Kaunas University of Technology

Faculty of Mathematics and Natural Sciences

Recurrent Disease Treatment with Volumetric Modulated Arc Therapy

Master's Final Degree Project

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Declaration of Academic Integrity

I confirm that the final project of mine, Ahmed Glayl, on the topic, Recurrent Disease Treatment with Volumetric Modulated Arc Therapy, is written completely by myself; all the provided data and research results are correct and have been obtained honestly. None of the parts of this thesis has been plagiarised from any printed, Internet-based or otherwise recorded sources. All direct and indirect quotations from external resources are indicated in the list of references. No monetary funds have been paid to anyone for any contribution to this project.

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Summary

Spine metastases are common and complex cancer, which induce severe pain and neurological problems, such as sensitivity reduction, paralysis, etc.

The primary lung localisation stereotactic radiotherapy was performed, using two different fractionation schedules (48Gy (6Gy/8 fr.) and 60 Gy (7.5 Gy/ 8 fr.)). Two additional plans for the recurrent disease treatment were planned (planning target volume (PTV)+spinal cord (SC) and PTV-SC), using volumetric modulated arc therapy technique. PTV+SC means, that the spinal cord was involved in PTV volume, while PTV-SC means, that the spinal cord was contoured separately as an organ at risk. These plans were evaluated, using 5 different dose fractionation schedules (30 Gy (3 Gy/10 fr.); 20 Gy (4 Gy/5 fr.); 20 Gy (5 Gy/4 Fr); 8 Gy (8 Gy/1 fr.) and 7 Gy (7 Gy/1 fr.)). These two cases for the recurrent disease (spine metastasis) irradiation were planned, trying to minimize side effects for SC.

Treatment planning results were evaluated dosimetrically (*DHI, DCI, DGI*) and biologically (*BED, EQD*). It was found, that 4 different fractionation schedules were in a tolerance level, while the other cases differed from the low risk of myelopathy up to the high risk of myelopathy. It means that the fractionation schedule is an important step for recurrent disease irradiation in the near vicinity of the primary tumour. Also, it is important to pay attention to the interval between two treatment courses.

Glayl, Ahmed. Atsinaujinusios ligos gydymas naudojant tūrinę moduliuoto intensyvumo arkinę radioterapiją/ vadovė doc. dr. Jurgita Laurikaitienė; Kauno technologijos universitetas, Matematikos ir gamtos mokslų fakultetas.

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Santrauka

Stuburo metastazės yra dažnas vėžio atvejis, sukeliantis pacientui stiprų skausmą ir neurologines problemas, tokias kaip jautrumo sumažėjimas, paralyžius ir kt.

Pirminis plaučių naviko apšvitos atvejis buvo suplanuotas, taikant stereotaksinę radioterapiją, naudojant du skirtingus frakcionavimo grafikus (48Gy (6Gy / 8). fr.) ir 60 Gy (7,5 Gy / 8 fr.)). Papilodmai buvo suplanuoti du stuburo metastazių gydymui skirti planai (planuojamas taikinio tūris (PTT) + stuburo smegenys (SS) ir PTT-SS), planavimui naudojant tūrinę moduliuotą arkinės terapijos metodą. PTT+SS reiškia, kad stuburo smegenys buvo apibrėžtos, kaip viena struktūra su planuojamu taikinio tūriu (PTT), o PTV-SS reiškia, kad nugaros smegenys buvo apibrėžtos atskirai, kaip kritinis organas, taip siekiant jas labiau apsaugoti. Šiems planams (PTT+SS ir PTT-SS) buvo naudotos 5 skirtingi dozės frakcionavimo atvejai ((30 Gy (3 Gy/10 fr.); 20 Gy (4 Gy/5 fr.); 20 Gy (5 Gy/4 Fr); 8 Gy (8 Gy/1 fr.) and 7 Gy (7 Gy/1 fr.))). Šie du metastazavusios ligos (stuburo metastazių) švitinimo atvejai buvo suplanuoti, siekiant sumažinti galimas SS šalutines reakcijas.

Gydymo planavimo rezultatai buvo įvertinti dozimetriškai (*DHI, DCI, DGI*) ir biologiškai (*BED, EQD*). Nustatyta, kad 4 skirtingi dozės frakcionavimo atvejai atitiko tolerancijos lygį, kai tuo tarpu kitiems atvejams buvo būdinga mažos, vidutinės ir didelės mielopatijos rizika. Tai reiškia, kad dozės frakcionavimo yra svarbus žingsnis atsinaujinusios arba metastazavusios ligos apšvitai. Taip pat svarbu atkreipti dėmesį į praėjusį laiko tarpą tarp dviejų gydymo kursų.

Acknowledgement

I would like to express my deepest gratitude to my Assoc. Prof. dr. Jurgita Laurikaitienė for the continuous support of my M.A study and related research, for her constant and invaluable guidance during my work. Her intellectual encouragement and constructive critique were useful in the preparation of my research. This research wouldn't have been possible without the guidance and the help of Assoc.Prof. dr. Jurgita Laurikaitienė.

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List of Abbreviations

MESCC - metastatic epidural spinal cord compression
VMAT – volumetric-modulated arc therapy
BOT - beam on time
IMRT - intensity modulate radiotherapy
Radiotherapy - RT
HI - homogeneity index
CI - Conformity index
MLC – Multi-leaf collimator
TPS – Treatment Planning System
PTV - Planning Target Volume
ITV - Internal Target Volume
CTV - Clinical Target Volume
GTV - Gross Tumor Volume
EBRT - External Beam Radiotherapy
CT – Computed Tomography
OAR – Organs at Risk
MRI – Magnetic Resonance Imaging
DGI – dose gradient index
MU - monitor unit
SSD - source surface distance
3DCRT - 3D-conformal radiotherapy
SC – spinal cord
Gy - Gray unit radiation dose
DVH - dose-volume histogram
BED – Biological effect dose
EQD- Equivalent dose
BM- bone metastases
RM- Risk myelopathy
SM- Spinal metastases
RTOG - Radiation Therapy Oncology Group
SBRT - Stereotactic Body Radiation Therapy
SRS - Stereotactic Radiosurgery

Introduction

Spinal metastases (SM) are a consequence of different cancers, which can lead to bone fractures, paralysis, neurological problems and induce severe pain [1]. Therefore, palliative radiotherapy (PRT) is a way of prevention SM induced complications. The main *problem* is re-irradiation of the same localisation or tumour localised in near vicinity/ recurrent disease, especially when the time-lapse is shorter than six months [2]. It is very *important* to mention, that PRT usually is used a non-standard fractionation schedule, for example, 3 Gy per fraction (30 Gy in total), 5 Gy/fr. (20 Gy in total), etc., instead of 2 Gy dose per fraction. It means that higher side effects could occur for the normal/healthy tissues and organs at risk (OARs) [3]. Due to this reason *advanced* treatment planning techniques, like inverse treatment planning (intensity-modulated radiotherapy or volumetric modulated arc therapy) could be a solution, ensuring better sparing of healthy tissues and OARs. Therefore, it is *relevant* to choose an appropriate schedule scheme of fractionation for SM PRT, if it is a case of re-irradiation of recurrent tumour or tumour localised in near vicinity [4].

The aim of this research project was to analyse and find the most appropriate fractionation schedule scheme for spinal metastasis, located in the near vicinity of the tumour, irradiation.

The tasks:

1. To plan recurrent disease (spinal cord) treatment, using volumetric modulated arc therapy.
2. To evaluate an outcome of the spine metastasis irradiation procedure, analysing the main dosimetrical parameters of the planned treatment plans.
3. To evaluate how different fractionation schedules influence the outcome of the whole treatment procedure.

Treatment planning was performed in a Hospital of Lithuanian University of Health Sciences Kaunas Clinics, Oncology Hospital.

1. Literature review

Approximately 40% of cancer cases are diagnosed with spinal metastases. Around 10% of cancer cases, metastatic epidural spinal cord compression (MESCC) occurs during this disease. The most frightening complications of metastatic cancer are paralysis, bone fractures, progressive pain, and sphincter dysfunction with a loss of senses [6]. In patients with single-level symptomatic MESCC, a randomized controlled trial showed, that surgical pressure followed by radiotherapy (10 fractions, total dose 30 Gy). Based on radiographic results after standard radiotherapy, one study reported that the local failure occurred within one year for 70% of patients [7]. Therefore, the results indicated, that tumour control is not sufficient after surgery irradiating with a total prescribed dose of 30 Gy. Local failure refers to re-irradiation of MESCC for patients with metastatic cancer [6]. The percentage distribution of incidence rates for the common cancers and the most cancer worldwide in the 2020 y. is presented in Figure 1 (A), while the percentages distribution of incidence rates for the most popular cancers in Lithuania is presented in Figure 1 (B) [8].

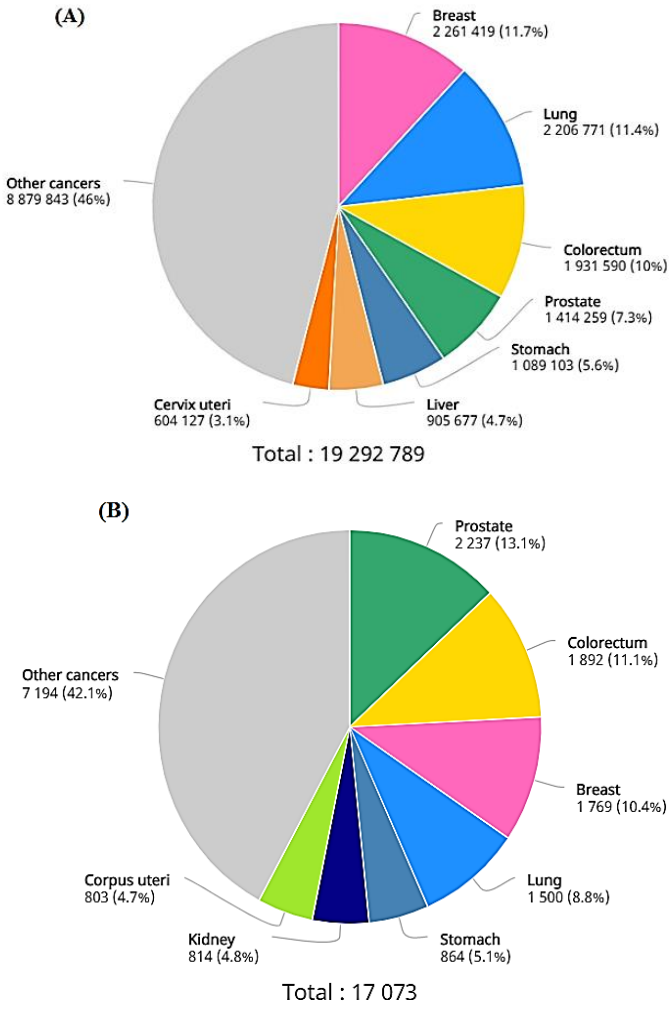

Fig. 1. Estimated number of cases in 2020, (A) worldwide, (B) Lithuania for all ages, both sexes [8]

Spinal metastases (SM) cause neurological and physical complications, which can cause poor quality of life. The standard radiotherapy (RT) cares for uncomplicated painful SM. It is known, that 70% of patients treated with radiotherapy alone have a partial response or are resistant to treatment. Patients with growing or persistent neurological deficits and mechanical instability of the spine are offered for surgery procedure [9]. The results of this study showed inconsistent results. Therefore, the predictive factors for palliative radiotherapy response have not been identified [10-11].

Radiation therapy has been used exclusively to relieve pain in palliative patients. Reduced and controlled disease symptoms were observed in ~80% of patients, treated with radiotherapy [12].

1.1. External beam radiotherapy

Radiation therapy may be considered as the primary treatment method or in combination with chemotherapy or used after surgery as an additional treatment. RT aims to irradiate the target with as high a prescribed dose as possible, at the same time trying to save healthy tissues and organs at risk (OARs). The main limitation to the prescribed dose is healthy tissues and OARs [13-15]. Harm depends on fractionation, RT localization, the volume of the tumour and total treatment dose. For example, it has been observed that a maximum dose, more than 20 Gy, causes damage to the salivary gland, while harm to the lacrimal gland is caused when the maximum dose is higher than 30 Gy [16]. Usually, the total treatment dose of RT is divided into several fractions, which are generally delivered in 5 days per week for several weeks period (it depends on the irradiated type of cancer [17]. Therefore, the idea of fractionated therapy ensures the effectiveness of the treatment, at the same time reducing toxicity for the healthy tissues, critical organs or/and OARs in the vicinity of the irradiated target [17]. Therefore, external beam radiotherapy (EBRT) is an effective and useful method to relieve pain. EBRT relieves pain symptomatology with partial response in 50–80% of the cases and decreases the myelopathy risk of the SM [18]. Stereotactic body radiation therapy (SBRT) and stereotactic radiosurgery (SRS) could be used for long-term pain relief in comparison with conventional RT [19]. The fractionation schedules for the palliative bone metastases (BM) irradiation usually are used for pain relief during irradiation [20]. It was observed, that effectiveness of pain relief depends on the fractionation schedule and the primary response. It is known that several fractions can give good rates of palliation (palliative radiotherapy), various prospective randomized experiments have explained that 24 Gy in 6 fractions, 20 Gy in 5 fractions, 30 Gy in 10 fractions, or 8 Gy in a single fraction can give great pain control and minimum side effects (Table 1) [21]. K. Suzuki et al. [20] showed that pain relief after ten-day of multi fraction RT was more efficient in comparison with a single fraction RT. The other study [22] showed that there is no difference in the effectiveness in pain relief between multi fraction and single-fraction RT, even the pathological fracture rate and re-irradiation rate were significantly higher after single-dose RT. It is known, that there is no data clear on the time lapse for the re-irradiation. Is thought, that the optimal time lapse

could be at least six months between the first and second irradiation procedures [23-25]. Y. Choi et al. [26] announced that in patients with relapse metastases close to the previous treatment SC, an interval time of ≤12 months, between the first and second irradiation was vital of local failure. Other authors [27-29] offer 6 months term for re-irradiation with the risk of toxicity reduction and with the possibility of local control progression within a time [30-32].

The two possible fractionation schedules could be used to define the relation of late complications and tumour control:

a) Hyper fractionation, size of dose/fr. is less than used in a standard schedule (2 Gy/fr.), without prolonging the total time of the treatment.
b) Accelerated fractionation, the total time of treatment is minimized and the overall dose/fraction is slightly decreased compared to the standard fractionation [33].

It is known, that stereotactic radiosurgery (SRS), is used 1-5 fractions per whole treatment. SRS and hypo fractionated RT is effective and saves for the treatment of SM. However, the ideal dose and fractionation plan for SC re-treatment is not defined [34]. A. Kaufman et al. [35] analysis regarding spine SBRT/SRS treatment efficiency and dosimetry with Eclipse/Truebeam, Vero, Tomotherapy and CyberKnife showed, that dosimetric advantages for CyberKnife and Vero are faster in comparison with duration using tomotherapy and True beam.

Table 1. Single-fraction versus multiple-fraction RT regimens for painful, uncomplicated BM (different studies overview) [21]

No. of patients	Fractionation (Fr)	Overall pain relief, %	Complete response, %	Acute toxicity, %	Late toxicity, %	Repeated treatment rate, %
775	8 Gy/Fr. 20 Gy/5Fr. or 30 Gy/10 Fr	78 78	57 58	30 32	2 1	23 10
160	8 Gy/1 Fr 30 Gy/10 Fr	75 86	15 13	13 18	Not report Not report	28 2
898	8 Gy/1 Fr 30 Gy/10Fr	66 66	15 18	10 17	4 4	18 19
327	4 Gy/1 Fr 6 Gy/1 Fr 8 Gy/1 Fr	59 73 78	21 27 32	32 29 37	6 7 7	42 44 38
376	8 Gy/1 Fr 30 Gy/10 Fr	Equivalent Equivalent	Not report Not report	Not report Not report	4 11	15 4
241	8 Gy/1 Fr 20 Gy/4 Fr	62 71	15 15	35 35	5 5	21 12
272	8 Gy/1 Fx 20 Gy/5 Fx	53 61	26 27	5 11	5 4	29 24
1,171	8 Gy/1 Fx 24 Gy/6 Fx	72 69	37 33	Equivalent Equivalent	4 2	25 7

1.2. The main “tools” used in external beam radiotherapy

Before irradiation procedure treatment has to be planned, prescribing irradiation dose and contouring the main volumes for irradiation and sparing healthy tissues and OARs.

So, one of the steps in the RT or treatment planning process for the target is to scan the patient (using one of the modalities: computed tomography (CT), magnetic resonance imaging (MRI), positron emission computed tomography (PETCT)) for the positioning purposes of every treatment fraction and contouring. The main volumes used for treatment planning are defined as gross tumour volume (GTV) that is determined by the visible tumour on clinical examinations and coregistered diagnostic images (CT, PET CT, MRI); clinical target volume (CTV) is defined as GTV taken into account the possible microscopic spread of the disease; internal target volume consists of an internal border attached to the CTV to recompense internal physiological variations and change in form, volume, and location of the CTV; planning tumour volume (PTV) is defined estimating additional geometric inaccuracies, such as uncertainty in patient positioning, due to the patient motion is added margin to the CTV (a typical margin is from 1 mm (in regions near OARs, for example, brainstem, spinal cord, etc.) or 3 mm to 5 mm); the treated volume (TV) is larger than the PTV and depends on a chosen treatment procedure (Fig.2) [36-37].

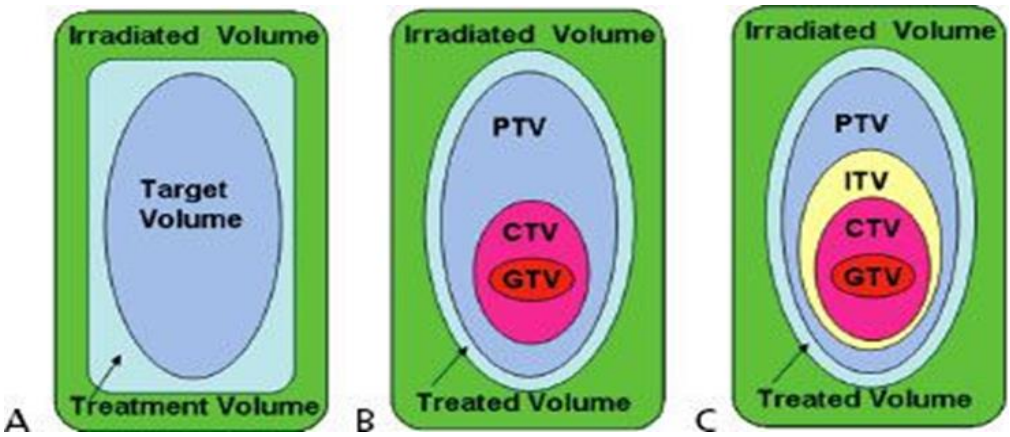

Fig. 2. Illustration of GTV, CTV and PTV [38]

External beam radiotherapy (EBRT) is performed from a radiotherapy unit outside the body. The most common equipment used for irradiation is a linear accelerator. The linear accelerator generates electrons and x-ray photons, which are used for the superficial or deep localized tumours treatment. Superficial treatment procedure using linear accelerator is performed using high energy electrons (common energies 6 MeV to 15 MeV), for skin tumours, total body irradiation procedures (lymphoma), and it is essentially useful treating shallow invasive tumours or tumours that are located near such organs as ears, eyes, lips, or nose [39, 40]. Irradiation using photons with energies from 4 MeV to 25 MeV allows performing treatment of deeper localisations. [41]. For example, breast cancer irradiation is usually performed with 6 MeV (maximum energy of the photons), while the prostate treatment – 15 MeV. Variation of the energy (from Co-60 (1.25 MeV) to 6 MeV) also leads to the difference in target coverage. It is known, that irradiating with Co-60 and 6 MeV is formed higher hot spots in comparison with photons 15 MeV photons [42]. How it is important to choose the right energy or type of beam for the planning, evaluating the depth of the target could be seen in Fig. 3. It is obvious, that correct energy could lead to better coverage of the target volume, also

decrease in so-called hot spots of the doses formed in a plan, which are useless, ineffective and could be even harmful to the patient [42-48].

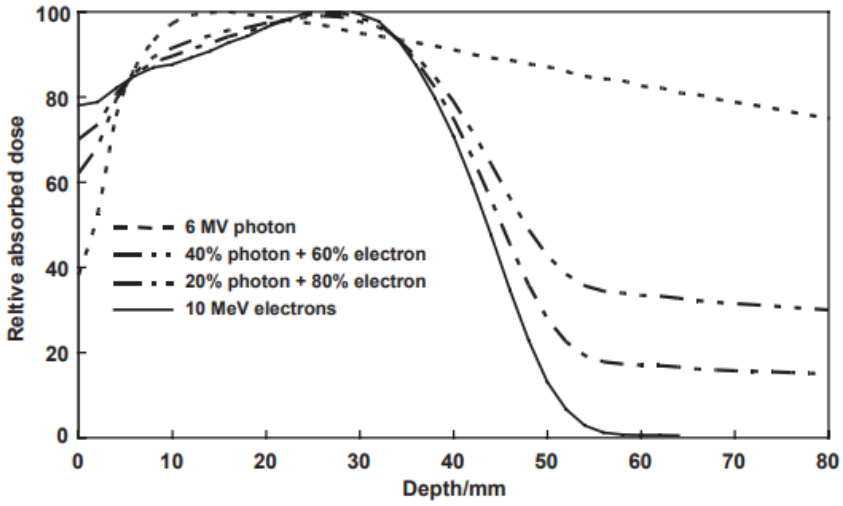

Fig.3. Depths/mm of photons and electrons according to the energy and type of the beam [45]

Therefore, the selection of the energy for the treatment plan depends on how deep the localised target is, for example, breast cancer irradiation is usually performed with 6 MeV (maximum energy of the photons), while the prostate treatment – 15 MeV. Variation of the energy (from Co-60 (1.25 MeV) to 6 MeV) also leads to the difference in target coverage, for example, Co-60 are common so-called hot spots (higher than 107 % doses from the prescribed dose) with a worse coverage in comparison with 6 MV (accelerated voltage) and 15 MV photons (the dose-volume histograms (DVHs) are usually used for the final evaluation of the treatment plans, analyzing PTV coverage and OARs toxicity) (Fig.4).

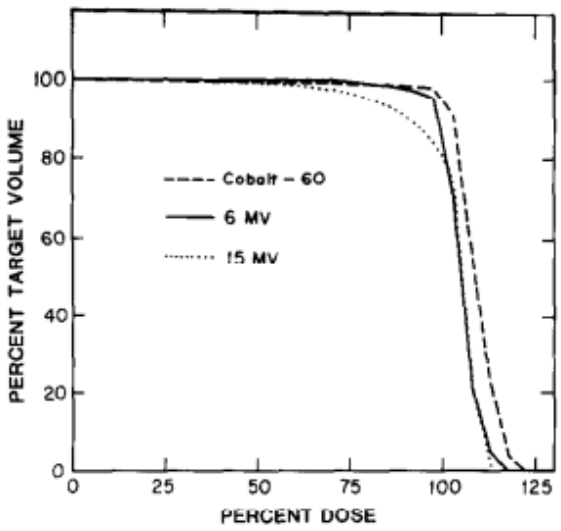

Fig. 4. Dose-volume histograms (DVH) to describe maximum and minimum receive dose in plans comparison for the target using different irradiation energies [92]

However, it was observed, that for 15 MV photons was significantly worse tumour coverage for the surface area [92]. It is obvious, that chosen energy could lead to better coverage of the target volume, also a decrease in hot spots of the doses formed in a plan, which are useless, ineffective and could be even harmful to the patient (Fig. 5) [48].

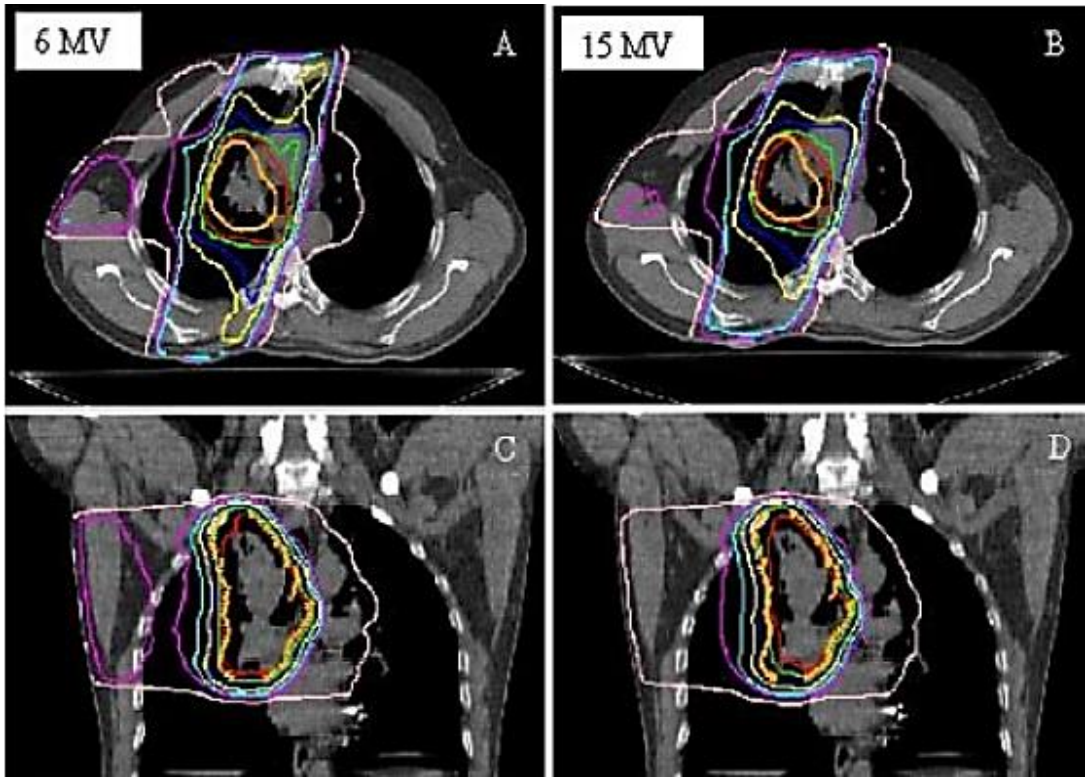

Fig. 5. Isodose distributions for 6 MeV and 15 MeV energies treatment plans (lung cancer case) [51]

Therefore, insufficient surface coverage as was already mentioned is dependent on the energy of the photons, which have a characteristic to form so called build-up region and it is defined by the maximum depth dose (Fig.6) [47-49]. It is known, that for the Co-60 beam the maximum depth of the dose is 0.5 cm, while for the linear accelerator maximum energies (E_{max}): 6 MeV, D_{max} is equal to 1.6 cm; 10 MeV, D_{max} = 2.0 cm; 15 MeV, D_{max} = 2.6 cm [50].

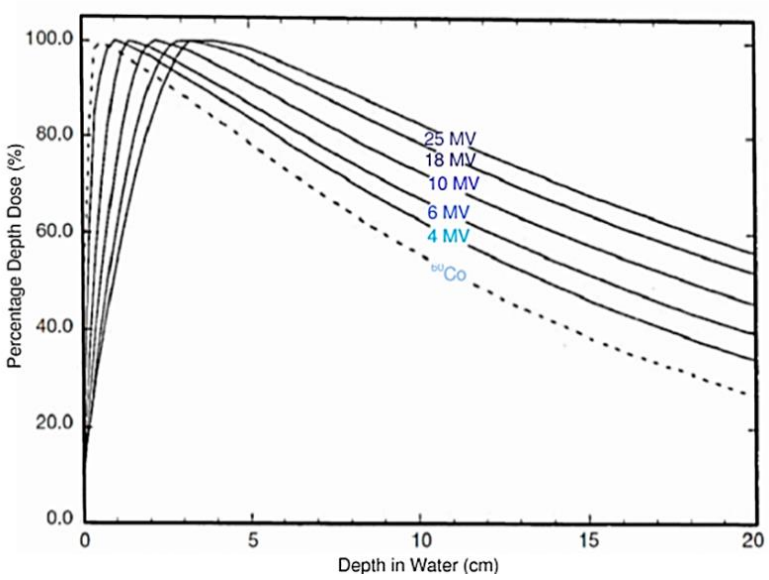

Fig. 6. Percentage depth dose curves in water for different accelerating voltage 25 MV, 18MV, 10 MV, 6 MV, 4MV and cobalt-60 beam for 10 cm x 10 cm field [47]

The other factor, which influences treatment planning for the patient is field size (FS). It is known, that then FS increases, the percentage depth dose will increase as well. Therefore, for the small fields, the scattering processes are insignificant and treatment planning with different FS usually is beneficial due to enhanced dose distribution. Treatment planning with larger fields can have a meaningful negative effect, for example, during intensity-modulated radiotherapy (IMRT) this may increase multi-leaf (MLC) scattering processes (Fig.7) [52, 53].

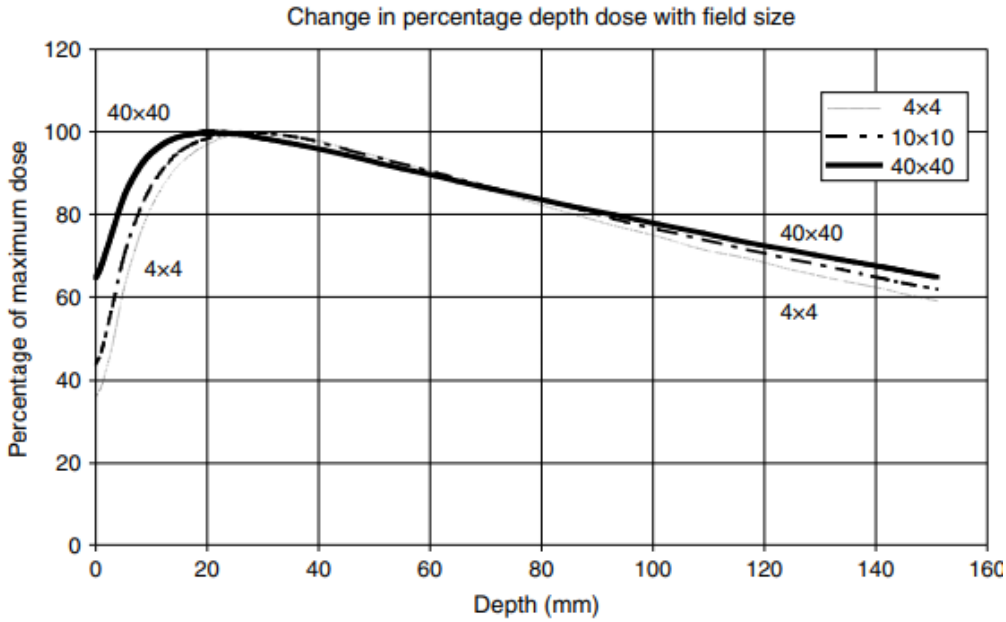

Fig. 7. Depth dose for different FS (40 cm x 40 cm, 10 cm x 10, and 4 cm x 4 cm) with energy 15 MeV [55]

Therefore, MLC is one more essential additional tool, which is used to form treatment fields regarding the shape of the target. MLC contains a maximum of 80 pairs of leaves that are flexible and independently moves, for the optimal dose distribution in the vicinity of the tumour [54-57].

Multi-leaf collimator. The multi-leaf collimator (MLC) has a movable leaf. Standard MLCs have from 80 to 160 leaves. MLC can form almost every desired field geometry, shape. MLC has also some disadvantages, like radiation leakage between leaves and problems to form complex field contours (Fig.8) [54]. The MLC consists of two banks of leaves, which can be controlled individually; it is possible to design a radiation field regarding the target size and shape with an accurate movement of the leaves.

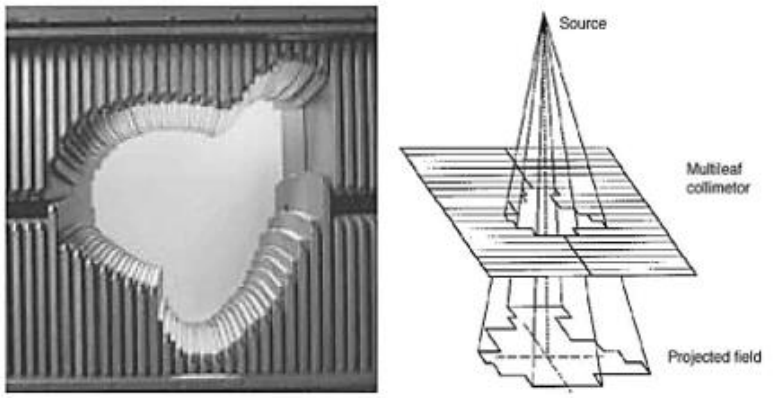

Fig.8. Illustration match MLC on the target [58]

The position of MLC affects the isodose distribution, which depends on the position of the collimator and on the scattering processes, which occur in the treatment unit head, patient or phantom. The isodoses for the standard plan is shown in (Fig.9) [59].

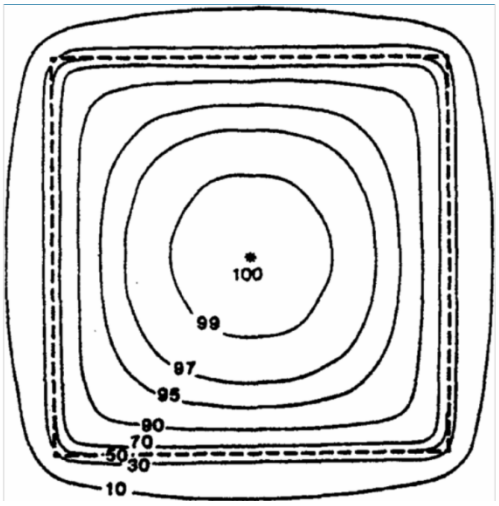

Fig.9. Isodose distribution for the plane cross-sectional, perpendicular to the central axis of the beam normalized to 100% at the centre of the field [59]

The effect of the scattering factor in the linear accelerator head depends mainly on the position of the leaves. It was found that the scattering factor for linear accelerator

"Varian" is smaller compared to "Elekta". Possible leaf fitting modes could be seen in (Fig.10). It shows that MLC may fit the PTV (shaded part) was uniformly for a margin *M* using 4 different fitting strategies: inside edge, centre, the outside edge and circle [60].

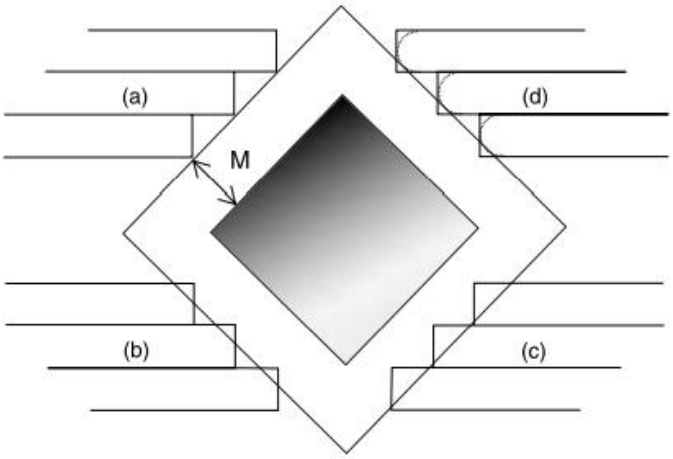

Fig.10. MLC fitting strategies: (a) inside edge (b) centre, (c) the outside edge, (d) circle [61]

1.2.1. The main treatment planning strategies

There are two main types of treatment planning techniques: forward (3D conventional radiotherapy (3DCRT)) and inverse (IMRT and VMAT) [62]. Forward treatment planning is focused on a beam used for the planning [63, 64, 65], while for inverse treatment planning the beam shaping is the second step and this type of treatment planning usually starts with a description of the desired dose-volume constraints for the target and OARs (Fig.11) [60].

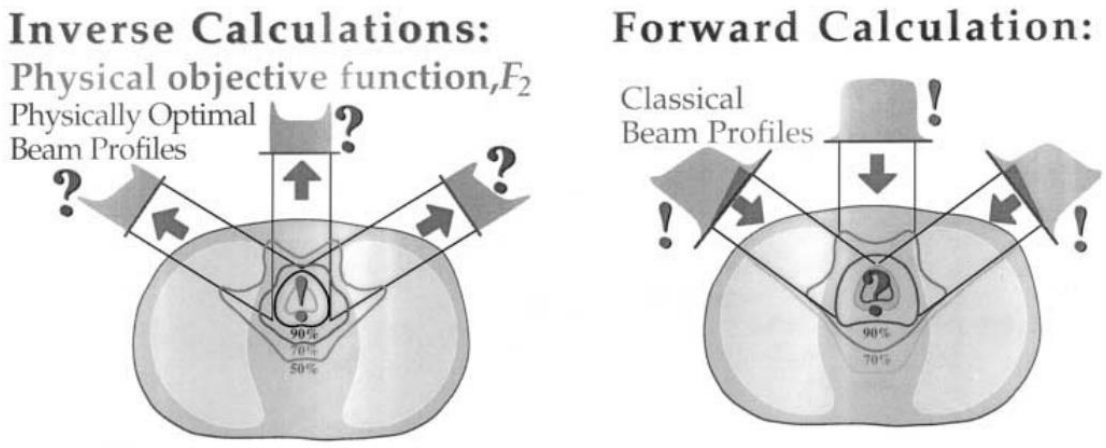

Fig.11. Comparison of forward planning and inverse planning [65]

The dose distribution of forward and inverse treatment planning techniques is shown in (Fig.12).

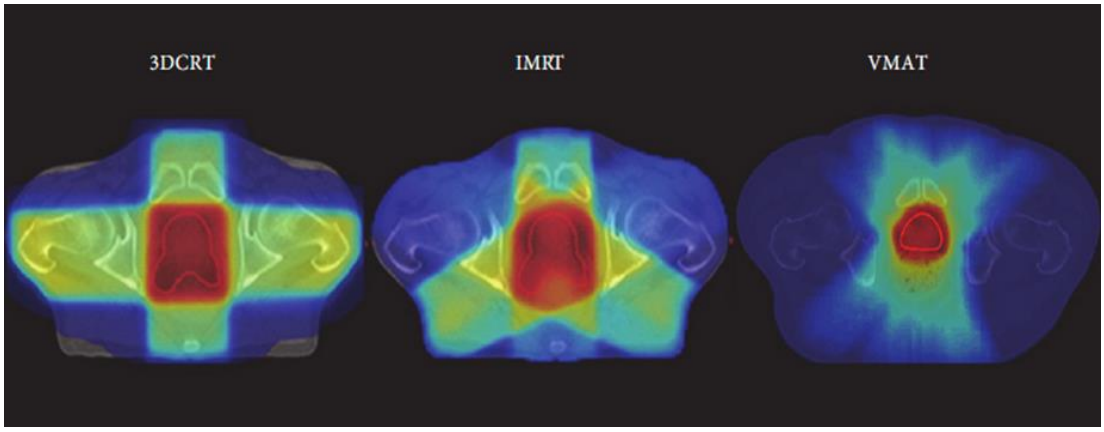

Fig.12. Isodose distribution for three techniques (3D-CRT, IMRT and VMAT): the azure blue covering represents the intermediate-dose areas, the dark blue covering the low-dose areas, the yellow covering the intermediate-high-dose areas and the red covering the high dose areas [66]

VMAT is a new volumetric RT technique based on simultaneous optimisation of MLC, dose rate, gantry rotation speed and shapes. The technology was examined in various studies giving an overall enhancement in avoiding healthy tissue and organs at risk (OAR), comparable target coverage, reduce the number of monitor units (MU) and decreased beam-on time compared to another IMRT technique.

It was observed, that using inverse treatment planning technique (VMAT) increased PTV coverage and sparing of OARs in comparison with forwarding treatment planning (3DCRT). Moreover, comparing inverse treatment planning techniques in between, it was observed, that the monitor unit (MU) is described as the average number of MU expected to achieve the prescribed dose and beam-on time (treatment duration) was decreased [66, 63].

Treatment plans evaluation criteria. The quality of planned treatment plans are one of main the steps, which let radiology oncologist and medical physicist to ensure the best treatment outcome.

Dose homogeneity and dose conformity indexes (DHI and DCI) are used to define how prescribed irradiation dose conforms to the shape, size (*DCI*) and is homogenously distributed (*DHI*) for the irradiated volume [68].

DHI and *DCI* are calculated using these equations [68]:

$$DHI = \frac{D_5}{D_{95}}; \quad (1)$$

$$DCI = \frac{V_{PI}}{TV}, \quad (2)$$

where D_{95} is the minimum dose, which covers 95% of the planned target volume; D_5 is the minimum dose, which covers 5% of the *PTV;* V_{PI} is the prescribed isodose volume and *TV* is the *PTV* covered by the prescribed isodose.

The standard value of *DHI* and *DCI* is equal to 1. It is known, that then the plan is less homogeneous, this value increases and is higher than 1, while *DCI* is higher than 1 when irradiated volume exceeds the boundaries of the irradiated target volume and covers some parts of OARs. *DCI* is usually lowering than 1 when the irradiated target volume is irradiated partially. While *DCI* is between 1 and 2, the treatment is following the main requirements/ protocol, if it is between 2.0-2.5 and 0.9-1.0 it is considered that there are some sort minor uncertainties related to the protocol; if it is more than 2.5 and smaller than 0.9 it is considered as a severe deviation from the protocol [69-70]. *DHI* let a comparison of various techniques or equipment and could be used as treatment protocols in the future, predicting, which treatment planning is a better quality can, etc. [71].

Dose gradient index (DGI) is the parameter used to quantify drop off of the dose, which is related to the radiation within the shape and size of the target, as well as with a dose distribution outside the target or the specified prescription range, which influences complications for the normal tissues [72].

The isodose represents the standard dose for the specific dose distribution for the target volume. To measure an average distance between two isodose distributions, the dose gradient index (*DGI*) is used [73-74]:

$$DGI = \frac{V_{50\%}}{V_{100\%,}}; \quad (3)$$

where *V50%* and *V100%* means irradiation of 50 % and 100 %volume with a prescribed dose.

The *DGI* is described as the ratio of the isodose volume of the 50% reference isodose volume to the isodose volume of the reference isodose volume and is estimated at the specific isodose volume (i.e., 90% and 80%) and the specific volume coverage values (i.e., *D85*, *D90*, *D95*, and *D99*). The modified gradient index (*mGI*), which analyses dose gradient based on the target volume is described as the ratio of the isodose volume of 50% reference isodose volume for the planning target volume and can be defined as follows:

$$mGI = DGI \times PITV, \quad (4)$$

where *PITV* represent the ratio of prescription isodose volume/target [105].

The low value of *DGI* means steeper dose falloff outside the target and better sparing of OAR during the comparison between two isodose distribution plans [69].

1.3. Palliative radiotherapy. Re-irradiation of bone metastases

Re-irradiation of bone metastases (BM) is effective and safe with response rates ranging from 33% to 84% in retrospective investigations applying a difference of dose per fractionation regimens. BM is a typical demonstration of malignancy that can generate debilitating and severe effects, including spinal cord pain, pathologic fracture, and

hypercalcemia compression. The proper care of BM patients' needs interdisciplinary care amongst radiation oncologists, radiologists, medical oncologists, pain medicine specialists, surgeons, and palliative care professionals. RT gives successful palliation of painful BM that is time effective and has been linked with some side effects. External beam radiotherapy (EBRT) can produce meaningful palliation of painful BM in 50–80% of patients, with up to 1/3 of patients obtaining full pain relief at the managed. A wide range of RT selections also exists for pain that has repeated after RT has been provided for BM. Amongst these possibilities is the second course of EBRT to the related localized position (repeated RT). Re-irradiation might be effective, safe, and important for patients with slight life likelihood [75]. Therefore, treatment planning technique is essentially an important step for the re-irradiation cases, trying more to spare organs at risk and healthy tissues [76]. In such cases, irreplaceable is inverse treatment planning techniques, like VMAT and IMRT, which showed promising results (sparing OARs) for re-irradiation procedures treating complex diseases and multiple metastases [77, 78]. Different studies of various fraction schedules for repeated treatment are presented in Table.2. It was observed, that re-irradiation needs more detailed analysis to define the main criteria for metastatic cases re-irradiation [76].

Table 2. Data representing retreatment of painful spinal metastases (CR = complete response; PR = partial response) [76]

Study	**No. of patients**	**Primarily dose**	**Re-irradiation fractionation**	**Pain relief**	**Notices**
Local repeated RT	30	Mostly30 Gy/10 Fr	10 Gy/5 Fx to 26 Gy/13 Fx	50%	Better pain relief for those with initial CR vs. PR
Prospective random selection experiment of 4 or 8-Gy single doses for BM pain	40	4 Gy/1 Fr 8 Gy/1 Fr	Most got 8 Gy/1 Fr; some got. 20 Gy/5 Fr	71% 44%	No variation in response by histologic kind
Single 4 Gy repeat RT for painful BM after single Fr RT	109 + 26	4 Gy/1 Fr 6 Gy/1 Fr 8 Gy/1 Fr	4 Gy/1 Fr	74% primary responders; 46% without responders	31% CR

Table 2. Data representing retreatment of painful spinal metastases (CR = complete response; PR = partial response) [76] (continued)

Study	No. of patients	Primarily dose	Re-irradiation fractionation	Pain relief	Notices
Secondary single 4 Gy repeated RT for painful BM	25	4 Gy/1 Fr, + repeat RT, 4 Gy/1 Fr 6 Gy/1 Fr + repeat treatment; 4Gy/1Fr 8 Gy/1Fr + repeat irradiation 4Gy/1 Fr	4 Gy/1 Fr (second re-RT)	80%	No pain control. variation in primary responders vs. no responders
Repeated-RT for painful BM	57	Single Fr therapy to 41%, fractionated irradiation to 59%	8 or 10 Gy/1 Fr, 26 Gy/6 Fr, 28 Gy/7 Fr, 30 Gy/10 Fr	87%	Patients irradiated. were primary. no responders
Low-dose, single-Fr RT for BM pain	11	4 Gy/1 Fr	4 Gy/1 Fx to primary responders, multi Fr or 8 Gy/1 Fr to no responders	100%, primary responders; 0%, non-responders	2 patients underwent re-irradiation second time
Single-6Gy RT): palliation of painful BM	18 ,different histologic types	6 Gy/1 Fr	6 Gy/1 Fr	72%	Long intervals Between primary and repeat irradiation
Repeat irradiation and Dutch BM Study cancer patients receiving RT for BM: results from randomized multicenter trial—Norway	173 , different histologic types	8 Gy/1 Fr 24 Gy/6 Fr	8 Gy/1 Fr, 46 cases Multifractions, 91 cases 8 Gy/1 Fr, 27 cases Multifractions in 9 cases	66% 46%	Single fraction RT effective primary Treatment or repeat irradiation

Lee, Y. K., et al. [79] BM treatment study showed, that the dose distribution of the thoracic and cervical spine is comparable for both IMRT and VMAT techniques. It was observed, that better conformity was observed in a VMAT plan (*CI*=1.3) (Fig.13 and Table. 3). *D50%* does not differ from the prescribed dose of 35 Gy for both IMRT and VMAT plans.

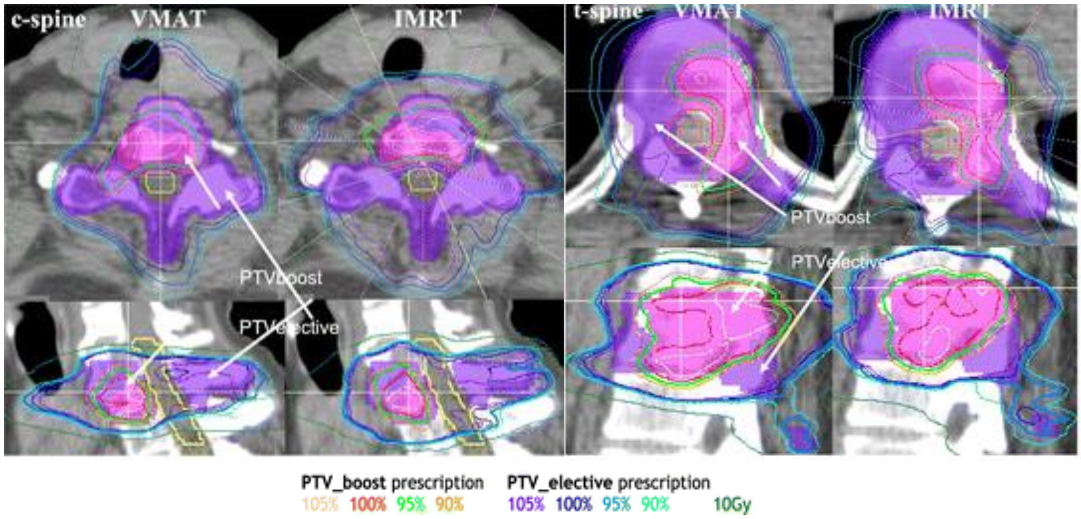

Fig.13. Isodose distribution for VMAT and IMRT treatment planning techniques [79]

Table 3. Median (range) dose statistics and CI (V95%/PTV) (PRVsc, planning risk volume of the SC; RVR, Remaining volume at risk; PTVe, elective, PTVm − sc, macroscopic PTV minus a 3-mm expansion of the SC) [79]

Region of interest	**Parameter**	**IMRT**	**VMAT**
DCI	$\frac{V_{95\%}}{PTV}$	1.54 (1.20–2.41)	1.30 (1.02–1.96)
	D95%	30.7 (30.3–32.4	31.4 (31.3–32.9)
PTVm − SC	*D90%*	31.9 (31.5–33.3)	32.8 (32.2–33.6)
	V95%	82.6 (77.6–90.2)	87.1 (81.0–92.5)
	D95%	19.8 (19.4–19.9)	19.8 (19.5–20.3)
Region of interest	**Parameter**	**IMRT**	**VMAT**
PTVe	*D90%*	20.1 (19.8–20.6)	20.4 (19.8–20.9)
	V95%	99.6 (99.2–100.0)	99.3 (98.6–99.6)
PRV-SC	*D1 cm3*	22.0 (21.9–22.2)	22.5 (21.9–23.5)
SC-ring	D_{min}	19.2 (18.2–19.5)	18.1 (15.8–19.6)
	D_{mean}	23.0 (22.5–24.4)	23.2 (22.3–25.1)
RVR	*V10 Gy*	14.6 (9.8–36.6)	11.0 (9.4–18.9)
	D_{mean}	4.9 (3.8–7.8)	5.1 (4.4–6.1)

Also, it was observed, that SC is irradiated with an IMRT and VMAT plans were within tolerance limits. Therefore, dose to the SC, i.e., dose to the SC-ring was 18.1 and 23.2 for D_{min} and D_{mean} respectively for VMAT, D_{min} and D_{mean} for the IMRT was 19.2 and 23, respectively. Fallow tolerance limits for the spinal cord (SC) is one of the critical steps in evaluating palliative repeated RT. However, it is known, that the risk of myelopathy due to radiation depends on biologically effective dose derived for the SC, which usually takes into account the total dose and dose per fraction [79, 80]. The risk score is based on three variables, which distinguish three various risk groups (Table 4 and Table 5) [81]. The range of the risk score differs from 0 ($BED \leq 120$ very low risk) to 9 ($BED > 200$ very high risks) [81].

Table 4. Risk score for development of RM [81]

Factor	0points	1 point	2point	3 point	4point	5point	6point	7point	8point	9point
Cumulative BED in 2Gy/fr.	≤120	120.1–130	130.1–140	140.1–150	150.1–160	160.1–170	170.1–180	180.1–190	190.1–200	>200
Interval <6 months					x (4.5)					
BED of one course ≥102 in 2 Gy/fr.					x (4.5)					

Table 5. Risk groups for the development of RM [81]

Group	Points	Myelopathy	Myelopathy updated	Myelopathy%	%Myelopathy updated
Low risk	≤3	0/24	1/30	0	3
Intermediate risk	4–6	2/6	2/8	33	25
High risk	>6	9/10	9/10	90	90

B. Shibamoto et al. [82] reported, that a thoracic SC dose of the 50.4 Gy delivered by 1.2 Gy/fr., 2 Gy/fr. per day, lead to higher risk myelopathy (RM) for hypofractionated RT. Marcus, et al [83] study showed, that the rat's tolerance of SC depends on the fractionation schedule. Cervical SC of 276 healthy rats was irradiated over 6 weeks using hypo fractionated schedule with a single-doses from 0.75 Gy to 2.5 Gy and the total dose from 45 Gy to 150 Gy (66 fr.), were conventionally schedule with a single-dose from 1.5 Gy to 4.0 Gy and the total dose from 45 Gy to 120 Gy (30 fr.) (Table 6).

Table 6. Rate of myelopathy for hyper fractionation and conventional fractionation [84]

Dose (Gy)	Rate of myelopathy	
	Conventional fractionation	Hyper fractionation
45	0.00	0.00
52.5	0.00	-
60	0.18	0.11
67.5	0.00	-
75	0.82	0.22
82.5	0.75	0.10
90	1.00	0.40
97.5	1.00	0.20
105	-	1.00
120	-	1.00
135	-	1.00
150	-	1.00

Myelopathy as neurological paralysis of the rat's legs was registered. Most deaths were caused spontaneously or by esophagitis arising neoplasms, while for hypo fractionation schedules death cases were registered during irradiation procedure (Table 7) [83].

Table 7. Occurrence of deaths [83]

	No. of the animals	**Dead within RT**	**Dead within Follow months**			
			0-5	**6-10**	**> 10**	**Evaluable**
Conventional fractions	120	3	3	7	1	106
Hyper-fractions	120	12	3	4	6	95
Control	36	0	0	1	5	30

Y. Hao [85] study showed that SC of rats irradiated with a 10.25 Gy/3Fr., led to forelimb paralysis, while any data about increased radiosensitivity of rats SC under 1 Gy were not registered. Van. Schueren, et al. [84] studied the main effects observed decreasing dose from 2 Gy/Fr. to 1 Gy/Fr. for the rat cervical SC, while the total treatment dose was 15 Gy/46 weeks, irradiated with 18 MeV photons. As a result, was observed white matter necrosis with foreleg disability due to demyelination.

1.4. Biologically effective dose and equivalent dose

Biologically effective dose. The basis of fractionation in RT means a better spare of OARs, due to repair of sublethal damage related to a repopulation of the cells and number of the dose fractions, if the overall time is enough long. It is known, that the ratio α/β for SC differs from 1.6 to 5.0 [86]. The Biologically effective dose (*BED*) is derived from the linear-quadratic (LQ) model, which shows the relationship between delivered dose and cell survival, also allows to predict the outcome for different fractionation schedules [96]. *BED* can be expressed as follows:

$$BED = nd\left(1 + \frac{d}{\frac{\alpha}{\beta}}\right) - log_e 2\,(T - TK)/\alpha\, Tp, \quad (5)$$

$$BED = D\,(1 + Fraction\ dose\ /\ \frac{\alpha}{\beta}), \quad (6)$$

where d dose per fraction; D total dose; α/β represents the irradiated tissue [86]; T days (regarding a cell doubling time Tp) and tumour repopulation day TK.

BED is defined through the meaning of effective dose, equivalent dose and absorbed dose. An absorbed dose is defined as s the quantity of the ionizing radiation energy derived in a matter (tissues or organ) per unit mass. The unit of the absorbed dose Gray (*Gy*) is equivalent to joule per kilogram. Equivalent dose shows an impact for the certain tissue on the type of radiation and is described as the absorbed dose in organ or tissue. Effective dose is known as the equivalent doses for certain tissues multiplied by their tissues weighting factors, which is used to represent the *BED* related to radiation, evaluating the influence of different radiosensitivity of the body tissues or organs (Table 8) [97].

Table 8. Described biological effect with the modified parameters for sensitive mucosal [80]

Dose/Fr	Overall dose (Gy)	Total time (days)	Tumour $\log_e 10$ cell kill assessment	Acute mucosal object < 49–52.5 EQD (Gy)	Late complications object < 70 EQD (Gy)
2 Gy/32Fr	64.0	21	11.50	54.1	64.2
1.7Gy/36Fr	63.0	23	11.05	51.2	60.0
2 Gy/35Fr	70.0	34	11.50	52.2	70.0
1.8Gy/39Fr	70.2	39	10.90	48.6	67.2
1.2 Gy/20Fr + 1.6Gy/Fr + 1.4Gy/20Fr +2Gy/4Fr	76.0	33	12.01	55.2	67.0
1.2Gy/36Gy + 1.5Gy/20Fr	73.2	37	11.00	49.0	63.6
1.3Gy/60Fr	78.0	39	11.60	52.3	67.1
1.3Gy/60Fr	78.0	42	11.30	50.3	67.1

Should be notice that *Tp* usually is shorter than the potential doubling time estimated before the tumour has got any cytotoxic therapy [80]. LQ model could be used for the prediction of *BED* per fraction in RT. It is known, that the biological effect of a physical dose depends on the dose rate, treatment time, fractionation scheme and character of the tissue. Report on the rate of repair in different tissues is necessary for choosing a proper interval time between radiation doses for certain situations. The interval time between each fraction has to be not longer than 3-6 hours according to which type of treatment schedule used [89].

As the patients' survival rate increase, oncologists usually meet difficulties of treatment due to late recurrence or secondary tumours located close to the primary irradiation site. The oncologist considering the re-irradiation of a location such as a thorax or a neck within which the SC has been earlier irradiated find out serious clinical issues sparing SC [89].

Relative effectiveness (RE) calculated, evaluating radiation damage of tissues in comparison with physical dose, related to fractionation schedule. It may be modified also by chemical, biological or genetic radiosensitisers or radio protectors, and particularly by repopulation or by dose rate, but the damage begins with a total dose RE. The damage occurs with cumulative dose relative effectiveness and it is related to Berendsen equation (8):

$$RE = (1 + d/(\alpha\ /\ \beta)) \tag{7}$$

$$BED\ =\ D\ x\ RE, \tag{8}$$

the total dose in 2Gy/Fr. is determined as the dose equal to the logarithmic survival of the cells.

Equivalent dose (EQD) in 2 Gy per fraction. Biologically equivalent dose (*EQD)* is normalised to 2Gy/Fr., using non-standard fractionation schedules (standard is, using non-standard fractionation schedules (standard is 2 Gy/Fr.)

$$EQD = D\ (d + \alpha/\beta)/\ (2 + \alpha/\beta) \quad (9)$$

How tumour *EQD* is related to the fractionation schedule (1Fr. and 2Fr. each day) is shown in (Fig. 14 and Table 9). It is observed, that extended the total treatment time should be as short as possible, evaluating the effectiveness of treatment radiobiology. For example, for head and neck radiotherapy dysphagia and mucositis are the main acute reactions, using an altered fractionation schedule. It was found, that the late complications could be avoided due to late BED, delivering 70 Gy of 2 Gy fractions (EQD3/2), which is equal to 117 Gy3, while the dose for the spinal cord is equal to 45–50 Gy (EQD2/2), with a late BED equal to 90–100 Gy2 [80]. BED of the used schedule for the overall dose required to the same log cell kill could be described as the overall dose in 2 Gy per fraction would be delivered to the same log-cell kill. Log cell kill was calculated by the simple linear-quadratic formula $log\ cell\ kill\ =\ \alpha d + \beta d^2$.

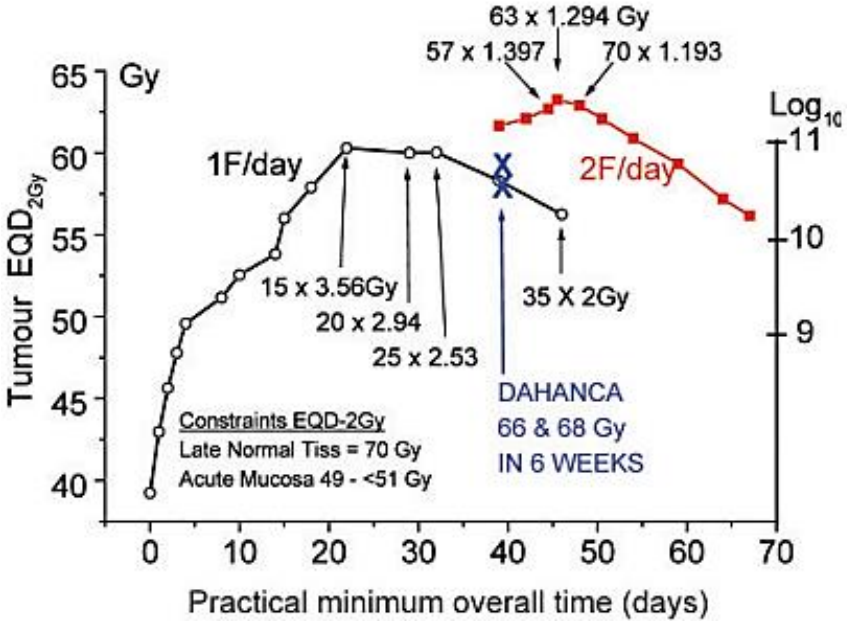

Fig.14. Illustration of the data for log-cell kill and tumour *EQD* [80]

Table 9. Recommendation ideal neck and head schedules [80]

Dose per fraction	Total dose
1.40 Gy/57Fr	79.80 Gy/45days
1.30 Gy/60Fr	78.00 Gy/48days
1.20 Gy/70Fr	84.00 Gy/89days
3.41 Gy/16Fr	54.56 Gy/23days
2.94 Gy/20Fr	58.80 Gy/28or27days
2.53 Gy/25Fr	63.25 Gy/32or31days

It was found, that dose per fraction, even so slightly changed, could be led to effective severe reactions, while prolonged overall treatment time reduced tumour control irradiating with equivalent 1–2 Gy per day [80]. Tumour local control depending on fractionation schedule led to both the actual repopulation doubling time *Tp* and kick-off time *Tk* (Table.10.). The strong schedules (1 and 2, Table 10) were connected to

boost and the hypofractionation of 61.2 Gy/68fr. The weak schedules (3 and 4, Table 10) were the standard 2Gy/Fr. in 7 weeks and the hypofractionated 1.6Gy/42Fr.

Table 10. The fractionation schedules: strong (one (HFr, hyper fractionated) and two) and weak (three (AFX, accelerated and split course) and four), (less dose per fraction than standard) [80]

No.	Fractionation schedule	Overall dose (Gy)	Total days	Tumour time corrected		Late complications EQD(Gy) (aim< 70)	Acute mucosal EQD Gy (<49-52.5)
				EQD (Gy)	Log_{10} Cell kill		
1	Hyper-fractions: 1.2Gy/68 Fr	81.6	45	73.0	11.1	66.6	51.0
2	concomitant boost, 1.8Gy/30Fr+1.5Gy/12Fr	72.0	39	72.4	11.0	67.8	49.2
3	split AFX, 1.6Gy/42Fr	67.2	39	65.8	10.0	61.7	43.8
4	Control 2Gy/35Fr	70.0	46	70.0	10.2	70.0	44.3

Similar data were observed for the practical overall time evaluation, related to a significant outcome for the equivalent late effects limitations and for their severe limitations of 51 Gy *EQD10/2*. This analysis explains how acute *EQD* (cycles) can follow the main recommendations due to the limitation level for the several days, extending the overall time (Fig. 15). The important practical outcome is that 2 Fr./day gives higher damage to the tumour than 1 Fr./day (with the same risk for the critical organs or normal tissues) [80].

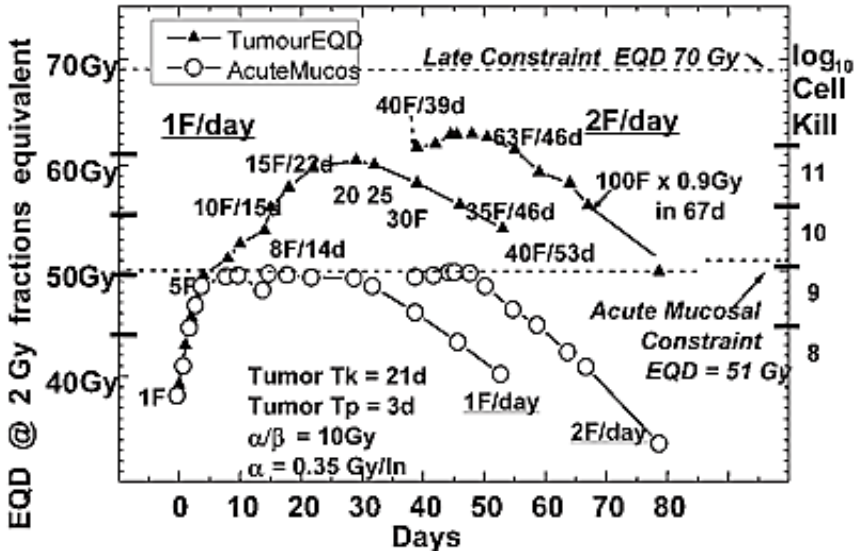

Fig.15. Tumour *EQD* and acute mucosal *EQD10/2* at or under 51 Gy is presented, evaluating 2 Fr./day and 4 Gy/1Fr [80]

G. Roger [90] reported the idea, that BED is a potential value in determining the best treatment planning way for rescheduling a treatment fractionation if the patient had a break and missed treatment session. So, BED is important when is needed to complete the radiation procedure for the rescheduled treatment, trying to get a sufficient dose per fraction and to finish the treatment without any losses of the disease control and healthy tissues or/ and organs at risk overdose.

S. Dische [91] reported a new so called incomplete or insufficient repair pattern of the tissues, evaluating intervals between irradiation (12 to 24 hour). This investigation was applied to evaluate the risk of the RM following continuous hypofractionated accelerated RT, considering modern trial data for the rat SC. The kinetics of the repair was explained as a continuous hyper fractionated accelerated RT and is related to a higher RM, than using equivalent dose delivered in traditional 2 Gy/Fr. It was found, that RM risk differs from 0.3 to 1.2% for hyper fractionated accelerated RT dose to the SC (total treatment dose was equal to 42 Gy). The continuous hyper fractionated accelerated RT experience is an important step in applying different fractionation schedules, evaluating how important long interval recovery of the irradiated of the SC for the monkey, guinea pig, rat and mouse [89]. A. Kathryn, [92] found that different factors influence the tolerance of SC during. Three cm region of lumbar SC of guinea pigs has been treated with 4.5Gy/5Fr. Pigs were irradiated with 40.5 Gy in 7 days, after 40 or 28 weeks, were re-irradiated with 4.5 Gy dose in 6-14 Fr. It was found, that around 8% of side effects were observed. J. Kleiboer, [93] studied the sensitivity of fractionation for the rat SC. All rats were irradiated with a 15 Gy dose (the first course), which represented about half of the effective dose (ED_{50}), while the second course of treatment was performed either at 6 months or 1-day delay after the initial treatment with a fractionated or single-dose irradiation. Different fractionation schedules are presented in (Table 11) for 1 day and six months after 15 Gy. It was observed, that after 6 months, the recovery after the first irradiation was approximately 45%.

Table 11. Functional factors and EQD50 for different fractionation schedules [93].

Irradiation	**ED_{50} (Gy)**			**Functional factors**	
	After 1 day	After 6 months		After 1 day	After 6 months
15 Gy	16.2	18.5	10 α Gy^{-1}	0.47	0.29
15 Gy +3Gy/Fr	56.6	-		-	-
15 Gy +4Gy/Fr	47.2	65.1	α/β Gy	2.3	1.9
15 Gy +6Gy/Fr	36.8	18.5	100 β Gy^{-2}	2.1	1.5

It is always an intriguing issue to find out the best outcome of the treatment, especially for re-irradiation procedures.

1.5 Summary of Literature review

Spine metastases (SM) induce neurological and physical complications, which can cause a poor quality of life. Conventional RT considers for uncomplicated painful spinal metastases. RT has been applied particularly to relieve pain for palliative patients. RT can minimize and control disease symptoms were observed in ~80% of cases, treated with radiotherapy. Approximately 40% of cancer cases are diagnosed with SM.

Therefore, it was noticed, that the predictive factors for palliative RT response have not been identified. The main limitation to the prescribed dose is healthy tissues and OARs. A linear-quadratic (LQ) model is applied to predict the BED in RT, which depends on fractionation, localization, the interval between irradiation procedures, the volume of the tumour and total dose. Different schedules of fractionation in RT evaluate repair related to a repopulation of the cells and spare of OARs. The idea of fractionated therapy is to ensure the effectiveness of the irradiation, at the same time minimizing the toxicity for the critical organs or OARs in the vicinity of the treated tumour.

Re-irradiation is one of the critical steps, evaluating possible side effects for the healthy tissues and OARs, which depends on the fractionation schedule.

2. Materials and methods

Recurrent disease (spinal metastasis) palliative radiotherapy was performed for the patient with a primary lung radiation case, using 10 different fractionation schedules (Table 12), trying to find the most appropriate schedule of the treatment.

Table 12. 10 different fractionation schedules used for primary and recurrent disease irradiation

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8	Case 9	Case 10
Primary irradiation procedure	6Gy/8Fr (48Gy)	6Gy/8Fr (48Gy)	6Gy/8Fr (48Gy)	6Gy/8Fr (48Gy)	6Gy/8Fr (48Gy)	7.5Gy/8Fr (60Gy)	7.5Gy/8Fr (60Gy)	7.5Gy/8Fr (60Gy)	7.5Gy/8Fr (60Gy)	7.5Gy/8Fr (60Gy)
Recurrent disease irradiation	3Gy/10Fr (30Gy)	4Gy/5Fr (20Gy)	5Gy/4Fr (20Gy)	8Gy/1Fr (8Gy)	7Gy/1Fr (7Gy)	3Gy/10Fr (30Gy)	8Gy/1Fr (8Gy)	7Gy/1Fr (7Gy))	5Gy/4Fr (20Gy))	5Gy/4Fr (20Gy)

Treatment planning. The treatment planning system (TPS) "Eclipse" was used for the dose calculation (Fig.16).

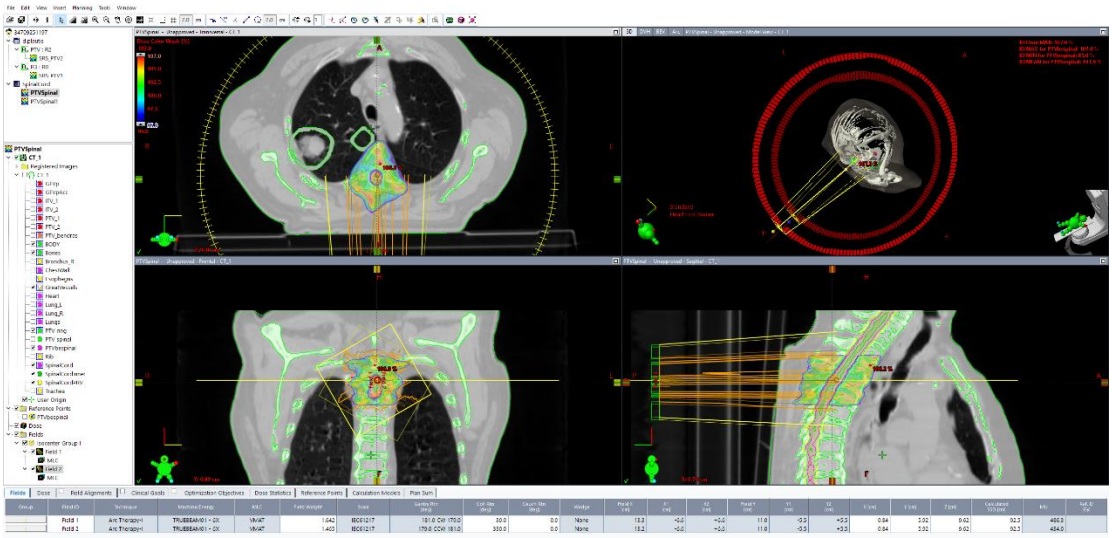

Fig. 16. TPS from Eclipse software

Two different plans for the second irradiation course (recurrent disease treatment) and 10 different fractionation schedules were chosen, trying to find the best option for the recurrent disease treatment.

The primary irradiation procedure was planned as stereotactic radiotherapy (SRT) procedure with two different fractionation schedules 6 Gy/Fr (8 fractions in total) and 7.5 Gy/Fr (8 fractions in total) (Table 12).

The second course (irradiation of recurrence disease) was planned, using volumetric modulated arc therapy (VMAT). The main irradiation data are: maximum energy 6 MeV (standardly used for SRS and VMAT treatment planning), 2 standard arcs (179°-181° and 181°-179°), prescribed dose for PTV differed from 95% to 107% [98]. Different fractionation schedules and different PTVs volumes were used for recurrent disease irradiation (spinal cord metastasis). Different PTVs volumes are known as

(PTV+SC) as a standard case (SC is involved in PTV region) and PTV-SC (with omitted SC) (Fig. 17)).

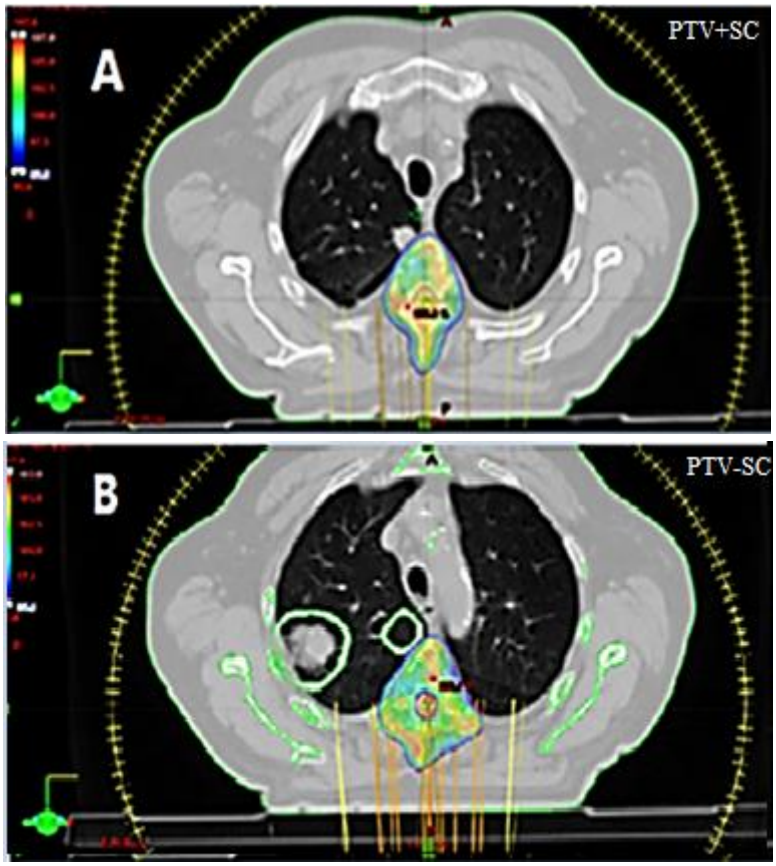

Fig. 17. A is a plan planned for PTV+SC, while B is a plan planned for PTV-SC

The main parameters of recurrent disease treatment plans are presented in Table 13.

Table 13. Main parameters used in treatment planning

Parameters	**Plan (PTV+SC)**	**Plan (PTV-SC)**
Energy	6MeV	
1ARC	181° - 179° (CW)	
2ARC	179° - 181° (CCW)	
collimator rotation	30° - 330°	
couch angle	0°	
Field weight	1.414 (1ARC) - 1.400 (2ARC)	1.642 (1ARC) - 1.465 (2ARC)
Total MU	836.7	920.3

2.1. Evaluation of the plans

Treatment plans were evaluated using different dosimetric parameters obtained from the DVH (Fig. 18 and Table 14) of the target and OARs as (more detailed description is presented in 1.2.1. section “The main treatment planning strategies”.

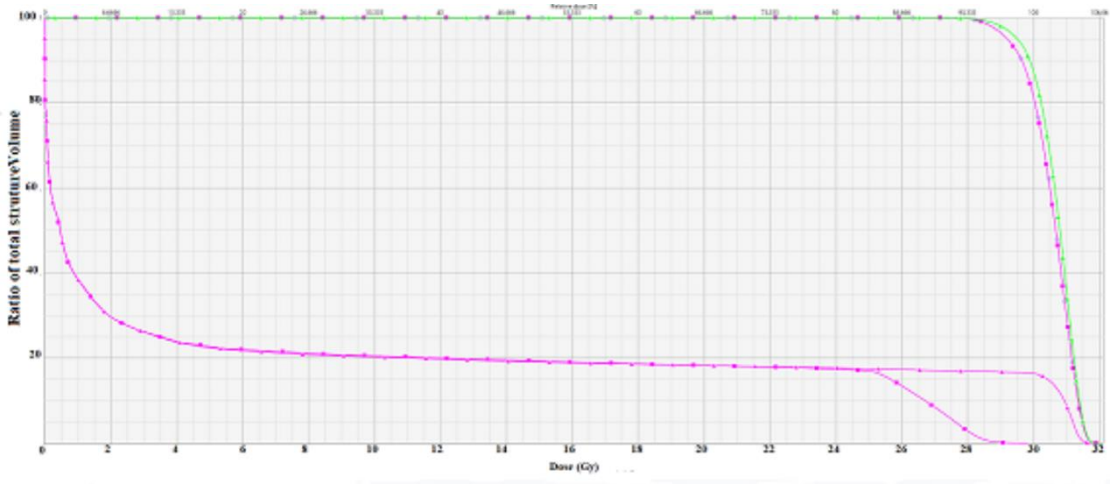

Fig. 18. DVH for a planPTV+SC and PTV=SC

Table 14. *DGI*, *DHI* and *DCI* for the PTV+SC and PTV-SC

Parameters	PTV+SC	PTV-SC
PTV	PTV+SC	PTV-SC
D5%	31.5003	31.475
D95%	29.5076	29.198
V50%	30.7978	30.6709
V100%	25.1847	27.4462

Dosimetrical criteria for the plan analysis:

- *DHI* – expressed by the minimum dose covers 95% of the planning object and is the minimum dose that covers 5% of the PTV. *DHI* values have been defined: *DHI* ≤ 2 treatment was considered to comply with the protocol. 2 < *DHI* <2.5- minor violation. *DHI* > 2.5- major violation.
- *DCI* - expressed by prescription isodose volume /and target covered by the prescription isodose volume. *DCI* values have been defined: *DCI* > 1 means irradiated target > target volume. *DCI* < 1 partially irradiated target volume. *DCI* = 1 ideal conformation. 2.5 *DCI* < 0.9 major violation. 0.9 < *DCI* < 1 minor violation. 1 < *DCI* < 2 comply with the treatment plan.
- *DGI* – where expressed by V50% and V100% means irradiation of 50 % and 100 %volume with a prescribed dose to the comparison between two isodose distribution plans.
- *BED* and *EQD* – is a measure of the effect response tissue with different fractionated radiotherapy in units expressed in (Gy). Where D total dose, d dose per fraction, *α/β* represent the property of irradiated tissue of the ratio for SC as reported from 1.6 to 5, according to the literature, the *α/β* value for the SC tissue was supposed to be 3 Gy. *EQD* Equivalent dose in 2 Gy fractions.

  Example of *BED* and *EQD* calculations:

  1. a) Plan with 60 Gy, 8fr, 7.5Gy/fr (before recurrent disease irradiation)

$$BED = D\,(1 + Fraction\ dose\ /\ \alpha/\beta) = 210\ Gy$$

$$EQD_2 = D\ (d\ +\ \alpha/\beta)\ /\ (2\ +\ \alpha/\beta)\ =\ 126\ Gy$$
$$D1cc\ (Gy)\ SC\ received\ 17.65\ Gy$$

b) Plan with 48 Gy, 8fr, 6Gy/fr (before re-irradiation)

$$BED\ =\ 144\ Gy$$
$$EQD_2\ =\ 86.4\ Gy$$
$$D1cc\ (Gy)\ SC\ received\ 17.01\ Gy$$

2. Recurrent disease irradiation was used 3 Gy per fraction (total treatment dose 30 Gy).

$$BED\ =\ 60\ Gy$$
$$EQD_2\ =\ 36\ Gy$$

3. Results and Discussions

The treatment plan for the primary disease was planned using a treatment planning system, using stereotactic radiotherapy (SRT) treatment planning technique (Fig. 19).

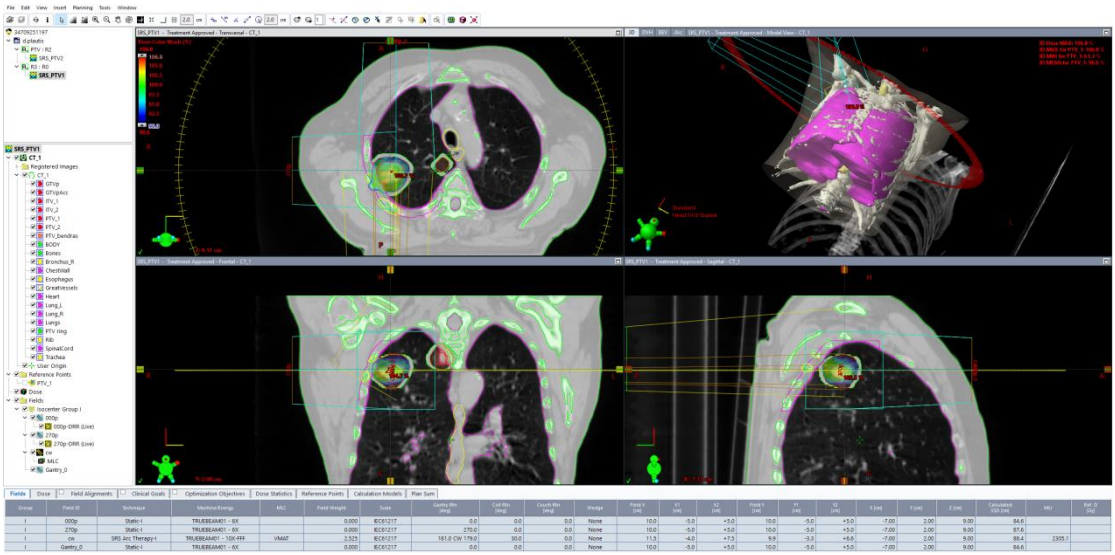

Fig. 19. Isodose distribution for the primary lung SRT procedure (planned using two different fractionation schedules (48 Gy (6 Gy/ 8 fr.) and 60 Gy (7.5 Gy/ 8 fr.)

Treatment plans for the recurrent disease were planned using computed tomography images, using different fractionation schedules 48Gy (6 Gy/ 8 fr.) and 60 Gy (7.5 Gy/ 8 fr.) for Primary irradiation procedure with 30 Gy (3 Gy/ 10 fr.), 8 Gy (8 Gy/ 1fr.), 7 Gy (7 Gy/ 1 fr.), 20 Gy (4 Gy/ 5 fr.) and 20 Gy(5 Gy/ 4 fr.) for recurrent disease irradiation. The Volumetric modulated arc therapy technique was chosen for the recurrent disease irradiation, trying to spare the spinal cord as much as possible irradiating spine metastasis (Fig. 20).

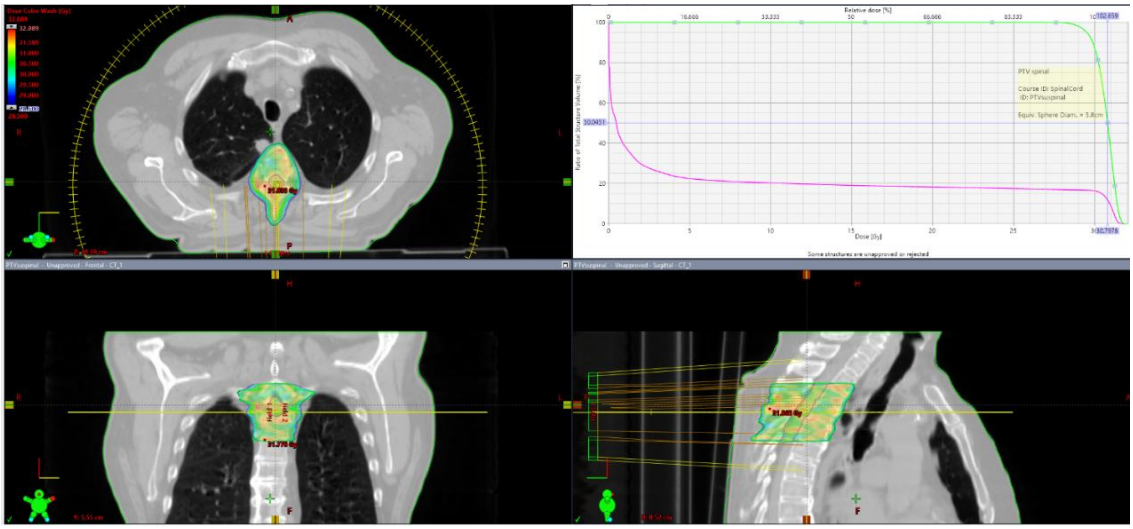

Fig. 20. Isodose distribution on coronal, sagittal and axial shows for one representative case. The DVHs lines are relative to PTV and SC

3.1. Dosimetric analysis of the plans PTV+SC and PTV-SC

Dose conformity index and dose homogeneity index. According to the Radiation Therapy Oncology Group (RTOG) [68]. Treatment plans ((PTV+SC) and plan (PTV-SC)) were estimated using *DCI*. Calculated *DCI* values were equal to 1.27 (PTV+SC) and 1.04 (PTV-SC). It is known that the ideal *DCI* is equal to 1, while a higher than 1 *DCI* value shows that the irradiated target exceeds the target volume and partially covers healthy tissues, or in near vicinity located OARs. *DCI* smaller than 1 indicates, that the target volume is partially irradiated, if the *DCI* values are within 2.0-2.5 or 0.9-1.0 it is supposed that there is an insignificant variation of the protocol, but if *DCI* is more than 2.5 and less than 0.9 it is related to significant inaccuracies and it does not follow the protocol, while if *DCI* values differ from 1 to 2, it means, that plans are following the protocol (1.27 (PTV+SC) and 1.04 (PTV-SC)).

Treatment plans were also estimated using calculated *DHI* values. It is known, that if *DHI* is equal to 1 the dose distribution of the plan is homogeneous if the value is between 2 to 2.5 minor inhomogeneity could be observed if it is more than 2.5 major inhomogeneity is characteristic for the plan. Analysing this research work data *DHI* values for PTV+SC and PTV-SC were equal to 1.06 and 1.07, respectively. It means, that dose distribution in the target volume is homogeneous (Table 15).

Table 15. *DHI* and *DCI* for the PTV+SC and PTV-SC

Parameters	PTV+SC	PTV-SC
DHI	1.06	1.07
DCI	1.27	1.04

Dose gradient index. Plan (PTV-SC) showed a significant rapid dose falloff outside the target volume than plan (PTV+SC). Calculated *DGI* values were equal to 1.22 (PTV+SC) and 1.11 (PTV-SC). This information is very important for recurrent disease irradiation, such as spine metastases, trying to spare it as much as possible.

3.2. Radiobiological analysis of the primary and recurrent disease irradiation

Biologically effective dose and equivalent dose. The BED calculated values are presented in Table 16. It was found, that using fractions of 48 Gy (6 Gy/ 8 fr.) for the first course (radical treatment), BED_I= 86.4 Gy, while using 5 different fractionation schedules (30 Gy (3 Gy/10 fr.) BED_{II}= 36 Gy; 20 Gy (4 Gy/5 fr.) BED_{II}= 28 Gy; 20 Gy (5 Gy/4 Fr) BED_{II}= 32 Gy; 8 Gy (8 Gy/1 fr.) BED_{II}= 17.6 Gy and 7 Gy (7 Gy/1 fr.) BED_{II}= 14 Gy) for the second course (palliative radiotherapy) BED_{II} differed from 14 Gy up to 36 Gy (Table 16). BED_{sum} calculation showed that Case2÷Case5 are within tolerance limits, while the Case1 risk factor of myelopathy was equal to 1.

Table 16. Dose prescription and cumulative BED for different fractionation schedules cases (1-5)

	Parameters	**Case1**	**Case2**	**Case3**	**Case4**	**Case5**
First irradiation	Dose per fraction (Gy)	6	6	6	6	6
	BED_I (Gy2)	86.4	86.4	86.4	86.4	86.4
	D_I (Gy)	48	48	48	48	48
Re-irradiation						
	Dose per fraction (Gy)	3	4	5	8	7
	D_{II} (Gy)	30	20	20	8	7
	D_{tot} (Gy)	78	68	68	56	55
	BED_{II}	36	28	32	17.6	14
BED_{sum}	$BED_I + BED_{II}$ (Gy2)	122.4	114	118.4	104	100.4
Risk factor		1	Tolerance	Tolerance	Tolerance	Tolerance

Five additional cases (Case6÷Case10), evaluating the influence of fractionation schedule on the rate of myelopathy, were studied. The main difference of these additional cases in comparison with Case1÷Case5, that was used the different the first irradiation course fractionation 60 Gy (7.5 Gy/8 fr.), while for the second-course irradiation fractionation schedules were the same. The main calculation results are presented in Table 17. Analysing these results were observed, that the risk factor for these studied cases differed from 2 to 5. It is known, that the risk score differs from 0 (BED ≤ 120 very low risk) to 9 (BED > 200 very high risks) and the risk of myelopathy equal to 5-factor risk (BED > 160) means high risk, while 1-factor risk (BED > 120) means low risk.

Table 17. Dose prescription and cumulative BED for different fractionation schedules cases (6-10)

		Case 6	**Case 7**	**Case 8**	**Case 9**	**Case 10**
1st irradiation	Dose per fraction (Gy)	7.5	7.5	7.5	7.5	7.5
	BEDI (Gy2)	126	126	126	126	126
	DI (Gy)	60	60	60	60	60
2nd irradiation						
	Dose per fraction (Gy)	3	8	7	4	5
	DII (Gy)	30	8	7	20	20
	Dtot (Gy)	90	68	67	80	80
	BEDII	36.0	17.6	14.0	28.0	32.0
BEDsum	BEDI + BEDII (Gy2)	162.0	143.6	140.0	154.0	158.0
Risk factor		5	3	2	4	4

The results of all 10 cases showed, that for Case1 and Case6÷Case10 the risk of myelopathy varied from low to high. The lowest risk (1-factor risk (BED > 120)) was observed for the Case1 (1st irradiation course fractionation schedule: (48) 6Gy/8Fr And the 2nd irradiation course fractionation schedule (30Gy) 3Gy/10Fr), the highest risk (5-factor risk (BED > 160)) was observed for the Case6 (1st: (60Gy) 7.5Gy/8Fr; 2nd: (30Gy) 3Gy/10Fr), while for the other Case7÷Case10 risks differed from 2 to 4 (intermediate risk of myelopathy) (Table 17 and Table 18).

Table 18. The risk evaluation of the myelopathy

No. of the cases	BEDsum (Gy)	Risk factor
1	122.4	1
6	162.0	5
7	143.6	3
8	140.0	2
9	154.0	4
10	158.0	4

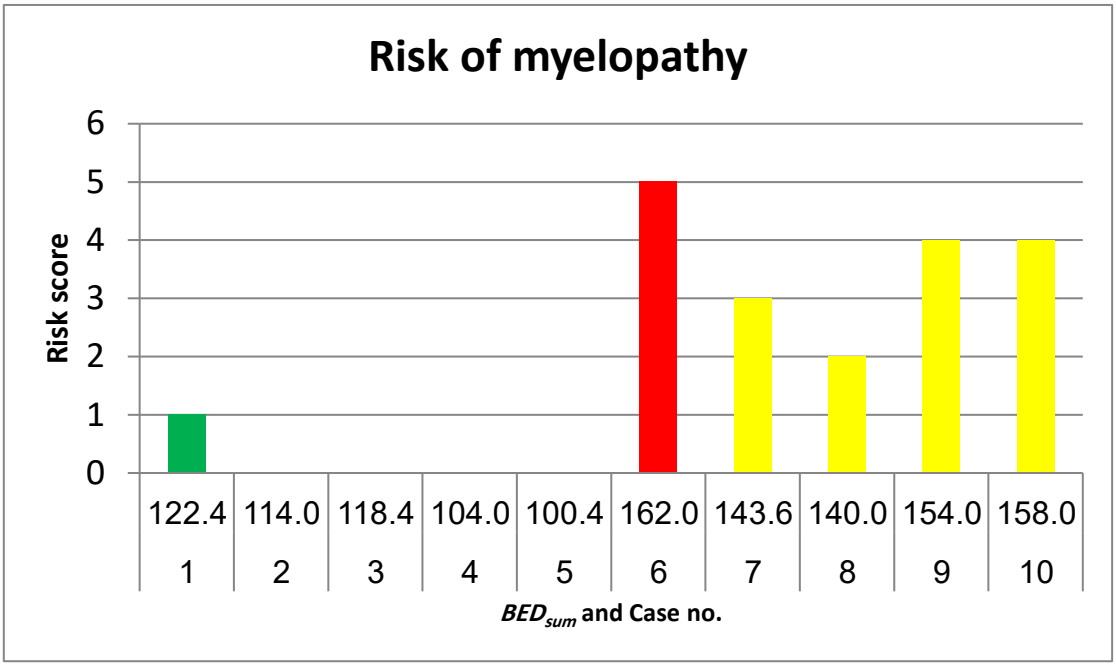

Fig. 21. BED_{sum} and risk of myelopathy RM for the all analysed cases

The same tendency was observed for a continuous hyperfractionated accelerated RT, with doses of 46.6 Gy, 48.3Gy, 45.2Gy, and 46Gy at the Mount Vernon Hospital [33]. SC reactions for some of the patients were unexpected, due to this reason radiobiological calculations of the BED was used for rescheduling fractionation for these patients, evaluating possible risks [33]. J. Van Dyk et al. [101] study results showed, that risk of RM for hyperfractionated accelerated RT was significantly higher than expected and the side effects of neurological disorders were registered as well.

Re-treatment or treating recurrent disease (spine metastasis) in close vicinity of the primary tumour irradiation spinal cord (tolerance dose is equal to a maximum of 45 Gy) dose has to be taken into account, especially as it was observed it depends on the dose of the primary tumour irradiation prescribed dose. J. Albert [103] study showed, that the overall tolerance of SC may be approximately 130 % of the tolerance dose for the initial irradiation. Also, it is known, that after 2 years of irradiation with 45 Gy of SC, spinal cord recovery was less than 50% [104].

Mancosu, Pietro et al. [99] registered less than 15% of cases with some motor function side effects, whereas in 36% of cases motor function were observed. This means, that the treatment with a BED_{tot} less than 120 Gy2 showed a sufficient decrease risk of

myelopathy. Nevertheless, it was shown, that when the interval between the first and the second courses was less than 6 months, the risk of myelopathy increased. Therefore, the risk of RM depends on the calculated *BED* for the SC, which takes into consideration both the dose per fraction and the total radiation dose. The SC is known, as the main dose-limiting organ during RT radiation or re-irradiation. The larger dose per fraction, the higher probability of RM could be observed [89].

Therefore, the most appropriate fractionation schedules could be used for this patient primary and recurrent disease (spine metastasis) irradiation following Case2÷Case5, then radical treatment is performed with a lower prescribed dose per treatment (48Gy (6 Gy/8 fr.) and the palliative recurrent disease irradiation with 20 Gy per treatment (5 Gy/ 4 fr. and 4 Gy/ 5 fr.) and with single-fraction irradiation (7 Gy/ 1 fr. and 8 Gy/ 1 fr.) (Table 16 and Table 19). These fractionation schedules could be recommended for the patient's treatment with the tolerable risk of myelopathy. It is known that a single dose of 8 Gy/ 1 fr. and 7 Gy/ 1 fr. is the shortest way and from the radiobiological point of view, multiple fractions as 20 Gy/ 5 fr.; 30 Gy/ 10 fr. are equivalent to a single 8 Gy/ 1 fr. and 7 Gy/ 1 fr. for the palliative patients irradiation [100]. So, the single fraction of irradiation could be really effective and sufficient for palliative therapy.

Table 19. Cases without risk of the myelopathy

No. of the cases	BEDsum (Gy)	Risk factor (BED ≤ 120)
2	114.0	0
3	118.4	
4	104.0	
5	100.4	

4. Conclusions

1. The volumetric modulated arc therapy technique seems to be a good choice for spine metastasis irradiation, trying to spare spinal cord additionally (PTV-SC). It was found, that for the plan PTV+SC (PTV and SC are delineated as one structure), the maximum received spinal cord dose was equal to 31.875 Gy, while for the PTV-SC plan it was equal to 29.818 Gy.

2. It was observed, that both treatment plans (PTV+SC and PTV-SC) planned for the metastatic disease irradiation could be successfully used ensuring efficiency of homogeneity ((PTV+SC) (1.06) and (PTV-SC) (1.07)) and conformity ((PTV+SC) (1.27) and (PTV-SC) (1.04)) of the target coverage.

3. Analysing biologically effective dose was observed, that 4 cases were in tolerance level, without any risk myelopathy ($BED < 120$), while for the other 6 cases risk myelopathy was low, intermediate or even high ($BED > 120$). It was found, that all the cases (Case6-Case10) with a $BED > 120$ were for the dose fractionation schedules, then the primary disease irradiation was performed with fractionation of 60 Gy (7.5 Gy/ fr.), just one of the cases (Case1) for the fractionation 48 Gy (6.0 Gy/ fr.) was out of tolerance level with a low risk of myelopathy (risk factor was equal to 1). However, the higher dose per fraction leads to a higher *BED* and a higher risk for the healthy tissues.

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