EVALUATION OF NOVEL RADIOTHERAPY APPROACHES IN BRAIN TUMOUR MANAGEMENT

PhD Thesis

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Szeged

2021

List of full papers that served as the basis of the PhD thesis

I) **Dobi Á**, Darázs B, Fodor E, Cserháti A, Együd Z, Maráz A, László S, Dodd L, Reisz Z, Barzó P, Oláh J, Hideghéty K. (2020) Low Fraction Size Re-irradiation for Large Volume Recurrence of Glial Tumours. Pathol Oncol Res. 26(4):2651-2658. *doi: 10.1007/s12253-020-00868-2*

(IF: 2.826, Q2)

II) **Dobi Á**, Fodor E, Maráz A, Együd Z, Cserháti A, Tiszlavicz L, Reisz Z, Barzó P, Varga Z, Hideghéty K. (2018) Boost Irradiation Integrated to Whole Brain Radiotherapy in the Management of Brain Metastases. Pathol Oncol Res. 2020 26(1):149-157. *doi: 10.1007/s12253-018-0383-y* (Epub 2018 Jan 17.)

(IF: 2.826, Q2)

List of other full papers

I) Végváry Z, Darázs B, Paczona V, **Dobi Á**, Reisz Z, Varga Z, Fodor E, Cserháti A, Oláh J, Kis D, Barzó P, Hideghéty K. (2020) Adaptive Radiotherapy for Glioblastoma Multiforme - The Impact on Disease Outcome. Anticancer Res. 40(8):4237-4244. *doi:10.21873/anticanres.14425*

(IF: 1.994, Q2)

II) Darázs B, Ruskó L, Végváry Z, Ferenczi L, **Dobi Á**, Paczona V, Varga Z, Fodor E, Hideghéty K. (2019) Subventricular zone volumetric and dosimetric changes during postoperative brain tumour irradiation and its impact on overall survival. Phys Med. 68:35-40. *doi: 10.1016/j.ejmp.2019.10.039*

(IF: 2.485, Q1)

III) Rusz O, Kószó R, Dobi Á, Csenki M, Valicsek E, Nikolényi A, Uhercsák G, Cserháti A, Kahán Zs. (2018) Clinical benefit of fulvestrant monotherapy in the multimodal treatment of hormone receptor and HER2 positive advanced breast cancer: a case series. Oncotargets and Therapy 11: 5459-5463. *doi: 10.2147/OTT.S170736*

(IF:3.046, Q2)

IV) Valicsek E, Kószó R, **Dobi Á**, Uhercsák G, Varga Z, Vass A, Jebelovszky É, Kahán Zs. (2015) Cardiac Surveillance Findings During Adjuvant and Palliative Trastuzumab Therapy in Patients with Breast Cancer. Anticancer Res. 35(9): 4967-73.
(IF: 1.895, Q2)

V) Hideghéty K, Cserháti A, Besenyi Z, Zag L, Gaál S, Együd Zs, Mózes P, Szántó E, Csenki M, Rusz O, Varga Z, **Dobi Á**, Maráz A, Pávics L, Lengyel Z. (2015) Role of 18FDG-PET/CT in the management and gross tumour volume definition for radiotherapy of head and neck cancer; single institution experiences based on long-term follow-up. Magy Onkol. 59(2):103-10.
(Q3)

VI) Hideghéty K, **Dobi Á**, Mózes P, Cserháti A. (2014) Sürgősségi sugárkezelés az onkológiában. Klin Onkol. 1: 4: 273-280.

VII) Uhercsák G, **Dobi Á**, Gyulai R, Oláh J, Kaizer L, Ormándi K, Cserháti A, Lázár G, Farkas Gy, Kahán Zs. (2013) Management of the case of a young female patient with multiple malignancies and germline R24P CDKN2A gene mutation. Journal of Cancer Therapy 4: 7A 18-20. *doi:10.4236/jct.2013.47A004*

VIII) **Dobi Á**, Kelemen Gy, Kaizer L, Weiczner R, Thurzó L, Kahán Zs. (2011) Breast cancer under 40 years of age: increasing number and worse prognosis. Pathol Oncol Res. 17(2):425-8. doi: *10.1007/s12253-010-9305-3*
(IF: 1.366, Q2)

Cumulative impact factor (full papers) = 16.438

1. Introduction

Brain tumours are arising from different cells of the central nervous system or originating from various primary cancers all over the body. The incidence of gliomas is rising, peaking between the fifth and sixth decades of life. The same steadily increasing tendency can be observed in the incidence of brain metastases (BMs), ranging 9-40% worldwide, alongside the improved efficacy of systemic treatments, providing longer survival for cancer patients in disseminated status. The treatment of primary and secondary brain tumours is highly challenging due to the special characteristics of CNS neoplasms. The prognosis of the patients with glioblastoma or with intracranial metastases remained dismal in spite of all common interdisciplinary efforts. On the other hand, due to the vulnerability of the CNS, longer survivals frequently affected by the serious consequences of the tumour and of exposing the brain to medical interventions, including surgery, radiotherapy and chemotherapy.

Therefore we focused our research on introduction and evaluation of novel radiotherapy approaches in the complex management of primary and secondary brain tumours.

1.1 Glial brain tumours

Gliomas, with incidence of 5/100 000 in adults, are the most common primary central nervous system malignancies, peaking between the fifth and sixth decades of life. After initial multimodal treatment, at least 70% recurrence rate of gliomas can be expected. By surgical therapy alone, the disease has a very poor prognosis (median survival 4-6 months), whereas surgery accompanied by radiotherapy (RT) ameliorates the median survival data to 8-9 months. Together with concomitant and sequential temozolomide (TMZ), an alkylating agent crossing through the blood brain barrier, better median survival values can be expected, such as 15 months for glioblastomas, or even 2-5 years for anaplastic gliomas.

In the case of recurrence with its considerable limitations, surgical treatment has the highest efficacy. As for other low grade and grade 3 cases, TMZ is the treatment of choice, if it was not administered during the initial management. Thereafter and for GBM second-line systemic treatment (such as chemo- or biological therapy) and re-irradiation is optional, in the lack of standardised treatment for recurrent gliomas. In the first part of the thesis, the

prospectively implemented 32 Gy re-irradiation in 20 fractions was evaluated in order to confirm the feasibility and to investigate the outcome influencing factors and potential benefit for patients with recurrent glial tumour after the first/second line tumour management.

1.2 Brain metastasis

Alongside the improved efficacy of systemic treatments, the incidence of brain metastases (BMs) steadily increases, ranging 9-40% worldwide. The overall prognosis remains poor: without any treatment 1-2 months, with palliative methods, 4-6 months of median survival can be expected with WBRT, depending (1) on the age and functional status of the patient, (2) the extent of the underlying systemic disease, and (3) the number of metastases.

In case of multiple BMs, palliative whole-brain irradiation (WBRT) is usually performed with the dose of 10x3 Gy, whilst the cases with less than three metastatic lesions (i.e. oligometastases) are considered for surgery and/or radiosurgery with or without WBRT.

In the case of multiple and/or large volume brain metastases, if the extracranial disease could be well controlled by means of simultaneous WBRT with < 2.5 Gy/fraction and focal boost to each metastatic lesion in 15 fractions.

In the present thesis we summarise our results on two separate clinical investigations addressing relevant clinical questions on enhancement of radiotherapy for patients with recurrent primary brain tumours, and with brain metastases.

2. Aims of the thesis

In the present thesis,

1) we aimed to investigate
   - the feasibility of re-irradiation with low fraction size in large volume recurrent gliomas,
   - the safety and clinical efficacy of re-irradiation for the patients affected, and
   - the clinical factors influencing the outcome of re-RT.

2) Our goal was by introducing the SIB (15x2.2 Gy WBRT+ 15x0.7 Gy boost) into the management of brain metastases to find a balance in improving the survival with dose escalation to the macroscopic metastases, maintaining the intracranial control and reducing the probability of treatment-related cognitive decline; meanwhile keeping the treatment duration reasonable for patients even with multiple brain metastases.
   In this thesis the outcome of escalated dose irradiation (SIB and WBRT+boost) was compared to WBRT in order to evaluate
   - whether the above defined main goal could be achieved in real-life clinical setting;
   - whether the applicability and safety of dose escalation for radiotherapy of brain metastases could be proven;
   - the patient groups with the highest benefit from SIB according to the primary tumour;
   - further clinical factors which provide improved outcome for appropriate patient selection; and
   - whether this concept is also feasible for patients with declined performance status.

3. Re-irradiation in the management of glial tumours

3.1 Patients

Between 2007 and 2018, at the Department of Oncotherapy, altogether 55 patients with recurrent glial tumours were subjected to re-irradiation. The whole present study was carried out according to the ethical permission No. 4209/2018-SZTE, issued by the Ethical Committee of our University.

The initial care consisted of surgery in each case. The patients with grade 2 and grade 3 brain tumours received radiotherapy only postoperatively and for GBM we applied adjuvant chemoradiation therapy followed by temozolomide monotherapy up to progression. Magnetic resonance imaging (MRI) were performed three monthly. Disease progression was defined independently by two experts. At the time of diagnosis, the tumour grading was based on histological assessment. At the time of re-RT, histological evaluation was performed only in the re-operated cases, in the case of the remaining patients (without re-operation), the grading was based on clinical and radiological evaluation. The majority of the patients (32 over 23) received bevacizumab therapy.

3.2 Method of re-irradiation

The re-irradiation volume was defined on the basis of planning CT (computed tomography) and MRI fusion. Patients were immobilised with a 3-point thermoplastic mask (ORFIT Industries, NL). The planning target volume encompassed the GTV (gross tumour volume) plus 0.3-1 cm margin. The re-RT dose was 32 Gy in 1.6 Gy daily fractions in all cases, in order to avoid serious neurotoxicity. Dependent on the location and extent of the recurrent glioma, 3 DCRT or IMRT or VMAT (Rapid Arch) therapy-plans (VMAT) were generated.

3.3 Management of side effects during radiotherapy in both studies

During brain irradiation patients received 12 mg methyl-prednisolone for prevention of brain oedema (with PPI/H_2 receptor inhibitor and potassium chloride, if needed), with gradually decreased dosing after radiotherapy. The dose of methyl-prednisolone was adjusted according to the symptoms of intracranial pressure elevation due to brain oedema.

3.4 Clinical data and statistical analysis of re-irradiation

We assessed retrospectively the overall survival (OS) from the diagnosis, and from the first day of the re-irradiation according to the, age, Karnofsky performance score (KPS), primary tumour grade and histopathology type, the primary tumour removal, size of GTV, size of PTV, time interval between two irradiations, time elapsed between diagnosis and 2nd RT, second line bevacizumab treatment. The data were evaluated by Kaplan-Meier statistical analysis and COX regression was used for univariate, as well as multivariate analysis.

3.5 Patients characteristics at re-irradiation

The mean age of the population at the time of the primary diagnosis detection was 39 years (range: 11-71 years). The mean age at the time of the re-irradiation was 42 years (range: 13-72 years). The average time interval between the diagnosis and re-irradiation was 47.4 months (range: 7.3-228 months) first and the re-irradiation was 36 months (range: 7.7-232 months) respectively.

Variables	No. of the patients
Number of the patients	55
Sex	
Male	27
Female	28
KPS	
>70 %	22
≤ 70%	33
Primary histopathology type	
astrocytoma grade 2	15
oligodendroglioma grade 3	6
anaplastic astrocytoma grade 3	6
glioblastoma multiforme	28
Salvage surgery	23
Prior temozolomide treatment	55
MGMT methylation status	
methylated	18
unmethylated	9
unknown	28

Table#1 Characteristics of re-irradiated patients.

3.6 Results

The most important factors significantly influencing the outcome of re-RT were the time interval between the diagnosis and re-RT, histology grade, GTV, and KPS at the re-irradiation.

Variable	n	OS (months) from initial diagnosis	± SE	p-value
entire group	55	42.6	2.6	
initial histopathology type				
grade 2	15	114.8	40.2	
grade 3	12	52.2	9.8	
grade 4	28	30.7	1.3	**p<0.001***
Variable	**n**	**OS (months) from re-RT**	**± SE**	**p-value**
entire group	55	8.37	1.9	
histopathology type at re-RT				
grade2 (n=12) + grade3 (n=14)	26	10	1.2	
grade 4	29	6	2	**p=0.031***
GTV re-RT mean 118 cm^3				
≤ mean	29	12.9	3.9	
> mean	23	5.5	0.3	**p=0.006***
KPS at re-RT				
≤70%	33	5.6	0.7	
>70%	22	10.4	1.9	**p=0.009***
Time between diagnosis (DG) and re-RT				
≤47 months	18	6.7	1.6	
>47 months	37	10.2	0.7	**p=0.029***
Time between the 1^{st} and the 2^{nd} RT				
≤37 months	31	6.7	1.5	
>37 months	24	10.2	3.7	**p=0.05***
PTV re-RT 316 cm^3				
≤ mean	33	10.1	1.5	
> mean	22	5.5	0.4	p=0.246
Age at re-irradiation				
≤40 year	27	8.3	2.2	
>40 year	28	6.6	2.7	p=0.704
bevacizumab therapy before re-RT				
no	32	6.5	1.1	p=0.35
yes	23	10.2	0.3	

Table#2 Survival data. Asterisk denotes significant difference (p≤ 0.05),In 3 cases, the former GTV data were not available due to transfer incompatibility to the new treatment planning system.**

3.7 Discussion

In our study, significant predictors for a longer survival after re-RT were the better performance status at re-RT, the longer interval from the diagnosis to re-RT and lower tumour grade both at diagnosis and at re-RT. The age at re-RT proved not to be a prognostic factor, however, the mean age was below 40 years. The tumour size (i.e. GTV) was one of the most significant factors for the prognosis of our patients, whilst the PTV exhibited no significant relationship to the OS. Recurrent tumour volume remained the strongest factor in multivariate analysis (p=0.038) and the time between the 1st and the 2nd RT (p=0.05). In our patient group, the median survival according to the histopathological grade was higher than in other reported studies (the median survival is around 55-60 months for grade 2 and 18-26 months for grade 3 tumours). Due to the therapy, amelioration of neurological signs and KPS were experienced in 58% of our patients. Control radiological imaging detected stable disease or partial remission in 44 cases (78.6%).

4. Radiotherapy of brain metastases

4.1 Patients

Between 2005 and 2013, at the Department of Oncotherapy, altogether 468 patients with BMs (arising from various primary malignancies) were subjected to palliative skull irradiation. For the present study, the ethical permission (No. 886/2006) was issued by the Ethical Council of the Faculty of Medicine, University of Szeged.

4.2 Methods of brain metastasis

The traditional palliative approach of 10x3 Gy WBRT (EQD2 37.5 Gy) was applied for 195 cases (Group A); in 273 cases WBRT combined with boost irradiation were performed. In addition to the 10x3 Gy /18x2Gy WBRT boost dose of 10x2 Gy (EQD2 57,5 Gy/ 56 Gy) to the surgical cavity (if the metastasis had been removed), or to the metastatic lesions for patients in good PS and/or better life expectancy were performed (Group B). Later, simultaneous integrated boost irradiation (SIB: 15x2.2 WBRT+ 15x0.7 boost, (WBRT EQD2 33,4Gy, metastasis EQD2 46.8 Gy) (Group C) had been given whenever it was applicable

with 3D conformal technique planned by XIO TPS. Boost volume was defined on the basis of planning CT and MRI fusion.

4.3 Analysis of the data

Retrospective assessment of overall survival (OS) according to the recursive partitioning analysis (RPA), Karnofsky performance score (KPS), number of metastases, metastasectomy, localisation and histological features of primary tumour was carried out. The data were evaluated by Kaplan-Meier statistical analysis. Multi-variance analysis of the prognostic factors was performed using the Cox proportional hazard regression model.

4.4 Results

Doubling of the survival time was detected in the escalated dose groups over the Group A ($p<0.001$). The OS was 3.2-3.3 months for all tumour types, if only WBRT was applied. OS difference was significant in the case of lung cancer and malignant melanoma between patients treated by WBRT only vs. those receiving escalated total dose. OS difference has not reached the statistical significance level for breast, kidney and gastrointestinal tumours.

Both in the case of low number of the BM (1-3) and in the case of multiple (>4) metastases, the OS difference between the 30 Gy and escalated groups were significant. If surgery was performed, statistically no OS benefit could be proven from the boost dose ($p=0.48$), in contrast to the significantly prolonged survival without neurosurgical removal ($p=0.002$).
The longer treatment with higher total dose (SIB or consecutive boost to WBRT) was significantly more beneficial for the survival of patients both in good and in poor condition.

As for the RPA 2 and RPA3 categories, the OS was significantly prolonged in case of patients received escalated dose, 4.0 vs. 7.7 months; ($p=0.002$) in class RPA2 and 2.6 vs. 4.2 months; ($p<0.0001$) in the class RPA 3. If no surgery was performed the SIB resulted in significantly longer OS of 6.5 months in contrast to the 3.9 months survival of the patients received WBRT only for class 1-2 ($p=0.05$).

In RPA class 3, the addition of both the consecutive or delayed boost and the simultaneous boost to the WBRT resulted in significant OS benefit ($p=0.001$). The OS of patients with KPS>70% and even the OS of patients with KPS<70% were equally proven better in case of

those receiving the escalated dose vs. WBRT without boost (9.4 vs. 4.2 months; $p<0.0001$ and 4.2 vs. 2.6 months; $p<0.0001$; respectively).

The multi-variance analysis yielded three, mutually independent prognostic factors for survival: RPA, surgery and therapy method.

4.5 Discussion

Our aim was to find a balance in improving the survival with dose escalation to the macroscopic metastases, maintaining the intracranial control and reducing the probability of treatment-related cognitive decline; meanwhile keeping the treatment duration reasonable for patients even with multiple brain metastases. Therefore, we have applied conventional fractionation for 3D conformal whole brain and consecutive boost irradiation using the classical conventional fractionation scheme, 18x2Gy+10 to 12x2Gy up to 56-60 Gy total dose for patients with relatively longer life expectancy. Later we have introduced a shortened regime of 15x2.2 Gy whole brain irradiation and simultaneously 0.7 Gy was delivered to the tumour or tumour bed after surgery. This technique allowed encompassing even 10-12 metastases into the boost volume, and lasted only 3 weeks, considered reasonable for patients with poorer condition.

In contrast, our retrospective analysis confirmed the significant survival benefit for the whole group of patients including multiple metastases from intensified treatments without difference between the long and the shortened (SIB) regimes. This relevant survival difference was achieved not only for oligometastatic diseases, but for patients with multiple metastases (>4), as well. No serious adverse event was detected during the treatment.

Our study has evident limitations. Its retrospective nature and consequent patient heterogeneity may have biased the results. Our effort to compare the outcome of the different treatment schemes by retrospectively dividing the patient population amongst similar prognostic groups could not completely compensate the lack of prospective patient enrolment. Furthermore, no objective assessment of late neurotoxicity has been performed. However, this study has several strengths. The large number of the patients allowed relevant statistical evaluation, and the three treatment approaches were clearly defined. Our aim to study the feasibility of SIB in 15 fractions even for patients, who cannot be enrolled into prospective clinical trials due to their bad prognostics, could be investigated. Conclusion could be drawn

from this analysis on the applicability of lower WBRT fraction dose approach with a boost RT.

Therefore, considering all the limitations, our study on large patient series in RPA2 and RPA3 categories seems to document survival advantage of intensified irradiation schemes, which has high importance for the daily clinical decisions, even for patients in poor condition (KPS<70%).

5. Findings and conclusion

5.1 Main points derived from the analysis of glial tumour re-irradiation

As for the first goal of the present thesis, during the optimising of radiotherapy, I investigated the question, whether the re-irradiation of glial tumours is plausible while keeping the adverse effects and complications at theirs minimum and respecting the quality of life of patients at the same time. The literature is not unanimous about the proper target volume size of the recurrent tumour to be contoured during radiotherapy planning. In case of reoperation, by encompassing the surgical cavity into the target volume, the possibility of large volume re-irradiation has been also examined, in addition to how to choose the appropriate patient group for re-irradiation.

(1) Smaller recurrent tumour size, better PS, longer intervals from the diagnosis to re-RT and also from primary RT to the re-RT, and lower tumour grade predict better outcome from re-RT.

(2) No radiation-associated serious adverse events were observed and the re-RT improved the performance status and neurologic symptoms in the majority of the cases.

(3) Re-irradiation with low fraction dose in large volume recurrent gliomas proved to be safe and seems to be clinically beneficial in selected patient group.

5.2 Main points of dose escalation in the radiation treatment of brain metastases

In the second part of the current thesis, we aimed to define the right total radiation dose for brain metastases and whether boost treatment is necessary in these cases. Further, if we opted for boost treatment, we investigated whether should it be performed together with WBRT or with a certain latency. The shortest delivery of WBRT+boost using the technique of SIB proved to be the most efficient, and gentle method.

(1) From our large series of evaluation, the applicability and safety of intensification of RT in the management of brain metastases could be confirmed.
(2) Patients with primary lung cancer or melanoma malignum achieved significant benefit from SIB.
(3) For RPA2, 3 and if no metastasectomy was performed, the higher total dose to the metastases yielded increased OS.
(4) The RT intensification improved the outcome of the total patient group suffering from brain metastases.
(5) The concept of dose escalation proved to be feasible and beneficial for patients with good and declined performance status equally.

6. Acknowledgements

First of all I am most grateful to my supervisor, ***Professor Katalin Hideghéty***, whose encouragement and generous support helped me in the completion of this thesis. Her patience, guidance and motivation helped me all the time during the research and writing this dissertation.

I wish to express my special thanks to ***Professor Zsuzsanna Kahán*** the former, and to ***Professor Judit Oláh,*** the current director of the Department of Oncotherapy, University of Szeged, who provided excellent working condition for me at the institute.

I would like to express my sincere gratitude to ***Ms Barbara Darázs*** and ***Zoltán Varga*** for the support in statistical analysis and to all of our fantastic physicist team, especially to ***Ms Emese Fodor***, for her invaluable help that significantly contributed my scientific work.

I am also obliged to the radiologists, ***Dr Adrienne Cserháti*** and ***Dr Angéla Csomor***, for their professional work and scrutiny when evaluating and re-evaluating the radiological images of our patients, and to their guidance for contouring for the radiotherapy treatments.

My definite thank is due to ***all my colleagues at our Department of Oncotherapy***, to the specialist physicians, residents and interns, to our assistants and nurses, for their participation and always kind help in the diagnostic-therapeutic processes of our patients.

I am grateful for the contribution of ***all my colleagues at the neuro-oncoteam***, especially to my ***neurosurgeon colleagues***, for their cooperation in the multi-modal treatment of our brain metastatic patients.

Lastly, but most importantly, my heartfelt gratitude is due to ***my family and friends*** for their unconditional love, care and measureless patience; and to my husband, ***Dr Roland Weiczner***, for his precious support and help that enabled me the completion of my present doctoral thesis.