radiotherapy can also induce delayed secondary primary cancers (brain and connective tissue) even after moderate primary doses (30–40 Gy). Lung, breast, stomach, lung, bone narrow, thyroid and soft tissues belong to the organs at risk. Generally, the risk of secondary tumors is low of about 2% in male and 1.5% in female in age >60 years and about 9% in age 40–50 years. Children, whose malignant tumors were cured in the past by radiotherapy are exposed on the 5% risk of post radiation secondary cancer (thyroid, breast, central nervous system) developing within about 12 years after a latency period.

Conclusions

Summarizing, patients are generally endangered on radiation side effects. Some of these effects are local and beneficial as local cancer curability TCP) accompanied with deterministic predictive local acute normal tissue effects which are sometimes severe, but usually transient and heal at the end of radiotherapy or shortly thereafter. Late local radiation induced complications are usually unpredictable and sometimes they are life threatening. Beside local side effects, some of patients cannot avoid unpredictable stochastic exposure on low dose radiation which may lead to the risk of various mutagenic, teratogenic, or cancerogenic side effects. Therefore, it is obligatory that all radiation protection constraints should be restrictively fulfilled.

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