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Moderní trendy v personalizované radioterapii mozkových metastáz

HABILITAČNÍ PRÁCE
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Děkuji své manželce Lence a celé rodině za trpělivost a podporu, kterou mi po celou dobu poskytují.
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Moderní trendy v personalizované radioterapii mozkových metastáz
Modern trends in personalized radiotherapy of brain metastases

Abstrakt:

Implementace moderních cílených léků a imunoterapie do léčebných algoritmů většiny nádorových onemocnění ve svém důsledku krom prodlouženého celkového přežití vede k nárůstu incidence mozkových metastáz. Jejich léčba je obecně omezena jednak inherentními vlastnostmi centrální nervové soustavy a jednak limity na straně předléčeného pacienta v konečné fázi jeho onkologického onemocnění.

V této habilitační práci je diskutována problematika mozkových metastáz včetně jejich epidemiologie, symptomatologie a diagnostiky. Nejvíce prostoru je věnováno léčbě pomocí ionizujícího záření, radioterapie, jakožto nejčastěji indikované konzervativní terapii. Protože se u všech pacientů jedná apriori o léčbu symptomatickou a protože se mediány celkového přežití navzdory všem obecným pokrokům v onkologické terapii v případě mozkových metastáz udávají nadále spíše v měsících než letech, je v poslední době kladen čím dál větší důraz na kvalitu života a neurokognitivní funkce jakožto na primární cíle současných klinických studií.

Současné portfolio radioterapeutických technik pro individualizovanou radioterapii mozkových metastáz zahrnuje cílenou stereotaktickou radiochirurgii a frakcionovanou radioterapii, celomozkové ozáření a jeho modifikace (hipokampus šetřící techniky, simultánní integrovaný boost na oblast makrometastáz), případně radioterapii oblasti lůžka po metastazektomii. Diskutovány jsou především vlivy jmenovaných způsobů ozařování na riziko iatrogenního ovlivnění neurokognitivních funkcí a kvality života. Detailněji rozebíráme výsledky našeho projektu prospektivně hodnotícího změny hipokampu po celomozkovém ozáření pomocí inovativního přístupu s využitím MR spektroskopie. Samostatně jsou také diskutovány současné prognostické indexy umožňující validní odhad prognózy konkrétního pacienta s možností přesnějšího zvážení poměru riziko/benefit jednotlivých léčebných algoritmů.

Lze uzavřít, že v současné době již není v případě pacientů s mozkovými metastázami místo pro dříve občas vídaný nihilismus a že individualizovaná léčba může pacientům přinést výrazný benefit, jako v případě prezentované kazuistiky v závěrečné části této habilitační práce.

Abstract:

The implementation of modern targeted therapy and immunotherapy in the treatment algorithms of most cancers, in addition to prolonged overall survival, leads to an increase in the incidence of brain metastases. Their treatment is generally limited both by the inherent properties of the central nervous system and by the limitations of the highly pretreated patients in the end stage of their disease.

In this habilitation thesis the question of brain metastases including their epidemiology, symptomatology and diagnosis is discussed. Most of the text is focused on ionizing radiation treatment, radiotherapy, as the most commonly indicated conservative treatment. As treatment is a priori with symptomatic intent in all patients and because median overall survival continues to be reported in months rather than years in spite of all the general advances in cancer therapy, there has been an increasing emphasis on quality of life and neurocognitive function as the primary objectives of current clinical trials.

Up-to-date portfolio of radiotherapy techniques for individualized radiotherapy of brain metastases includes targeted stereotactic radiosurgery and fractionated radiotherapy, whole brain radiotherapy and its modifications (hippocampus avoiding techniques, simultaneous integrated boost to macrometastases), or radiotherapy of tumor bed after metastasectomy. Especially the effects of the above mentioned radiation approaches on the risk of iatrogenic alteration in neurocognitive functions and quality of life are discussed. We analyze in more detail the results of our study prospectively assessing changes in hippocampus after whole brain radiotherapy utilizing an innovative approach of MR spectroscopy. Current prognostic indices are also discussed separately, allowing a valid estimate of the patient's prognosis with the possibility of more precise risk / benefit assessment of individual treatment algorithm.

It can be concluded that at present there is no longer a place for previously seen nihilism in patients with brain metastases and that individualized treatment can bring significant benefits to patients, as in the case report presented in the final part of this habilitation thesis.

1. Úvod

Sekundární mozkové nádory (mozkové metastázy) vznikají metastazováním do mozku z nejrůznějších primárních nádorů, kdy mezi nejčastější patří bronchogenní karcinom, nádory prsu, ledvin a maligní melanom (1). Jedná se tedy o velice heterogenní skupinu pacientů, jejichž terapeutické možnosti jsou dány také typem a rozsahem extrakraniálního onemocnění.

Prognóza pacientů s mozkovými metastázami je i přes současné úspěchy moderní onkologické léčby nadále velice vážná s mediány celkového přežití udávanými v řádu měsíců. V souvislosti s reportováním klasických onkologických léčebných cílů (celkové přežití nebo přežití do progrese) je nutné poznamenat, že se v případě léčby mozkových metastáz jedná vždy o léčbu s paliativním záměrem (s tzv. krátkodobým nebo tzv. dlouhodobým paliativním záměrem), kdy apriori není hlavním cílem prodloužení celkového přežití, ale udržení, v ideálním případě zlepšení, kvality života a neurokognitivních funkcí (NCF) (2). Teprve v posledních letech jsou k dispozici výsledky randomizovaných studií, které jsou přímo designované k posouzení vlivu jednotlivých léčebných intervencí na kvalitu života jakožto primárního cíle těchto studií (3)(4).

Tato habilitační práce s názvem „Moderní trendy v personalizované radioterapii mozkových metastáz“ je zpracována formou komentovaného souboru prací autora zabývajících se jednotlivými radioterapeutickými technikami v léčbě mozkových metastáz s důrazem na toxicitu ve smyslu iatrogenní alterace NCF a kvality života jako takové. Prezentované práce jsou věnovány především roli hipokampu v patogenezi změn po radioterapii v oblasti centrálního nervového systému (CNS).

Habilitační práce je rozdělena do kapitol zabývajících se epidemiologií, diagnostikou a léčbou mozkových metastáz. Podstatná část je věnována radioterapii a jejím nežádoucím účinkům. Vlastní příspěvky k diskutované problematice jsou vkládány přímo do jednotlivých kapitol.

Ve snaze o rozšíření čtenářské obce tohoto díla a textů vzniklých při psaní této habilitační práce (1–3/2019), především kapitol, jež obecně shrnují diagnostiku, chirurgickou, systémovou, podpůrnou, symptomatickou a samozřejmě radioterapeutickou léčbu mozkových metastáz, předpokládáme další využití části textů při přípravě souhrnných publikací na jmenovaná témata (zejména následné prvoautorské přehledové práce a kazuistiky publikované v roce 2019, event. 2020, v českých odborných časopisech zabývajících se onkologickou a neuroonkologickou problematikou).

2. Epidemiologie mozkových metastáz

Mozkové metastázy jsou nejčastějším nádorovým onemocněním mozku s asi desetinásobně vyšší incidencí v porovnání s primárními mozkovými nádory. Starší populační studie popisují incidenci mozkových metastáz zhruba mezi 8 a 14 na 100 000 obyvatel, nicméně odhaduje se, že skutečná incidence bude mnohem vyšší. Výskyt mozkových metastáz ve starších pitevních studiích byl totiž mnohem vyšší a metastázy byly popsány u několika desítek procent všech pitvaných onkologických pacientů (5). Aktuálnější epidemiologická data nejsou k dispozici. Odhaduje se, že k rozvoji mozkových metastáz dochází až u 30 % pacientů se solidními nádory (1)(5)(6). Lze důvodně předpokládat, že incidence bude vzhledem k větší dostupnosti magnetické rezonance (MR) a především kvůli rozšiřujícím se indikacím moderní systémové terapie (cílená léčba, imunoterapie, precizní onkologie) nadále vzrůstat. Jejich užívání vede k obecně delšímu celkovému přežívání pacientů s extrakraniálními metastázami, u kterých pak stoupá riziko další diseminace do oblasti CNS. Jedním z možných mechanismů je obecně horší pronikání léků hematoencefalickou bariérou umožňující event. již přítomným mikrometastázám selekční výhodu. Příkladem jsou monoklonální protilátky o vysoké molekulární hmotnosti, jako je trastuzumab, IgG1 humanizovaná monoklonální protilátka proti extracelulární doméně receptoru lidského epidermálního růstového faktoru (HER), používaný v terapii HER2-pozitivních nádorů prsu. Mnoho autorů dokumentovalo brzy po zahájení rutinního užívání trastuzumabu nárůst incidence mozkových metastáz v porovnání s historickými kohortami (7).

Pokud budou potvrzeny předpokládané úspěchy precizní medicíny s tranzicí nádorových onemocnění z kategorie smrtelných onemocnění do kategorie nemocí chronických, bude výrazně stoupat prevalence onkologických pacientů. Pacienti s mozkovými metastázami pak mohou tvořit významnou část pacientů, s kterými se onkologové setkají v rámci rutinní praxe, což podtrhuje význam této problematiky.

Nejčastějším primárním nádorovým onemocněním metastazujícím do CNS je bronchogenní karcinom (až 50 % všech pacientů referovaných s mozkovými metastázami). Z tohoto důvodu je někdy zvažována profylaktická radioterapie u pacientů s malobuněčnými i nemalobuněčnými nádory plic, jak je dále zmiňováno v kapitole 7. Spektru primárních diagnóz popisovanému v literatuře odpovídá neselektovaná kohorta 473 pacientů s mozkovými metastázami léčená na našem pracovišti v letech 2011–2014 (8). Většina pacientů byla s nádory plic (220/473; 46,5 %) následována pacientkami s karcinomem prsu

(81/473; 17,1 %) a pacienty s maligním melanomem (59/473; 12,5 %). Naopak u jiných častých primárních diagnóz, jako je kolorektální karcinom nebo nádory prostaty, jsou mozkové metastázy pozorovány zřídka (v naší zmiňované kohortě 6 pacientů s nádorem prostaty, 6/473; 1,3 %), a to pravděpodobně vlivem dosud ne zcela přesně popsaných mechanismů patogeneze metastáz, které limitují invazi do mozkového parenchymu (9).

Z klinického hlediska je zásadní rozdíl mezi pacientem s jednou mozkovou metastázou a s mnohočetným postižením CNS. Jako *single* mozková metastáza se označuje jedna metastáza při přítomnosti dalších extrakraniálních metastáz a jako *solitární* mozková metastáza se označuje jedna metastáza CNS coby jediné místo metastatické choroby u pacienta s kontrolovaným primárním nádorem. Jak bude diskutováno dále v příslušných kapitolách, léčebné cíle a možnosti neurochirurgie a radioterapie jsou odlišné dle počtu metastáz se zřejmou lepší prognózou pacientů bez mnohočetného metastatického postižení. Nicméně zastoupení pacientů s jednou metastázou (případně pouze s oligometastatickým onemocněním) je závislé také na dostupnosti zobrazovacích metod, především magnetické rezonance (MR). Robustní analýza neselektované skupiny téměř 2 500 pacientů léčených v Medical University of Vienna v letech 1990–2011 popisuje téměř 50 % pacientů s jednou mozkovou metastázou (10). Tabulka 1 srovnává tyto pacienty s kohortou z našeho pracoviště.

Tab. 1: Srovnání počtu metastáz u pacientů léčených na našem pracovišti a ve Vídni.

	Vídeň	**Brno**	**Brno**
Autor	Berghoff (2016) (10)	Kuklová (2017) (11)	Kazda (2018) (12)
Počet pacientů	2 419 (neselektovaní pacienti)	473 (neselektovaní pacienti)	260 (pouze pacienti s MR)
Rok	1990–2011	2011–2014	2011–2014
Počet pacientů/rok	115	118	
Bronchogenní karcinom	43,3 %	46,5 %	46,2 %
Nádory prsu	15,7 %	17,1 %	18,5 %
1 metastáza	48,7 %	32 %	36 %
2–3 metastázy	27,7 %	25 %	22 %
>3 metastázy	23,5 %	43 %	42 %

3. Klinické příznaky a diagnostika mozkových metastáz

V naší skupině postupně zavádíme RANO hodnocení v rámci vlastních retrospektivních i prospektivních vědeckovýzkumných projektů a studií (např. akademická multicentrická prospektivní randomizovaná studie GlioART: analýza recidiv glioblastomů (patterns of failure) a závislost na taktice adjuvantní radioterapie; principal investigator dr. Kazda). Jak bylo zmíněno výše, nutnou podmínkou validního hodnocení primárních i sekundárních mozkových nádorů pomocí RANO kritérií je úzká spolupráce radiologa a radioterapeuta, především při přesném reportování cílových objemů radioterapie, které jsou pro radiologa důležité v rámci hodnocení event. pseudoprogrese (23). Správně aplikovaná RANO kritéria pak mohou definovat progresi na jiné MR, než kdyby RANO kritéria použita nebyla, což má ve svém důsledku extrémní vliv na hodnocení doby do progrese (PFS), které reprezentuje častý endpoint studií zabývajících se lokálními metodami léčby, jako je operace nebo radioterapie (24). Poslední dvě citované práce jsou vlastním příspěvkem k problematice RANO kritérií ((23) – Belanova R, Sprlakova-Pukova A, Standara M, Janu E, Koukalova R, Kristek J, Burkon P, Kolouskova I, Prochazka T, Pospisil P, Chakravarti A, Slampa P, Slaby O, Kazda T*. In silico study of pseudoprogression in glioblastoma: collaboration of radiologists and radiation oncologists in the estimation of extent of high dose RT region. Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub 2019; 163 a (24) – Kazda T, Hardie JG, Pafundi DH, Kaufmann TJ, Brinkmann DH, Laack NN. Evaluation of RANO response criteria compared to clinician evaluation in WHO grade III anaplastic astrocytoma: implications for clinical trial reporting and patterns of failure. J Neurooncol. 2015 Mar; 122(1): 197–203. Obě práce ale pojednávají o primárních mozkových nádorech, nejsou proto blíže diskutovány. Jsou ale důležitou prerekvizitou postupné implementace RANO-BM kritérií v hodnocení pacientů s mozkovými metastázami na našem pracovišti.

V případě nejasných nálezů na standardních metodách MR lze v rámci diferenciální diagnostiky (včetně již zmíněné pseudoprogrese) s výhodou využít různých nástavbových metod MR zobrazování, jako je MR difuze, MR perfuze nebo MR spektroskopie (MRS). Pro náš další výzkum poradiačních změn mozku je důležitá především MR spektroskopie. Protonová MRS představuje metodu tzv. metabolického zobrazení, umožňující zobrazení prostorového rozložení koncentrace vybraných metabolitů. Výběrem analyzované oblasti lze graficky vyjádřit rozdílné zastoupení např. laktátu, cholinu nebo N-acetyl aspartátu v normální nebo patologické oblasti mozku. MR spektra zdravého mozku jsou velmi

konstantní. K jejich změně dochází většinou v důsledku nežádoucích biochemických procesů, které jsou např. součástí růstu nádorů. I když MRS nedokáže určit specifické metabolity pro nádorovou tkáň, může stanovit specifické rozdíly ve změnách koncentrací metabolitů v porovnání s koncentrací těchto metabolitů ve zdravé mozkové tkáni. Například glioblastomy jsou charakteristické zvýšenou úrovní cholinu (marker buněčných membrán) a redukcí intenzity signálů N-acetylaspartátu (marker viability a počtu neuronů), čehož lze využít v odlišení poléčebných recidiv a pseudoprogresí, případně radionekróz. V dále diskutovaném výzkumu poradiačních změn mozku jsme pomocí MRS hodnotili změny na úrovni hipokampů po ozáření mozkových metastáz. Následující publikace diskutují krom metodiky MRS validaci aplikace MRS v diferenciální diagnostice poléčebných změn u gliomů v rámci prospektivní studie.

3.1 PUBLIKACE 1

Bulík M, Kazda T, Jančálek R. Protonová MR spektroskopie v neuroonkologii. Neurol pro Praxi, 2016; 17(5): 248–251.

Kategorie publikace: přehledový článek v domácím recenzovaném časopise bez IF

Anotace: V úvodu přehledového článku jsou shrnuty základní fyzikální aspekty získání MR spekter v průběhu vyšetření MRS. Pro neuroonkologické indikace jsou nejdůležitější následující metabolity, dále v textu blíže charakterizované: N-acetylaspartát, kreatin, cholin a laktát. Poměry jejich koncentrací mohou přispět při rozlišení nádorových a nenádorových lézí, odlišení primárních nádorů a metastáz, upřesnit grading nádorů (především v případě histologicky verifikovaných anaplastických astrocytomů bez sycení na strukturální MR lze pomocí MRS identifikovat event. místa agresivnější složky tumoru), při navigacích neurochirurgických intervencí (včetně navigace biopsie do míst nejagresivnější porce tumoru u primárně inoperabilních nádorů), při hodnocení progrese gliomů, respektive v diferenciální diagnostice pseudoprogrese a radionekrózy. Hodnocením N-acetylaspartátu lze usuzovat na přítomnost viabilních neuronů.

MR spektroskopie bude dále diskutována ve vztahu k hodnocení poradiačního poškození mozku po radioterapii mozkových metastáz.

Protonová MR spektroskopie v neuroonkologii

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Protonová MR spektroskopie umožňuje neinvazivní hodnocení metabolitů vyšetřované tkáně, poskytuje informaci o složení intrakraniálních lézí, zvyšuje specificitu strukturální magnetické rezonance a tudíž ovlivňuje léčbu pacientů a případná rozhodnutí o změně léčebné strategie, jako je tomu například u rozlišení poléčebných změn a recidivy vysokostupňových gliomů po komplexní onkologické léčbě. Biochemické změny intrakraniálních nádorů se mohou lišit v závislosti na histologii a stupni malignity. Výsledky spektroskopie lze využít v neuroonkologii v mnohých klinických indikacích. Při interpretaci těchto závěrů je nutné mít na paměti limitace spektroskopie a nutnost adekvátní zkušenosti provádějícího pracoviště.

Klíčová slova: magnetická rezonance, spektroskopie, nádory mozku.

Proton MR spectroscopy in neurooncology

Proton MR spectroscopy provides the non-invasive assessment of metabolites in examined tissue, can be used to get intracranial neoplasms structural information, increases the specificity of structural magnetic resonance and may serve as an additional examination for evaluation of the response to treatment and decisions to change the treatment strategy as it is in diferentiation of posttreatment changes and recurrence after comlex oncologic treatment of glioma patients. Biochemic changes in glioma differ according to histology and tumor grading. The results of MR spectroscopy can be used for several indications in neurooncology. However, it is important to remember spectroscopy limitations and the necessity of an adequate institutional experience.

Key words: magnetic resonance, spectroscopy, glioma.

Úvod

Každoročně je v České republice nově diagnostikováno kolem 850 pacientů s primárním nádorem mozku (Incidence zhoubných novotvarů v ČR v roce 2011). Histologicky jsou nejčastěji zastoupeny gliomy. V současnosti je zlatým standardem diagnostických, stagingových i pooperačních vyšetření provedení magnetické rezonance (MR) s aplikací kontrastní látky. I když je konvenční magnetická rezonance velmi senzitivním nástrojem k zobrazení oblastí s porušením hematocefalické bariéry, neposkytuje informace týkající se tkáňové specificity, takže v některých případech je obtížné její výsledky interpretovat. Příkladem takovýchto diagnostických úskalí může být nově zjištěný okrsek postkontrastního sycení v ozařovaném objemu u pacientů v průběhu sledování po komplexní onkologické léčbě vysokostupňových gliomů.

MR spektroskopie (MRS) umožňuje neinvazivní hodnocení metabolitů vyšetřované tkáně a poskytuje informaci o složení intrakraniálních lézí. Oproti konvenčním strukturálním MR metodám tak může poskytnout informaci o charakteristice vlastní nádorové tkáně. MRS tedy zvyšuje specificitu konvenční magnetické rezonance a může tak ovlivnit léčbu pacientů a případná rozhodnutí o změně léčebné strategie. Moderní multimodalitní zobrazování pomocí magnetické rezonance použitím difuzně a perfuzně vážených obrazů i MR spektroskopie umožňuje přesnější a zároveň stále neinvazivní náhled na mozkové nádory s dosažením vyšší specificity zobrazování zejména v kombinaci s pozitronovou emisní tomografií (PET)-CT.

Strukturální MR a MR spektroskopie jsou založeny na stejných fyzikálních principech snímání signálu, ale odlišují se způsobem, kterým jsou data zpracovávána, zobrazena a interpretována. Namísto strukturálních obrázků je jejich výstupem křivka, tzv. spektrum (obr. 1), koncentrací metabolitů ve vyšetřovaném objemu v závislosti na typu vyšetřované tkáně. Tyto metabolity jsou zachyceny v daném spektru, pokud se skládají z protonů (H+), jsou obsaženy v koncentraci ≥0,5 mmol/l, rezonují podél osy chemického posunu v různých frekvencích a je-li zároveň dosaženo potlačení signálu vody.

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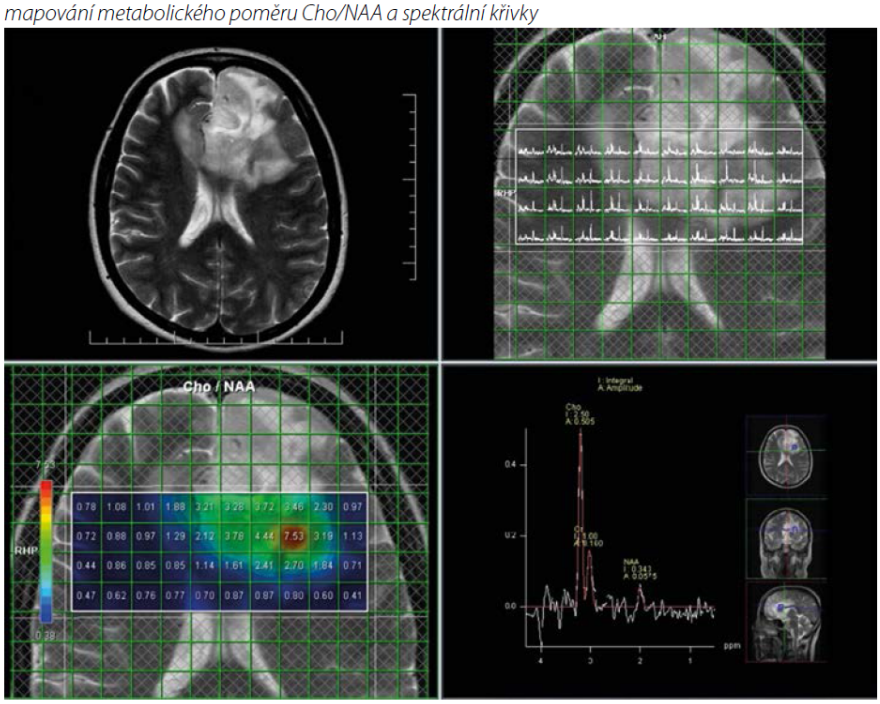
Obr. 1. *Příklad lokalizace spektroskopie u pacienta s tumorem frontálního laloku vlevo, barevného mapování metabolického poměru Cho/NAA a spektrální křivky*



Pro dané spektrum je pozice jednotlivých metabolitů na horizontální ose určena principy chemického posunu, vyjádřeno jednotkami pars per million (ppm). Po zpracování příslušných faktorů, jako jsou například počet protonů nebo relaxační časy, může být signál převeden na koncentrace metabolitů výpočtem plochy pod křivkou (AUC, area under curve). Stanovení absolutních koncentrací metabolitů je velice komplexní proces. Kromě technických úskalí s nutností změření interní reference je nutné brát v úvahu i fakt, že jejich koncentrace závisí na lokalizaci vyšetřovaného objemu a na věku vyšetřovaného. Z těchto důvodů je v běžné klinické praxi častější používání metabolických poměrů neboli relativních koncentrací metabolitů.

MR spektroskopie může vznikat prostřednictvím jakýchkoliv atomových jader s vhodným spinem. Ve skutečnosti jsou v medicínských indikacích používány většinou vodík (H), fosfor (P) a uhlík (C). Nejčastěji jsou používány v provedení in vivo spektroskopie atomy vodíku (protony), protože jsou přirozeně v nadbytečné míře obsaženy v lidském těle a ve srovnání s ostatními prvky jsou více senzitivní magnetickému poli. Použitím spektroskopie je možné simultánně hodnotit různé okrsky léze, mapovat její heterogenitu a identifikovat oblasti vyšší nebo nižší nádorové aktivity dané léze. Dále umožňuje stranové srovnání s kontralaterální zdravou hemisférou, získávání spekter z oblasti léze i okolní mozkové tkáně a redukcí efektu parciálního objemu i hodnocení z malé velikosti vyšetřovaného objemu (kolem 1 cm^3).

Metabolické změny gliomů

Zdravá mozková tkáň má relativně konstantní složení vnitřního prostředí. Ke změnám homeostázy ovšem dochází v důsledku nežádoucích biochemických procesů, tedy onemocnění. V důsledku nádorového bujení dochází ke kvalitativním i kvantitativním změnám v koncentrací některých metabolitů, čehož lze využít diagnosticky. I když dokáže MR spektroskopie v závislosti na technických parametrech MR přístroje detekovat různé metabolity, pro využití v rámci neuroonkologie hodnotíme nejčastěji N-acetylaspartát (NAA), cholin (Cho), kreatin (Cr), lipidy (Lip), laktát (Lac), myoinositol (mI) a glutamát-glutamin (Glx). Změny přítomnosti a koncentraci těchto metabolitů se pak mohou lišit v závislosti na histologii a stupni malignity intrakraniálních nádorů.

N-acetylaspartát

N-acetylaspartát se považuje za marker denzity a viability neuronů. Redukce NAA a metabolického poměru NAA/Cr lze proto pozorovat u gliomů v souvislosti se sníženým počtem neuronů, respektive „naředění" neuronální populace nádorovými gliálními buňkami. Pokud jsou koncentrace NAA ve fyziologickém rozmezí, ve vyšetřované oblasti se většinou o přítomnost nádorové tkáně, s výjimkou několika specifických situací, nejedná. Například u nízkostupňových gliomů mohou být metabolické změny podobné těm v běžné mozkové tkáni. Dále v případech kdy je vyšetřovaná léze mnohem menší, než je velikost vyšetřovaného objemu. Tehdy efekt parciálního objemu okolní nepatologické tkáně falešně zvyšuje hodnoty signálu NAA. Někdy i u infiltrativně rostoucích nádorů s nepočetnou populací nádorových buněk mohou být hodnoty NAA zachovány.

Kreatin

Kreatin představuje biomarker energetického metabolizmu. Vzhledem k energetické náročnosti metabolizmu neuronů je hladina Cr udržována za většiny situací relativně konstantní. Proto se Cr často využívá k výpočtu metabolických poměrů (například NAA/Cr, Cho/Cr). Pokles koncentrace Cr může být ovšem patrný u vysoce maligních gliomů vlivem jejich vysokého energetického obratu (Bulik et al., 2013).

Cholin

Cholin je považován za hlavní metabolit v neuroonkologických indikacích. Zvýšení koncentrace Cho souvisí se zvýšeným obratem buněčných membrán ve smyslu destrukce a novotvorby buněk a s vyšší buněčnou hustotou vyplývající z proliferace nádorových buněk. Vyšší hladiny Cho běžně nacházíme u grade II a III gliomů. Naopak u glioblastomů (GBM) mohou být jeho koncentrace kvůli vysokému podílu centrální nekrózy nižší než u tumorů nižší malignity a dokonce redukovány pod úroveň normální mozkové tkáně, pokud měříme spektra z centra nekrotického okrsku. Z těchto důvodů je nutné umístit vyšetřovaný objem tak, aby obsahoval co největší podíl solidní nádorové tkáně a zároveň se snažit vyhnout nekrotickým částem. Při splnění těchto podmínek je možné zachytit zvýšení absolutních hodnot Cho a metabolických poměrů Cho/Cr a Cho/NAA typických pro intrakraniální tumory (Dowling et al., 2001). Mezi dnes asi nejčastěji sledovaný metabolický poměr u neuroonkologických pacientů patří Cho/NAA, který odráží jak vzestup koncentrace Cho, tak i pokles koncentrace NAA charakteristický pro gliální nádory.

Laktát

Laktát je za fyziologických okolností v nervové tkáni obsažen v minimálních koncentracích, jelikož se jedná o marker anaerobního metabolizmu. Ke zvýšení jeho koncentrace dochází za stavů anaerobního metabolizmu, jako je tomu například při nepoměru mezi cévním zásobením a metabolickými nároky nádorové tkáně, naopak v nenádorových souvislostech může tento stav imitovat přítomnost ischemie v určitých lokalitách a působit tak diferenciálně diagnostické obtíže. Úroveň laktátu má přímou úměru ke stupni malignity gliomů u dospělých jedinců, tedy čím vyšší koncentrace Lac na spektroskopické křivce, tím vyšší stupeň malignity. V případě primárních mozkových nádorů u dětí se laktát vyskytuje v podstatě u většiny z nich (Wang et al., 1995).

Lipidy

Přítomnost měřitelných koncentrací lipidů je jasným indikátorem přítomnosti nekrotické tkáně a často ji lze pozorovat u pacientů s mozkovými nádory či zánětlivými procesy, jako jsou abscesy (Lai et al., 2005). V neuroonkologii je tedy vysoká koncentrace Lip v centrální nesytící se oblasti (nekrotická tkáň) charakteristická především pro glioblastom a metastázy. Samotná přítomnost Lip ovšem není patognomická pro maligní nádory, jelikož je možné Lip detekovat také u výše zmíněných abscesů nebo akutních demyelinizačních lézí v souvislosti s narušením myelinové pochvy.

Myoinositol

Hodnoty ml a metabolického poměru ml/Cr ve vyšetřovaném objemu upřesňují hodnocení stupně malignity gliomů (Bulik et al, 2013). Poměr ml/Cr je většinou vyšší u nízkostupňových nádorů než u vysoce maligních a lze jej využít i v primární diagnostice intrakraniálních ložisek. Jeho výrazné zvýšení bývá spojováno s výskytem nenádorových lézí.

Glutamát-glutamin

Pokud koncentrace Glx dosahuje jedné třetiny NAA, můžeme jej označit za zvýšený. S výjimkou meningeomů, pro které je zvýšení koncentrace Glx typické, signifikantní zvýšení tohoto metabolitu naznačuje výskyt nenádorové léze, jako například infekce a encefalitidy, ischemie, jaterní encefalopatie, či nedostatek některých enzymů.

Klinické indikace spektroskopie v neuroonkologii

Rozlišení nádorových a nenádorových lézí

Protonová MR spektroskopie umožňuje odlišení lézí s obdobnými charakteristikami dle vyšetření konvenční magnetickou rezonancí. Spolehlivost rozlišení nádorových a nenádorových lézí má velmi vysokou přesnost, a pokud ji kombinujeme se strukturálním zobrazením, zvyšuje se tak vzájemná diagnostická specificita. Za nejspecifičtější marker intrakraniální neoplazie je považován cholin. Proto je zvýšení koncentrace Cho či metabolického poměru Cho/Cr a Cho/NAA pro nádorový růst typické. Ve studii s použitím MR spektroskopie McKnight (McKnight et al., 2002) prokázal senzitivitu a specificitu hodnoty metabolického poměru Cho/NAA>2 k rozlišení nádorových a nenádorových lézí 96 % a 70 %. Pro hodnotu poměru vyšší než 2,5 se snížila specificita zachycení nádoru na 90 %, ale specificita vzrostla na 86 %. Je důležité mít na paměti, že získané spektrum není specifické pro jednu patologii, a proto je zcela zásadní kombinace multimodalitního přístupu v diagnostice. Mezi nejčastěji kombinované metody patří strukturální MR, difuzně a perfuzně vážené zobrazování, protonová MRS a PET-CT.

Histologie

Na základě spektrální analýzy lze nastínit histologickou povahu vyšetřované léze a závěry MR spektroskopie je možné dále zpřesnit použitím multimodalitního přístupu. Například meningeomy a schwanomy jsou non-neuronální tumory a jako takové takřka neobsahují NAA a Cr. Pokud je u těchto nádorů patrný vzestup alaninu a glutaminu, většinou se jedná o meningeom (Crisi, 2011). V případě meningeomů však mohou spektra obsahovat pouze lipidy. Signifikantní vzestup hladiny lipidů u sellárních a suprasellárních lézí budí podezření na diagnózu kraniofaryngeomu. Pokud zvažujeme diferenciální diagnostiku lymfomu a GBM, tak nález zvýšení hladiny lipidů v solidní složce nádorového ložiska favorizuje výslednou diagnózu lymfomu (Castillo et al., 1998).

Odlišení primárních nádorů a metastáz

Kompletní či částečná absence hladin NAA a Cr naznačuje přítomnost metastatického ložiska, které není neuronálního původu. Další možností je podrobit spektrální analýze perifokální oblasti. Dle dostupné literatury je patrné, že pokud se v nich nacházely zvýšené hladiny Cho, šlo ve většině případů o pacienty s primárním mozkovým nádorem, naopak pokud tyto hladiny byly v normě, šlo o pacienty s vazogenním edémem v okolí intrakraniálních metastáz (Server et al., 2010).

Grading gliomů

Výhodou MRS v hodnocení gradingu mozkových nádorů oproti biopsii je možnost hodnocení většího objemu dané léze. Navíc biopsie často nebývá cílena do oblasti nejvyšší celularity, a proto může falešně podhodnocovat grading heterogenních nádorových lézí. Mezi nejčastěji hodnocené metabolity patří na prvním místě Cho. Existuje vysoká shoda mezi in vivo měřením koncentrací cholinu a in vitro stanovením markerů nádorové proliferace (např. Ki-67). Na základě těchto zjištění je stanovování hladin Cho považováno za vhodné měřítko proliferační aktivity tumorů in vivo (Bulik et al., 2013). S výjimkou GBM, u kterých tato závislost bývá ovlivněna přítomností nekrotických okrsků, hladiny cholinu souvisí s buněčnou hustotou, a proto se u vysokostupňových gliomů nachází vyšší hladiny cholinu. Rovněž u laktátu byla prokázána přímá úměra mezi jeho koncentrací a nádorovým gradem, jelikož vyšší hladiny Lac jsou patrné u vysoce maligních nádorů (Law et al., 2003). Výskyt lipidů je charakteristický pro high-grade nádory s nekrotickými okrsky, ale rovněž se mohou vyskytovat u low-grade gliomů. U vysoce maligních tumorů bývá patrná výrazná redukce hladiny NAA a Cr. Důležité informace může přinést i stanovení ml. U většiny nízkostupňových nádorů je hodnota metabolického poměru ml/Cr vyšší než u tumorů vyššího maligního potenciálu.

Navigace neurochirurgických intervencí

Použitím MRS je možné identifikovat oblasti nádorové infiltrace s nejvyšší hodnotou absolutní koncentrace Cho či metabolického poměru Cho/NAA a Cho/Cr a tím pádem i nejvyšší nádorovou aktivitou. Právě tato místa jsou ideálním cílem stereotakticky navigované biopsie (Bradac et al., 2014). Daným postupem se sníží riziko podhodnocení stupně malignity,

kterým je stereotaktická biopsie navigovaná podle strukturální MR významně zatížena.

Hodnocení rozsahu gliomů

Rozsah nádorové infiltrace bývá většinou větší než rozsah postkontrastně se sytících okrsků dle strukturální MR. Na druhou stranu T2 hypersignální oblasti v okolí nádorových ložisek reprezentují perifokální edém, nádorovou infiltraci a poléčebné změny vlivem radioterapie a chemoterapie. Z těchto důvodů bývá nutné ke zhodnocení skutečného rozsahu gliomů provést MR spektroskopie (Wagnerova et al., 2012).

Hodnocení progrese gliomů

MR spektroskopie má také potenciál predikovat riziko progrese nádorové neoplazie a sledovat průběh onemocnění. Za prognostické faktory bývají u pacientů s intrakraniálními neuroepiteliálními tumory označovány hladiny Cho a Lac. Vzestup koncentrací Cho v rámci vyšetřované léze je spojován s vyšším rizikem nádorové progrese. Současná přítomnost lipidů a daného vzestupu hladiny Cho je spojována se špatnou prognózou. Opakované MRS mohou být součástí sledování u pacientů po onkologické léčbě primárních nádorů mozku. Jako progrese bývá v literatuře označován vzestup hladin Cho o více jak 45 % oproti předchozímu vyšetření. Jako stav bez progrese bývá označován pokles hladin Cho, jejich stabilní hodnota či vzestup o méně než 35 % oproti předchozímu vyšetření (Tedeschi et al., 1997).

Poradiační změny a rekurence gliomů

Protonová MRS se může významně uplatnit také v poléčebném sledování intrakraniálních nádorů. Umožňuje sledovat odpověď na komplexní onkologickou léčbu, odhalit reziduum či recidivy původního tumoru, i když pacient vykazuje klinické zlepšení. MR spektroskopii lze využít také k odlišení rezidua či recidivy původního tumoru od poléčebných změn, poranění ve smyslu pseudoprogrese či radionekrózy (Kazda et al., 2016). Jako nejvhodnější v hodnocení těchto situací se jeví korelace strukturálního nálezu a výsledku protonové MRS.

Použití spektroskopie v dalších neurologických indikacích

MR spektroskopie lze účelně využít nejen v rámci neuroonkologie, ale také u neonkologických diagnóz, jako jsou neurodegenerativní a metabolická onemocnění CNS, vaskulárních onemocněních, hypoxie, epilepsie, demyelinizační onemocnění, v případě intrakraniálních infekcí, poranění mozku a psychiatrických diagnóz.

Závěr

Použití protonové MR spektroskopie má v neuroonkologických indikacích svá opodstatnění a na mnoha pracovištích v celosvětovém měřítku bývá součástí standardních vyšetřovacích algoritmů pomocí magnetické rezonance u pacientů s intrakraniální neoplazií. Jak při indikacích, tak při interpretaci spektroskopie, je vždy důležité mít na paměti její limitace. Například přítomnost rozsáhlé nekrózy, zakrvácení, kalcifikací, melaninu a rovněž anatomická lokalizace (v blízkosti kosti, dutin, atd.) může negativně ovlivnit diagnostickou výtěžnost naměřeného spektra. Neurochirurgický materiál může působit susceptibilní artefakty. Kortikosteroidy mohou ovlivňovat absolutní koncentrace metabolitů, ale neprojeví se v metabolických poměrech. Vzhledem k diskrétní dislokaci mozkové tkáně a v ní obsažených lézí po otevření kalvy je otázkou, zda zůstává proveditelnost MRS v rámci peroperačních indikací (Zhang et al., 2015). Vzhledem k výrazné interinstitucionální variabilitě výsledků MR spektroskopie je zcela zásadní adekvátní zkušenost provádějícího pracoviště a hodnotícího neuroradiologa.

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3.2 PUBLIKACE 2

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Anotace: Přesná identifikace progrese glioblastomů je klíčová v managementu pacientů s tímto závažným nádorem CNS. Cílem této prospektivní studie je stanovit a ověřit prahové hodnoty pro hlavní koncentrace metabolitů naměřené pomocí MR spektroskopie (MRS) a hodnoty aparentního difuzního koeficientu (ADC – difuzně vážené MR zobrazování), aby bylo možné odlišit recidivu nádoru od pseudoprogrese. Třicet devět pacientů po standardní léčbě glioblastomu podstoupilo pokročilé zobrazování pomocí MRS a ADC v době podezření na recidivu. Střední doba do progrese byla 6,7 měsíců. Nejvyšší senzitivita a specificita pro diagnózu recidivy glioblastomu byla pozorována u celkového poměru koncentrace cholinu (tCho) k celkové koncentraci N-acetylaspartátu (tNAA) s prahem ≥ 1,3 (citlivost 100,0% a specificita 94,7%). Hodnota ADCmean >1313 × 10–6 mm^2/s byla spojena s pseudoprogresí (citlivost 98,3%, specificita 100,0%). Kombinace MRS zaměřená na koncentrační poměr tCho/tNAA a hodnoty ADCmean představuje nástroj pro časnou neinvazivní diferenciaci mezi recidivou glioblastomu a pseudoprogresí po onkologické léčbě. Individuální institucionální vymezení a ověření prahových hodnot pro diferenciální diagnostiku je nutné vzhledem k rozdílným hodnotám MRS v závislosti na nastavení daného MR přístroje.

Práce prezentuje využití MR spektroskopie ve výzkumu poradiačních změn mozku jednak na úrovni tumoru a dále pak na úrovni zdravé mozkové tkáně, jak je dále diskutováno v případě radioterapie mozkových metastáz a změn v oblasti hipokampů.

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Advanced MRI increases the diagnostic accuracy of recurrent glioblastoma: Single institution thresholds and validation of MR spectroscopy and diffusion weighted MR imaging

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ABSTRACT

The accurate identification of glioblastoma progression remains an unmet clinical need. The aim of this prospective single-institutional study is to determine and validate thresholds for the main metabolite concentrations obtained by MR spectroscopy (MRS) and the values of the apparent diffusion coefficient (ADC) to enable distinguishing tumor recurrence from pseudoprogression. Thirty-nine patients after the standard treatment of a glioblastoma underwent advanced imaging by MRS and ADC at the time of suspected recurrence — median time to progression was 6.7 months. The highest significant sensitivity and specificity to call the glioblastoma recurrence was observed for the total choline (tCho) to total N-acetylaspartate (tNAA) concentration ratio with the threshold ≥1.3 (sensitivity 100.0% and specificity 94.7%). The ADCmean value higher than 1313×10^{-6} mm^2/s was associated with the pseudoprogression (sensitivity 98.3%, specificity 100.0%). The combination of MRS focused on the tCho/tNAA concentration ratio and the ADCmean value represents imaging methods applicable to early non-invasive differentiation between a glioblastoma recurrence and a pseudoprogression. However, the institutional definition and validation of thresholds for differential diagnostics is needed for the elimination of setup errors before implementation of these multimodal imaging techniques into clinical practice, as well as into clinical trials.

1. Introduction

The critical biological characteristic of a glioblastoma (GBM), the most frequent and serious primary brain tumor in adults is an inevitable progression after standard therapy with the median of 6.9 months (Dusek et al., 2014; Stupp et al., 2005). Tumor recurrence develops in almost all patients despite the aggressive standard first line treatment, which comprised of radiotherapy and temozolomide usage (RT and TMZ) (Stupp et al., 2005). GBM recurrence, however, has often similar radiologic characteristics on conventional MRI as therapy-related changes, like a pseudoprogression (PsP). Thus, the early and accurate diagnosis of GBM relapse constitutes to be an important clinical need, especially when more and more potentially active drugs are currently being investigated for salvage treatment.

In comparison with standard structural MRI techniques, advanced imaging methods, such as diffusion-weighted imaging (DWI) with apparent diffusion coefficient (ADC) mapping, and the proton MR spectroscopy (MRS), allow much deeper and still non-invasive insight into the interpretation of brain lesions, resulting in greater specificity of diagnostic imaging (Ahmed et al., 2014; Bulik et al., 2015; Kao et al., 2013; Roy et al., 2013). In our previous report of the consecutive series of 24 patients with GBM, we described significant differences in ADC and MRS data between those with GBM relapse and PsP after standard RT and TMZ treatment (Bulik et al., 2015). However, thresholds with

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higher statistical power and intra-institutional validation have been required before these methods can be implemented into our institutional imaging protocols on a routine basis and used in the decision-making process. In this report, we present our final results of this prospective study with extended number of patients, as well as the results from an independent retrospective intra-institutional validation.

2. Methods

2.1. Characteristics of patients

Patients suitable for this study included the ones with histologically proven GBM after gross total resection, as stated by an early post-surgery MRI examination, who underwent the standard adjuvant treatment consisting of concurrent RT (dose 60 Gy) and TMZ followed by adjuvant TMZ alone (Stupp et al., 2009). The standard follow-up imaging protocol at our institution is the classic structural MRI after 6 weeks and every 3 months thereafter. Patients were eligible for study enrollment when suspected radiographic progression on the structural MRI was found based on the neuro-radiologist's discretion. After they signed an informed consent, the patients underwent the investigational advanced MRI, namely MRS and DWI. The final evidence of the disease status was realized by means of biopsy/resection or early repeated structural MRI depending on the clinical situation, patient's performance status, de facto his or her best interest. The advanced imaging protocol was approved by the Institutional Review Board of the St. Anne's University Hospital Brno. Patients previously described in our initial analysis are also included in the current study cohort (Bulik et al., 2015). The validation cohort consisted of the independent series of previous patients with GBM treated by surgery and adjuvant RT and TMZ, who underwent MRS and DWI/ADC exams according to the same protocol. Initially, the derived thresholds for pertinent MRS spectra and ADCmean values were subsequently applied to predict a GBM recurrence or treatment related changes, such as PsP and radionecrosis.

2.2. MR data acquisition

The advanced MRI examination was performed at 3.0T clinical MR scanner (GE Medical Systems Discovery MR750), following the same setup parameters as in our initial report (Bulik et al., 2015). MRS was focused on gadolinium-enhanced lesions suspected of recurrence by means of the chemical shift imaging (CSI) technique in two orthogonal planes respecting the long axis of the lesion and the proximity to structures increasing noise in MR spectra (point-resolved spectroscopy sequence — PRESS, TR/TE 1800/144 ms, 16-cm FOV, 15-mm slice thickness, and voxel size $10 \times 10 \times 15$ mm^3). Automatic prescanning was performed prior to each spectroscopic scan to ensure adequate water suppression. The MR spectra of all measured voxels were automatically post-processed for each patient by LCModel version 6.3 (Provencher, 2001). The output of MRS processing by LCModel were the concentrations of N-acetylaspartate and N-acetylaspartylglutamate (tNAA), choline-containing compounds (tCho), total creatine (tCr), lipids at 0.9–1.3 ppm, and lactate (Lac). Afterwards, the ratios of the metabolite concentrations (tCho/tNAA, tCho/tCr, tNAA/tCr, Lac + Lip1.3/tCr, Lac + Lip0.9–1.3/tCr) were calculated and visualized by jSIPRO 1.0 beta version (Jiru et al., 2013). The signal-to-noise ratio for each MR spectrum and an error map showing the error in a measured concentration for each metabolite were calculated by using the jSIPRO software. The concept of error images in jSIPRO was developed to help rejection of low quality spectra (Jiru et al., 2006). From the voxels covering gadolinium-enhancing region, these with the signal-to-noise ratio > 3 and the error of measured metabolite concentrations <20% where selected and arranged based on the value of the Cho/NAA ratio. The voxels with the highest Cho/NAA ratio were selected for further analyses.

An axial echo planar SE sequence (TR/TE 6000/100 ms), 5-mm slice thickness, and diffusion gradient encoding in three orthogonal directions ($b = 0$ and 1000 mm^2/s, and 240-mm FOV) were utilized for DWI imaging. ADC maps were calculated using the OsiriX software version 6.0.2 64-bit (Pixmeo SARL, Switzerland) with the ADC Map Calculation plugin version 1.9 (Stanford University). The mean ADC value (ADCmean) of the voxel corresponding to the measured MRS voxel was calculated.

2.3. Data analysis

The optimal diagnostic cut-offs and the description of their sensitivity and specificity for the final diagnosis of recurrence were derived from the receiver operating characteristic (ROC) analysis with the area under the ROC curve (AUC) for distinguishing between the two diagnostic groups (GBM relapse and PsP). Fisher's exact test for categorical data and Mann–Whitney U test for continuous variables were used to estimate the significance of measured differences. Censoring the patients who were lost for the follow up, the overall survival was defined as the time elapsed between the GBM diagnosis and death from any cause. The time to progression was measured since the end of RT and TMZ with suspected progression at structural MRI as the event of interest. The probability value $p < 0.05$ was considered statistically significant in all tests. All statistical evaluations were performed using the statistical software Statistica 12 (StatSoft, Inc.).

3. Results

3.1. Study patient characteristics

Between May 2013 and March 2015, the total of 39 patients (median age 51, 72% men) with suspected GBM progression on the structural MRI was prospectively included into this study. The basic characteristics of patients are summarized in Table 1. The median time to suspected progression and the median overall survival were 6.7 months (95% CI 2.9–9.6) and 14.5 months (95% CI 12.9–17.4), respectively. The final diagnosis was established by a biopsy in 26 patients (67%) and by follow-up imaging in 13 patients (33%). The diagnosis of a GBM recurrence yielded in 29 patients (75%) with the rest having PsP. No case of radionecrosis was found in our cohort of patients.

Table 1
Basic characteristics of the study cohort: T = temporal, F = frontal, P = parietal, O = occipital, F–P = frontoparietal, 3D-CRT = Three-Dimensional Conformal Radiotherapy, IMRT = Intensity-Modulated Radiotherapy.

Basic characteristics	*Study cohort* $n = 39$	*Validation* $n = 16$	*p*
Age at initial diagnosis (years)			
Median	51	54	0.7
Range	29–66	35–64	
Sex (n)			
Men	28 (72%)	10 (63%)	0.5
GBM location (%)			
T/F/P/O/F-P	38/29/19/5/9	34/31/14/7/14	0.7
Radiotherapy			
Median dose (Gy)	60	60	0.9
Technique 3D-CRT/IMRT (%)	30/70	40/60	0.8
Cycles of adjuvant TMZ			
Median	6	6	0.9
Range	1–12	4–10	
Time to graphic progression (months)			
Median (95% CI)	6.7 (2.9–9.6)	6.1 (4.8–8.8)	0.8
Diagnosis validation			
Biopsy/subsequent imaging (%)	67/33	75/25	0.6
Final diagnosis			
Tumor recurrence	29 (75%)	12 (75%)	1
Pseudoprogression	10 (25%)	4 (25%)	
Overall survival (months)			
Median (95% CI)	14.5 (12.9–17.4)	14.0 (13.1–15.2)	0.8

Table 2
Calculated cut-offs for the diagnosis of a tumor recurrence with related sensitivity and specificity for the most important concentration ratios of the metabolites measured by MRS and for ADCmean.

Metabolite	AUC (95% CI)	p	Cut-off for recurrence	Sensitivity	Specificity
tCho/tNAA	0.993 (0.978; 1.000)	<0.001	≥1.3	100.0	94.7
tCho/tCr	0.691 (0.539; 0.843)	0.013	≥0.7	74.6	63.2
tNAA/tCr	0.949 (0.873; 1.000)	<0.001	≤0.7	96.6	94.7
Lac + Lip 1.3/tCr	0.714 (0.559; 0.868)	0.003	≥1.6	76.3	68.4
Lac + Lip 0.9–1.3/tCr	0.723 (0.568; 0.879)	0.004	≥2.0	78.0	68.4
ADCmean [10^{-6} mm^2/s]	0.998 (0.993; 1.000)	<0.001	≤1313	98.3	100.0

3.2. Advanced imaging characteristics

The values of metabolite concentration ratios are summarized in Table 2, the percentage distribution of patients in Table 3, and typical imaging findings are presented in Fig. 1. The mean and standard deviation of the signal-to-noise ratios of MR spectra in the analyzed voxels was 4.75 ± 0.80. The average number of voxels with acceptable spectra quality per patient was 3.75 ± 1.13 and varied based on the proximity of the skull and a resection cavity as the most significant noise-conducting factors.

A significant difference in the tCho/tNAA and tNAA/tCr ratios was found between the GBM relapse and PsP. The GBM relapse was characterized by the tCho/tNAA ratio ≥ 1.3 with sensitivity of 100% and specificity of 94.7% ($p < 0{,}001$). All patients with GBM recurrence had the value of tCho/tNAA above this cut-off; yet, there were still 5.3% (1/19) lesion assigned as PsP reaching the same tCho/tNAA cut-off as GBM recurrence. Another metabolite ratio with statistical significance was tNAA/tCr characterized by the threshold ≤0.7 for calling the GBM recurrence with sensitivity of 96.6% and specificity of 94.7% ($p < 0{,}001$). There were 93.2% (55/59) lesion considered as the GBM recurrence that had the tNAA/tCr values below the cut-off, just as 5.3% (1/19) as PsP.

The calculated ADCmean values were significantly lower in the GBM relapse group than in the PsP group ($p < 0.001$), with the cut-off of 1313×10^{-6} mm^2/s (sensitivity 98.3% and specificity 100.0%). Ninety-eight percent of patients with the GBM relapse had the ADCmean $\leq 1313 \times 10^{-6}$ mm^2/s while all the patients with PsP had the ADCmean $> 1313 \times 10^{-6}$ mm^2/s.

3.3. Characteristics of the patients in the validation cohort

The basic characteristics of the patients in the validation cohort are summarized in Table 1 and are balanced with the study cohort. Their pertinent metabolite concentrations and ADCmean values are reported in Table 4 together with the level of success in the prediction of diagnosis by each measured characteristic. The tCho/tNAA ratio assigned diagnosis correctly in 15/16 (94%) patients, the ADCmean value in 15/16 (94%) patients, the concentration ratio of tNAA/tCr in 13/16 (81%) patients, while tCho/tCr, Lac + Lip 1.3/tCr and Lac + Lip 0.9–1.3/tCr only in 8/16 (50%) patients. These results confirm expected specificity for the measured MR characteristics. The combination of tCho/tNAA and ADCmean led to the highest accuracy while establishing the final diagnosis.

Table 3
The percentage distribution of patients with the pseudoprogression and glioblastoma recurrence as the function of calculated cut-offs.

		Pseudoprogression (n = 19)	Recurrence (n = 59)	p
tCho/tNAA	<1.3	18 (94.7%)	0	<0.001
	≥1.3	1 (5.3%)	59 (100.0%)	
Median (min; max)		0.74 (0.33–1.77)	2.13 (1.35–9.60)	<0.001
tCho/tCr	<0.7	11 (57.9%)	15 (25.4%)	0.013
	≥0.7	8 (42.1%)	44 (74.6%)	
Median (min; max)		0.64 (0.28–1.37)	0.89 (0.44–2.83)	0.013
tNAA/tCr	>0.7	18 (94.7%)	4 (6.8%)	<0.001
	≤0.7	1 (5.3%)	55 (93.2%)	
Median (min; max)		0.99 (0.28–1.59)	0.41 (0.11–0.96)	<0.001
Lac + Lip 1.3/tCr	<1.6	12 (63.2%)	14 (23.7%)	0.004
	≥1.6	7 (36.8%)	45 (76.3%)	
Median (min; max)		1.13 (0.07–10.65)	2.69 (0.40–15.63)	0.005
Lac + Lip 0.9–1.3/tCr	<2.0	13 (68.4%)	13 (22.0%)	<0.001
	≥2.0	6 (31.6%)	46 (78.0%)	
Median (min; max)		1.33 (0.08–12.35)	3.26 (0.54–17.42)	0.004
ADCmean	>1313	19 (100.0%)	1 (1.7%)	<0.001
	≤1313	0	58 (98.3%)	
Median (min; max)		1372 (1317–1476)	1155(756–1344)	<0.001

4. Discussion

The accurate and timely identification of a tumor relapse is the most essential prerequisite of an efficient salvage therapy emphasizing the importance of precise assessment of the response to the initial treatment. Well-known difficulties with distinguishing between a GBM recurrence and treatment related changes caused by the administration of concomitant RT and TMZ (pseudoprogression) or angiogenesis inhibitors (pseudoresponse) (Hygino da Cruz et al., 2011; Chakravarti et al., 2006) are already expressed in the current RANO (Response Assessment in Neuro-Oncology) criteria (Wen et al., 2010). Nevertheless, the evolution of the response criteria that is a continuing process and implementation of advanced MRI methods is expected, most likely by MRS and DWI because of their high availability. Especially for these advanced MRI methods, the standardization of MRI protocols is needed in order to be used optimally in the evaluation of results from multicentric studies. The topicality of this need is expressed by the current consensual recommendations for the standard brain tumor imaging protocol in clinical trials published in September 2015, which already include pre-contrast, axial 2D, 3-directional DWI (Ellingson et al., 2015). Before similar recommendations for other advanced MRI modalities are established, centers utilizing these methods to resolve ambiguous findings in the classic structural MRI should develop their own thresholds and cut-offs for a valid image description.

The MRS seems to be a promising method that is complementary to the widely used structural MRI and can be used to increase the diagnostic accuracy of the brain tumor imaging protocol. The results of this study proved very high sensitivity and specificity of the tCho/tNAA concentration ratio (100.0% and 94.7%, respectively) for a non-invasive differentiation between a GBM recurrence and PsP. The underlying pathophysiology of the MRS observations is well described especially from the experience with glioma grading (Bulik et al., 2013). Choline represents the marker of cell membrane integrity and turnover and is associated with the presence of an increased tumor cell proliferation, while NAA is the marker of the density and viability of neurons. Thus, their mutual ratio forms the best approach when using the MRS for brain tumor diagnostics. The result of the MRS, though, depends on the type of the MR scanner, specific acquisition setup parameters, and is very sensitive to the proximity of FOV to the surrounding structures decreasing signal/noise ratio of the brain spectra (i.e. bone). As the spectrum quality is also highly influenced by the personal experience of a radiologist, it is useful to establish an institutional protocol with the adjustment of thresholds and cut-offs for the main metabolite concentrations measured by the MRS. Moreover, there is the significant

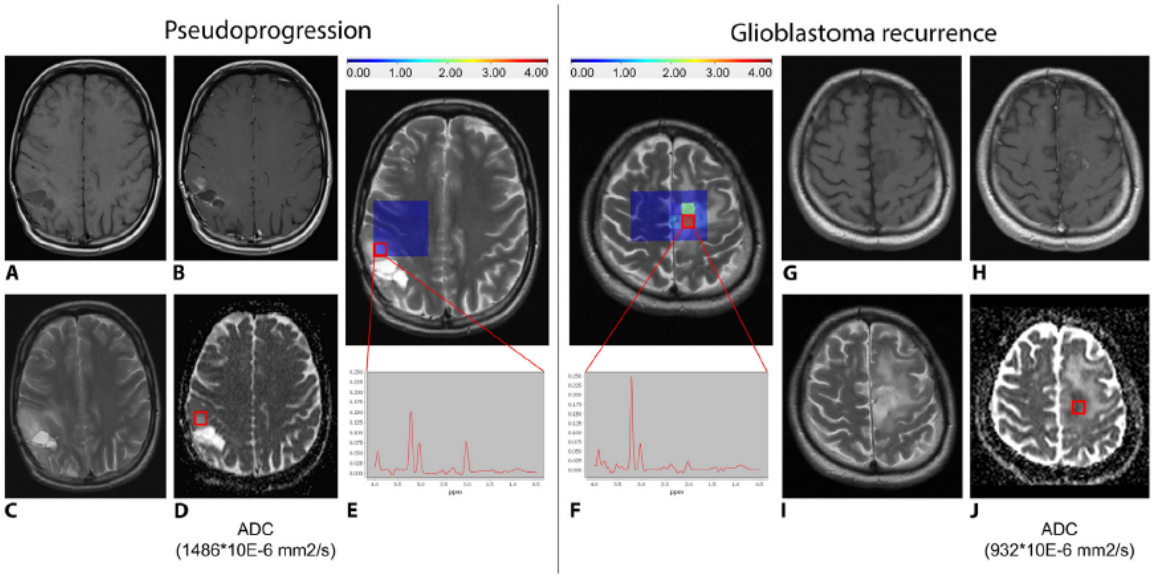

Fig. 1. The pseudoprogression and glioblastoma recurrence findings on MRI. Representative MRI examples of the pseudoprogression (A–E) and glioblastoma relapse (F–J): (A) + (G) show T1WI, (B) + (H) show T1WI with gadolinium, (C) + (I) show T2WI, (D) + (J) show the ADC maps with marked VOI and corresponding ADCmean values, and (E) + (F) show the proton MR spectroscopy maps focused on tCho/tNAA concentration ratio with marked VOI, corresponding values and spectra. The MR spectra illustrate concentrations of the main metabolites within the selected voxel. The color scale for the tCho/tNAA ratio corresponds to the color map shown for the MRSI grids overlaid on top of the MR images. The signal-to-noise ratio of the presented MR spectra is 4.98 in pseudoprogression and 4.86 in glioblastoma recurrence as well as the error of tCho/tNAA concentration 7% and 4%, respectively.

heterogeneity of glial tumor tissue and many suspected recurrences are localized in close proximity to the bone increasing noise in the acquired MR spectra. Thus, it is useful to perform the MRS by means of a Spectroscopic Imaging technique in two orthogonal planes covering most of the enhancing brain regions. We faced all the described difficulties in MRS voxel analysis since the patients of our cohort underwent gross total resection (GTR). This patients' selection was needed, whether we wanted to analyze the ability of MRS and ADC maps to distinguish strictly between the pseudoprogression and tumor recurrence with no bias by a residual tumor. The probability to achieve GTR is higher in the case of small and superficial tumors located in the proximity of the skull. In addition, the majority of gadolinium-enhancing lesions were heterogeneous, irregular in shape, and small due to a frequent follow-up that further underline necessity to use the Spectroscopic Imaging technique and strict voxel selection. Compare to our methodology, Single Voxel MR spectroscopy is often used in published studies but it is highly influenced by the partial volume effect where the obtained spectra are distorted by surrounding tissue (Lee et al., 2013).

There are several studies focusing on MRS for the purpose of differentiating glioma recurrence from treatment related changes. The current meta-analysis by Zhang et al., involving 18 studies and 455 patients, showed only moderate sensitivity and specificity of the tCho/tNAA ratio (88% and 86%, respectively) for differentiating a recurrent glioma from radiation necrosis (Zhang et al., 2014). However, the late treatment related changes of RT and TMZ have some similar histopathologic features as a high-grade glioma relapse (e.g. the presence of necrosis) that can lead to a decreased accuracy of MRS diagnostic and can explain our superior results because we observed only patients with PsP. Moreover, most studies reviewed by Zhang and colleagues used Single Voxel MRS where average values from larger voxels are produced. The analysis of individual small voxels may also explain higher sensitivity and specificity observed in the presented study. Nevertheless, as we can expect lower sensitivity and specificity of the MRS in the general diagnostic protocol for differential diagnostic in neuro-oncology, we agree with the recommendation of Zhang et al. to combine MRS with other multimodal imaging methods. For example, that would be definitely the case of the patient number 12 from our validation cohort where conflicting results of MRS and DWI were presented. Fortunately, this patient was able to undergo biopsy validation confirming the tumor recurrence. Otherwise, close follow-up with early repeated imaging studies would be indicated.

Diffusion-weighted imaging describes changes in water diffusivity mainly as the function of changes in cell density. The diffusion changes can be quantified by the ADC. Generally speaking, decreased diffusivity is the consequence of an enhanced tumor cell proliferation and is reflected by the water diffusion restriction that lowers ADC values. In the present study, the evaluation of mean ADC values led to the highest sensitivity and specificity with the cut-off of 1313×10^{-6} mm^2/s in distinguishing between a GBM recurrence and PsP that was proved in our validation cohort of patients. For all patients with PsP from this study cohort, the ADC mean value was $>1313 \times 10^{-6}$ mm^2/s. However, evaluating the diagnostic quality of DWI in differentiating glioma recurrence from radiation necrosis, the current meta-analysis by Zhang et al. from April 2015 pooled and weighted data from 284 patients, and showed only moderate diagnostic performance in differentiating the glioma recurrence with sensitivity of 82% (95% CI: 75,87) and specificity of 84% (95% CI: 76,91) (Zhang et al., 2015). In the present study, the higher sensitivity and specificity observed can be explained by the same way as in the case of the MRS mentioned above — treatment related changes represented exclusively by PsP with no case of radionecrosis.

The lack of radionecrosis in our cohort can be explained by a time factor. The aim of our study was to describe early MRI changes after oncology treatment; however, radionecrosis is more often related to the late effect of radiotherapy. Regardless of low radionecrosis incidence in selected group of patients after RT and TMZ (9.3% of patients), Ruben with co-authors described that mean interval from the completion of radiotherapy to the diagnosis of radionecrosis was 11.6 months in the cohort of 426 patients treated for glioma (Ruben et al., 2006). The lack of radionecrosis may be also related to the gross total extent of resections and generally less aggressive strategy in delivery of radiotherapy (normalization to 95% of prescribed dose, strict limitations of Dmax, less generous target definition strategy with reference to RTOG rather than to EORTC approach).

This study has also some inherent limitations. The fact that a biopsy for proving the final diagnosis (recurrence vs. treatment related

Table 4
The validation of the calculated metabolite concentration ratios and ADCmean cut-offs for the GBM recurrence by the respective cohort of patients. The gray color indicates discrepancy between the predicted value and the real measured value. R — recurrence, PsP — pseudoprogression.

Validation cohort n = 16	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Final diagnosis R / PsP	R	R	R	R	PsP	R	R	R	R	R	R	R	R	PsP	PsP	PsP
tCho/tNAA cut–off ≥ 1.3	1.5	2.0	2.4	2.7	1.1	2.7	5.1	3.3	3.6	1.8	5.1	1.2	2.0	0.5	1.0	1.0
tCho/tCr cut–off ≥ 0.7	0.6	0.7	0.6	0.6	0.4	0.5	0.3	0.5	0.7	0.8	0.8	0.4	0.4	0.5	0.5	0.6
tNAA/tCr cut–off ≤ 0.7	0.4	0.3	0.2	0.2	0.4	0.2	0.1	0.2	0.2	0.4	0.2	0.4	0.2	1.1	0.6	0.6
Lac +Lip 1.3/tCr cut–off ≥ 1.6	0.5	1.1	3	0.6	2.2	0.8	1	0.7	1.7	1.4	2.8	0.9	1.7	0.4	0.5	0.4
Lac + Lip 0.9–1.3/tCr cut–off ≥ 2.0	0.6	1.3	4.7	0.9	3.8	2	1.7	1.1	2.2	1.8	3.4	1.6	2.1	0.7	0.8	0.7
ADCmean cut–off ≤ 1313	1248	1157	928	1189	1387	1287	1038	917	838	1348	937	1197	1298	1503	1425	1398

changes) was missing in 33% of patients, as their best interest was reflected, may prevent the deeper explanation of the observed metabolite concentrations or the ADC data. It may be assumed that some patients develop the overlapping imaging features of both PsP and early GBM recurrence at the same time, which lowers the tCho/tNAA ratio and increases the ADCmean value due to the predominance of initial PsP changes. On the other hand, patients with PsP are more often those with a favorable prognosis and the concurrent presence of PsP and early GBM progression is not a case of all patients with PsP. Moreover, the use of biopsy samples may also be difficult to interpret because of the above mentioned tissue mixture, as well as the post radiotherapy changes. It means that the single target stereotactic needle biopsy of the lesion suspected of a tumor recurrence may be inaccurate (Hygino da Cruz et al., 2011). Patients who are not able to undergo tumor resection or at least biopsy validation may most benefit from the non-invasive nature of advanced MRI methods and, in clinical practice, they may be candidates for further imaging studies including MR perfusion or positron emission tomography examination. With this consideration, we can agree with the recommendation of Zhang et al. to combine DWI imaging results with other multimodal imaging methods (Zhang et al., 2014, 2015). Thus, combination of ADC values and metabolite concentrations measured by MRS could produce a single prediction with a significant clinical impact; however, other studies with more patients included are needed for valid recommendations.

5. Conclusion

In conclusion, there is the increasing evidence for routine utilization of advanced MRI methods such as DWI and MRS in brain tumor imaging protocols. This study has proved that the combination of ADCmean values $\leq 1313 \times 10^{-6}$ mm2/s and the tCho/tNAA concentration ratio ≥1.3 have the high validity for a non-invasive differentiation between a GBM recurrence and pseudoprogression. However, institutional definition and validation of the thresholds of the advanced MR methods is needed in order to implement the multimodal imaging into routine clinical practice, as well as clinical trials.

Conflicts of interest

The authors declare that they have no conflicts of interest.

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4. Prognostické indexy

Tab. 3: RPA klasifikace k odhadu prognózy pacientů s nově diagnostikovanými mozkovými metastázami (31)

Skupina	Charakteristika	Celkové přežití (měsíce)
RPA_1	KPS 70–100; kontrolováno primární onemocnění; věk < 65 let, bez extrakraniálních metastáz	7,1
RPA_2	ostatní	4,2
RPA_3	KPS < 70	2,3

Zkratky: RPA: Recursive Partitioning Analysis; KPS: výkonnostní stav dle Karnofského indexu.

I přes široké užívání v rámci rutinní ambulantní praxe vykazoval tento systém řadu nedostatků. Většina pacientů byla v praxi kategorizována do RPA_2 skupiny a klasifikace nesplňovala další současné požadavky na efektivní prognostický index:

- hodnoty přežití se mezi jednotlivými skupinami signifikantně liší
- pacienti v rámci jednotlivé skupiny mají podobné hodnoty přežití
- pacienti jsou rovnoměrně rozloženi mezi jednotlivé skupiny
- kategorizace pacientů do jednotlivých skupin vede k rozdílnému terapeutickému postupu

Poté, co byl s nástupem cílených stereotaktických radioterapeutických technik popsán význam cílené vysokodávkové radioterapie, a tedy význam velikosti a počtu mozkových metastáz, byl počet mozkových metastáz zohledněn v dalším široce používaném systému pro odhad prognózy GPA (Graded Prognostic Assessment) publikovaném v roce 2008 (32), tabulka 4.

Obr. 3: Čtvrté revidované vydání WHO klasifikace mozkových nádorů. Ačkoliv jsou mozkové metastázy desetkrát častější, nejsou v porovnání s primárními mozkovými nádory dosud blíže klasifikovány

Diffuse astrocytic and oligodendroglial tumours	
Diffuse astrocytoma, IDH-mutant	9400/3
Gemistocytic astrocytoma, IDH-mutant	9411/3
Diffuse astrocytoma, IDH-wildtype	*9400/3*
Diffuse astrocytoma, NOS	9400/3
Anaplastic astrocytoma, IDH-mutant	9401/3
Anaplastic astrocytoma, IDH-wildtype	*9401/3*
Anaplastic astrocytoma, NOS	9401/3
Glioblastoma, IDH-wildtype	9440/3
Giant cell glioblastoma	9441/3
Gliosarcoma	9442/3
Epithelioid glioblastoma	*9440/3*
Glioblastoma, IDH-mutant	9445/3*
Glioblastoma, NOS	9440/3
Diffuse midline glioma, H3 K27M–mutant	9385/3*
Oligodendroglioma, IDH-mutant and 1p/19q-codeleted	9450/3
Oligodendroglioma, NOS	9450/3
Anaplastic oligodendroglioma, IDH-mutant and 1p/19q-codeleted	9451/3
Anaplastic oligodendroglioma, NOS	*9451/3*
Oligoastrocytoma, NOS	*9382/3*
Anaplastic oligoastrocytoma, NOS	*9382/3*
Other astrocytic tumours	
Pilocytic astrocytoma	9421/1
Pilomyxoid astrocytoma	9425/3
Subependymal giant cell astrocytoma	9384/1
Pleomorphic xanthoastrocytoma	9424/3
Anaplastic pleomorphic xanthoastrocytoma	9424/3
Ependymal tumours	
Subependymoma	9383/1
Myxopapillary ependymoma	9394/1
Ependymoma	9391/3
Papillary ependymoma	9393/3
Clear cell ependymoma	9391/3
Tanycytic ependymoma	9391/3
Ependymoma, *RELA* fusion–positive	9396/3*
Anaplastic ependymoma	9392/3
Other gliomas	
Chordoid glioma of the third ventricle	9444/1
Angiocentric glioma	9431/1
Astroblastoma	9430/3
Choroid plexus tumours	
Choroid plexus papilloma	9390/0
Atypical choroid plexus papilloma	9390/1
Choroid plexus carcinoma	9390/3

Neuronal and mixed neuronal-glial tumours	
Dysembryoplastic neuroepithelial tumour	9413/0
Gangliocytoma	9492/0
Ganglioglioma	9505/1
Anaplastic ganglioglioma	9505/3
Dysplastic cerebellar gangliocytoma (Lhermitte-Duclos disease)	9493/0
Desmoplastic infantile astrocytoma and ganglioglioma	9412/1
Papillary glioneuronal tumour	9509/1
Rosette-forming glioneuronal tumour	9509/1
Diffuse leptomeningeal glioneuronal tumour	
Central neurocytoma	9506/1
Extraventricular neurocytoma	9506/1
Cerebellar liponeurocytoma	9506/1
Paraganglioma	8693/1
Tumours of the pineal region	
Pineocytoma	9361/1
Pineal parenchymal tumour of intermediate differentiation	9362/3
Pineoblastoma	9362/3
Papillary tumour of the pineal region	9395/3
Embryonal tumours	
Medulloblastomas, genetically defined	
Medulloblastoma, WNT-activated	9475/3*
Medulloblastoma, SHH-activated and *TP53*-mutant	9476/3*
Medulloblastoma, SHH-activated and *TP53*-wildtype	9471/3
Medulloblastoma, non-WNT/non-SHH	9477/3*
Medulloblastoma, group 3	
Medulloblastoma, group 4	
Medulloblastomas, histologically defined	
Medulloblastoma, classic	9470/3
Medulloblastoma, desmoplastic/nodular	9471/3
Medulloblastoma with extensive nodularity	9471/3
Medulloblastoma, large cell / anaplastic	9474/3
Medulloblastoma, NOS	9470/3
Embryonal tumour with multilayered rosettes, C19MC-altered	9478/3*
Embryonal tumour with multilayered rosettes, NOS	*9478/3*
Medulloepithelioma	9501/3
CNS neuroblastoma	9500/3
CNS ganglioneuroblastoma	9490/3
CNS embryonal tumour, NOS	9473/3
Atypical teratoid/rhabdoid tumour	9508/3
CNS embryonal tumour with rhabdoid features	*9508/3*
Tumours of the cranial and paraspinal nerves	
Schwannoma	9560/0
Cellular schwannoma	9560/0
Plexiform schwannoma	9560/0

Melanotic schwannoma	9560/1
Neurofibroma	9540/0
Atypical neurofibroma	9540/0
Plexiform neurofibroma	9550/0
Perineurioma	9571/0
Hybrid nerve sheath tumours	
Malignant peripheral nerve sheath tumour	9540/3
Epithelioid MPNST	9540/3
MPNST with perineurial differentiation	9540/3
Meningiomas	
Meningioma	9530/0
Meningothelial meningioma	9531/0
Fibrous meningioma	9532/0
Transitional meningioma	9537/0
Psammomatous meningioma	9533/0
Angiomatous meningioma	9534/0
Microcystic meningioma	9530/0
Secretory meningioma	9530/0
Lymphoplasmacyte-rich meningioma	9530/0
Metaplastic meningioma	9530/0
Chordoid meningioma	9538/1
Clear cell meningioma	9538/1
Atypical meningioma	9539/1
Papillary meningioma	9538/3
Rhabdoid meningioma	9538/3
Anaplastic (malignant) meningioma	9530/3
Mesenchymal, non-meningothelial tumours	
Solitary fibrous tumour / haemangiopericytom	
Grade 1	8815/0
Grade 2	8815/1
Grade 3	8815/3
Haemangioblastoma	9161/1
Haemangioma	9120/0
Epithelioid haemangioendothelioma	9133/3
Angiosarcoma	9120/3
Kaposi sarcoma	9140/3
Ewing sarcoma / PNET	9364/3
Lipoma	8850/0
Angiolipoma	8861/0
Hibernoma	8880/0
Liposarcoma	8850/3
Desmoid-type fibromatosis	8821/1
Myofibroblastoma	8825/0
Inflammatory myofibroblastic tumour	8825/1
Benign fibrous histiocytoma	8830/0
Fibrosarcoma	8810/3
Undifferentiated pleomorphic sarcoma / malignant fibrous histiocytoma	8802/3
Leiomyoma	8890/0
Leiomyosarcoma	8890/3
Rhabdomyoma	8900/0
Rhabdomyosarcoma	8900/3
Chondroma	9220/0
Chondrosarcoma	9220/3
Osteoma	9180/0

Osteochondroma	9210/0
Osteosarcoma	9180/3
Melanocytic tumours	
Meningeal melanocytosis	8728/0
Meningeal melanocytoma	8728/1
Meningeal melanoma	8720/3
Meningeal melanomatosis	8728/3
Lymphomas	
Diffuse large B-cell lymphoma of the CNS	9680/3
Immunodeficiency-associated CNS lymphomas	
AIDS-related diffuse large B-cell lymphoma	
EBV-positive diffuse large B-cell lymphoma, NOS	
Lymphomatoid granulomatosis	9766/1
Intravascular large B-cell lymphoma	9712/3
Low-grade B-cell lymphomas of the CNS	
T-cell and NK/T-cell lymphomas of the CNS	
Anaplastic large cell lymphoma, ALK-positive	9714/3
Anaplastic large cell lymphoma, ALK-negative	9702/3
MALT lymphoma of the dura	9699/3
Histiocytic tumours	
Langerhans cell histiocytosis	9751/3
Erdheim–Chester disease	9750/1
Rosai–Dorfman disease	
Juvenile xanthogranuloma	
Histiocytic sarcoma	9755/3
Germ cell tumours	
Germinoma	9064/3
Embryonal carcinoma	9070/3
Yolk sac tumour	9071/3
Choriocarcinoma	9100/3
Teratoma	9080/1
Mature teratoma	9080/0
Immature teratoma	9080/3
Teratoma with malignant transformation	9084/3
Mixed germ cell tumour	9085/3
Tumours of the sellar region	
Craniopharyngioma	9350/1
Adamantinomatous craniopharyngioma	9351/1
Papillary craniopharyngioma	9352/1
Granular cell tumour of the sellar region	9582/0
Pituicytoma	9432/1
Spindle cell oncocytoma	8290/0
Metastatic tumours	

V rámci denní onkologické praxe lze doporučit online dostupné indexy jako zmiňovaný DS-GPA z http://brainmetgpa.com/, pro využití v rámci vědeckovýzkumných analýz jsou výhodnější tabulkové editory vhodně upravené pro automatické výpočty zvolených prognostických indexů na základě vkládaných surových dat (30).

4.1 PUBLIKACE 3

Kazda T, Kuklova A, Pospisil P, Burkoň P, Slavík M, Hynková L, et al. Utilization of Prognostic Indexes for Patients with Brain Metastases in Daily Radiotherapy Routine – is the Complexity and Intricacy Still an Issue? Klin Onkol. 2015; 28(5): 352–358. (30)

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Východiska: Existuje několik prognostických indexů pro pacienty s mozkovými metastázami, které mohou pomoci při rozhodování o nejlepší léčbě zahrnující mimo jiné i paliativní radioterapii. Jejich výpočet ale bývá poměrně složitý. Připravili jsme praktickou tabulku pro jejich jednoduchou kalkulaci, pomocí které jsme retrospektivně vyhodnotili vybrané prognostické indexy (RPA, GPA a $WBRT_{30}$) u pacientů podstupujících radioterapii na našem pracovišti.

Soubor pacientů a metody: Byla vyhodnocena konsekutivní série pacientů ozařovaných v roce 2011 pro nově diagnostikované mozkové metastázy a jejich přežití bylo porovnáno s odhadovanou prognózou dle jednotlivých prognostických indexů a s použitou ozařovací technikou.

Výsledky: Celkem bylo ozářeno 121 pacientů (61 % s mnohočetnými metastázami), většina pacientů podstoupila celomozkové ozáření. Medián celkového přežití od data indikace radioterapie byl 3,13 měsíce. Rozložení pacientů do jednotlivých podskupin prognostických indexů bylo nerovnoměrné s 8 (7 %), 89 (73 %) a 24 (20 %) pacienty přiřazenými do RPA 1, 2 a 3 podskupiny, 3 (3 %), 9 (7 %), 57 (47 %) a 52 (43 %) pacienty přiřazenými do GPA 3,5–4, GPA 3,0, GPA 1,5–2,5 a GPA 0–1,0 podskupiny a 10 (8 %), 88 (73 %) a 23 (19 %) pacienty přiřazenými do $WBRT_{30}$ podskupiny D, B a A. Celkové rozdíly v přežití jednotlivých podskupin byly statisticky signifikantní.

Závěr: Odhad prognózy pacientů s mozkovými metastázami je důležitý a používání prognostických indexů je užitečné pro diagnosticko-terapeutickou rozvahu. Jejich výpočet je usnadněn vhodně připravenými široce dostupnými tabulkovými editory.

Utilization of Prognostic Indexes for Patients with Brain Metastases in Daily Radiotherapy Routine – is the Complexity and Intricacy Still an Issue?

Použití prognostických indexů pro pacienty s mozkovými metastázami v denní radioterapeutické praxi – je jejich složitý výpočet ještě stále problém?

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Summary

Background: Many prognostic indexes are available for patients with brain metastases in order to estimate remaining lifetime before selection of appropriate treatment including palliative radiotherapy. Their routine utilization is often deprecated for their complexity. We developed a practical tool based on widely available spreadsheet editors for facilitation of daily clinical use of selected indexes (RPA, GPA and WBRT-30) and evaluated its usage for retrospective single institutional survival analysis of patients irradiated for brain metastases. ***Patients and Methods:*** Spreadsheet platform was prepared and adjusted for automatic calculation of selected prognostic indexes after input of the relevant parameters. The consecutive series of newly diagnosed patients referred during 2011 to the palliative brain radiotherapy were analyzed, and real calculated survival parameters of individual subgroups of RPA, GPA and WBRT-30 were compared with estimated ones. Correlation of radiotherapy technique and estimated survival at the time of treatment indication was evaluated. ***Results:*** Total of 121 patients (61% with multiple metastases) were irradiated with the majority undergoing whole brain radiotherapy. Median overall survival from the time of radiotherapy indication was 3.13 months. Non-balanced distribution into individual scoring systems subgroups was observed with 8 (7%), 89 (73%) and 24 (20%) patients assigned to RPA 1, 2 and 3 subgroup, 3 (3%), 9 (7%), 57 (47%) and 52 (43%) patients assigned to GPA 3.5–4, GPA 3.0, GPA 1.5–2.5 and GPA 0–1.0 subgroup and 10 (8%), 88 (73%) and 23 (19%) patients assigned to WBRT-30 subgroup D, B and A. Entire differences in overall survival between subgroups are significant among all three scoring systems. ***Conclusion:*** Routine calculation of available prognostic indexes is useful in decision making regarding the best radiotherapy of brain metastases, and their calculation is greatly facilitated by properly prepared widely available spreadsheet tools.

Key words

prognosis – nomograms – cranial irradiation – RPA – GPA – WBRT-30

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Souhrn

Východiska: Existuje několik prognostických indexů pro pacienty s mozkovými metastázami, které mohou pomoci při rozhodování o nejlepší léčbě zahrnující mimo jiné i paliativní radioterapii. Jejich výpočet ale bývá poměrně složitý. Připravili jsme praktickou tabulku pro jejich jednoduchou kalkulaci, pomocí které jsme retrospektivně vyhodnotili vybrané prognostické indexy (RPA, GPA a WBRT-30) u pacientů podstupujících radioterapii na našem pracovišti. ***Soubor pacientů a metody:*** Byla vyhodnocena konsekutivní série pacientů ozařovaných v roce 2011 pro nově diagnostikované mozkové metastázy a jejich přežití bylo porovnáno s odhadovanou prognózou dle jednotlivých prognostických indexů a s použitou ozařovací technikou. ***Výsledky:*** Celkem bylo ozářeno 121 pacientů (61 % s mnohočetnými metastázami), většina pacientů podstoupila celomozkové ozáření. Medián celkového přežití od data indikace radioterapie byl 3,13 měsíce. Rozložení pacientů do jednotlivých podskupin prognostických indexů bylo nerovnoměrné s 8 (7 %), 89 (73 %) a 24 (20 %) pacienty přiřazenými do RPA 1, 2 a 3 podskupiny, 3 (3 %), 9 (7 %), 57 (47 %) a 52 (43 %) pacienty přiřazenými do GPA 3,5–4, GPA 3,0, GPA 1,5–2,5 a GPA 0–1,0 podskupiny a 10 (8 %), 88 (73 %) a 23 (19 %) pacienty přiřazenými do WBRT-30 podskupiny D, B a A. Celkové rozdíly v přežití jednotlivých podskupin byly statisticky signifikantní. ***Závěr:*** Odhad prognózy pacientů s mozkovými metastázami je důležitý a používání prognostických indexů je užitečné pro diagnosticko-terapeutickou rozvahu. Jejich výpočet je usnadněn vhodně připravenými široce dostupnými tabulkovými editory.

Klíčová slova

prognóza – nomogram – ozařování mozku – RPA – GPA – WBRT-30

Introduction

The best radiotherapy (RT) practice concerning patients suffering from brain metastases (BM) is currently becoming more challenging, and optimal therapeutic approach remains controversial [1]. With increasing incidence of BM and overall survival (OS) time [2,3] and with wider availability of different RT systems, proper selection of patients is required to support adequate treatment recommendation in personalized cost-effective care [4,5]. Additionally, decision making between different RT approaches is intended to minimalize late adverse effects, especially in patients with better prognosis.

The portfolio of possible RT techniques is becoming more available, including classical whole brain radiotherapy (WBRT), stereotactic radiotherapy (SRT) or radiosurgery (SRS), simultaneous integrated BM boosting (WBRT + SIB) or currently investigated hippocampus sparing concept [6–9]. Indeed, more attention is paid to preserving cognitive function during palliative brain irradiation as highlighted also during the 2015 American Society of Clinical Oncology Annual Meeting at plenary session lecture about NCCTG N0574 trial – a phase III randomized trial of WBRT in addition to SRS in patients with one to three brain metastases [10]. Results of this potentially practice changing trial reveal more cognitive declines after combination of WBRT with SRS, while no improvement in OS was described. Thus, identification of patients amenable for more local RT approach will be further emphasized.

Many prognostic scoring systems were developed in order to provide objective prognosis assessment and to define criteria for inclusion and stratification of patients with BM eligible for randomized clinical trials. Recursive partitioning analysis (RPA) was developed in 1997 by Gaspar et al. and is generally the best known scoring system [11]. RPA is based on prognostic factors identified in three seminal Radiation Therapy Oncology Group BM clinical trials. Adding number of metastases to the prognosis estimation, Sperduto et al. in 2008 [12] introduced Graded Prognostic Assessment (GPA). The latest system WBRT-30 was developed based solely on the data from patients treated by WBRT with dose 30 Gy delivered in 10 fractions [13,14]. It predicts 6-month-survival probability compared to median OS estimation provided by the other scoring systems.

However, using scoring systems in routine daily clinical practice may be depreciated for their complexity and intricacy; therefore, estimation based on the clinical experiences is often preferred. The goal of present study was to develop a practical tool based on widely available spreadsheet editors to facilitate daily clinical use of selected established prognostic scoring systems (RPA, GPA and WBRT-30) and to evaluate their usage for retrospective single institutional survival analysis of unselected patients irradiated for newly diagnosed BM.

Patients and methods

Patients and data selection

The consecutive series of newly diagnosed BM patients who were referred in 2011 to palliative brain RT in the Department of Radiation Oncology, Masaryk Memorial Cancer Institute, were enrolled into this study. Electronic medical records were reviewed for obtaining following preselected variables: age, sex, Karnofsky performance status (KPS) before brain irradiation, presence of extracranial metastases (yes/no), systemic treatment prior to WBRT (yes/no), status of primary tumor (controlled/uncontrolled), number of BM, cancer type (breast, melanoma, small cell lung cancer (SCLC), non-small cell lung cancer (NSCLC), gastrointestinal cancer (GI), renal cell carcinoma (RCC), other), the date of RT indication, the date of the end of RT, the date of death or last follow-up visit, RT technique (whole brain radiotherapy (WBRT), stereotactic radiotherapy (SRT) or radiosurgery (SRS), WBRT with simultaneous integrated boost to metastasis (WBRT + SIB)) and the delivered dose.

Prognostic scoring systems

The prognostic systems were utilized for patients' stratification into individual groups. RPA divides patients into three subgroups based on the evaluation of KPS, age, primary tumor status and presence of extracranial metastases [11]. GPA considers four criteria (age, KPS, number of BM and primary tumor sta-

tus) and divides patients into four subgroups [12]. WBRT-30 divides patients into four subgroups by assigned points for KPS, age, extracranial metastases and systemic treatment prior to WBRT status (Tab. 1): group A (6–9 points), group B (10–14 points), group C (15–17 points) and group D (18–19 points) [13,14]. Above mentioned prognostic scoring indexes were calculated by interactive spreadsheet editor (Microsoft Office Excel 2007 (computer software), Redmond, Washington: Microsoft) designed for easy automatic enumeration of appropriate variables (age, KPS, etc.) and survival estimation (Fig. 1).

Tab. 1. Scoring of different clinical variables and related points for calculation of WBRT-30 prognostic system [14].

KPS		Age		Extracranial metastases		Systemic treatment prior to WBRT	
< 70	1	< 50	5	yes	2	yes	3
= 70	4	51–60	4	no	5	no	2
> 70	6	61–70	3				
		> 70	1				

KPS – Karnovsky performance status, WBRT – whole brain radiotherapy

Statistical analysis

OS was estimated using Kaplan-Meier methodology as the time from the end of the RT course (a) and the date of the initial indication of RT till death or the last follow-up examination (b). Log-Rank test evaluated survival difference between subgroups defined by scoring systems. Particular scoring systems were compared with regard to positive predictive value (PPV) of correct estimation of survival longer than six months. Standard descriptive statistics were performed for categorical and continuous variables. Statistical analysis was conducted using JMP 10 Software (SAS Institute) and two-sided $\alpha = 0.05$ was considered statistically significant for all analyses.

Results

Patients' characteristics

Total of 121 patients (56% women, mean age 60.3 years, 28% with KPS ≥ 90%) met the inclusion criteria. The most common primary diagnosis was NSCLC (25%) and breast cancer (17%). Twenty-five percent had solitary or single metastasis while 61% had > 3 BM. The other patient's characteristics are summarized in Tab. 2. Two out of 10 patients with WBRT + SIB did not finish prescribed course of radiation because of deteriorating overall clinical status and received only seven and nine fractions, resp.

Prognostic scores and survival

Median OS from the time of RT indication was 3.13 months (95% CI 2.5–4.9 months) with a median of 2.4 months (95% CI 1.7–3.7 months) since the date of the end of RT. Corresponding 6-month-survival was 37% and 31%, resp. According to RPA, 8 (7%), 89 (73%) and 24 (20%) patients were assigned to group RPA 1, 2 and 3, resp. Results of other scoring system are listed in Tab. 3 along with achieved survival rates. No patient has met criteria for being assigned to WBRT-30 subgroup C (15–17 points). Entire differences in OS between subgroups are significant among all three scoring systems. On the other hand, for specific analysis of survival differences between two adjacent subgroups, significant differences are between RPA 2 and 3, GPA 1.5–2.5 and 0–1.0 and WBRT-30 A and B subgroups. Overall 12 patients were categorized to have favorable GPA score (> 3.0), out of 75% of them (9/12) had one BM. Corresponding Kaplan-Meier plots for OS calculated from the date of RT indication are in Fig. 2. PPV to correctly estimate survival longer than six months was 75%, 67% and 54% for RPA, GPA and WBRT-30, resp.

Calculated prognostic indexes for patients separated in accordance to RT techniques are summarized in Tab. 4. All four patients who received WBRT and had excellent RPA 1 score exhibited unfavorable GPA as well as unsatisfactory WBRT-30 score (survival 7.3, 6.0,

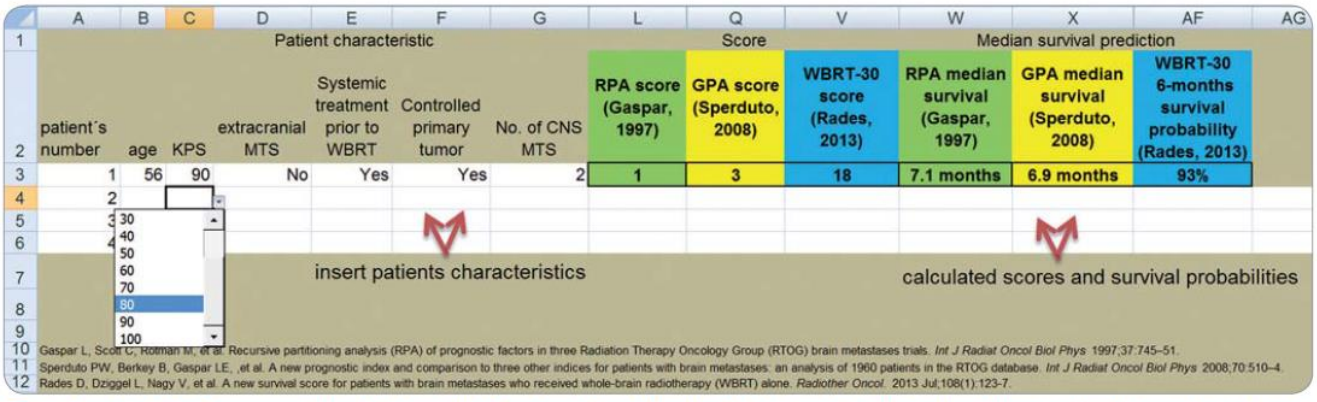

Fig. 1. Screenshot of prepared spreadsheet editor for recording of patient's information from electronic medical records and for automatic calculations of RPA, GPA and WBRT-30 scores.

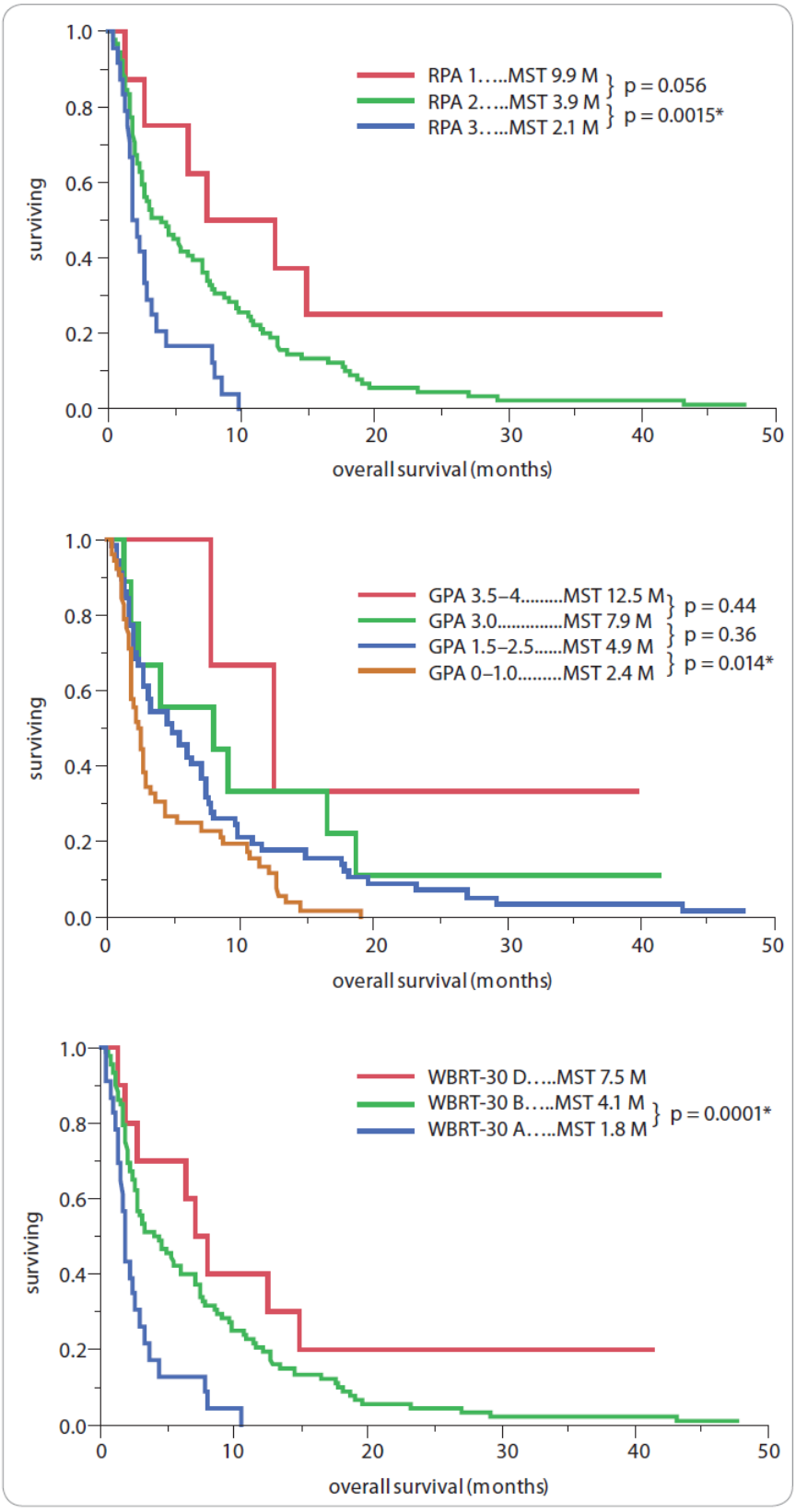

Fig. 2. Kaplan-Meier´s survival estimation for RPA, GPA and WBRT-30 subgroups. No patient has met criteria for being assigned to WBRT-30 C subgroup.
MST – median survival time, M – months

39.7 and 41.3 months). One patient who had received WBRT + SIB with unfavorable RPA 3 also lacked in GPA and WB-30 score. However, his survival was 6.1 months from the end of RT.

Discussion

A total of 121 patients irradiated for BM during one year represent a significant cohort of patients which is without a doubt getting more heterogeneous. As such, heterogeneous treatment modalities are needed to address all patients' needs. The heterogeneity is also expressed by survival outcomes in our cohort when the median OS from the end of RT was only 2.4 months however, with 6-months actuarial survival rate of 31%. Furthermore, increasing availability of MRI examination (sometimes also done as part of inclusion criteria for enrollment into some specific clinical trials) may reveal more patients with single asymptomatic BM. Thus, more aggressive treatment approach as surgery, SRT or simultaneous BM boosting may be suitable for increasing number of patients. Their identification may be inconsistent and problematic but could be facilitated by calculations of prognostic indexes for estimation of remaining lifetime. Developed prognostic indexes are designed with competing demands to be simple for usage in routine practice as well as accurate and as valid as possible. Therefore, all existing indexes have their pros and cons, and their refinement is an ongoing process with evaluation of new candidate parameters reflecting new investigations on biomarkers or radiomics signatures [15]. Moreover, many indexes are tailored for specific primary cancer diagnosis [16] or certain RT approach [13,17]. In the current systematic review of BM prognostic indexes published by Rodrigues et al. in 2012, a total of nine different prognostic indexes and eight validation studies were identified with a wide range of results in terms of PPV, negative predictive value, accuracy, likelihood ratio and other operating characteristics [18]. Altogether, selection of the best index for routine practice is problematic and significantly contributes to the common preference of survival estimation based on the treating physician's subjective evaluation.

Multiple assessments of results obtained from more indexes may be the key for survival estimation in unselected patient cohort in routine daily practice. However, this approach requires even more substantial effort and complexity which is actually the major disadvantage of prognostic indexes. Based on the widely available spreadsheet platform, we developed a simple tool enabling automatic calculation of many indexes (Fig. 1). After filling the relevant parameters (age, KPS, etc.), predefined prognostic indexes are automatically calculated. Spreadsheet platform is especially useful for collecting information for subsequent research statistical analysis while smartphone- or web-based applications (in development) are more useful for routine usage in the outpatient department.

With our developed spreadsheet tool, we easily calculated RPA, GPA and WBRT-30 for a cohort of patients who underwent RT for newly diagnosed BM in 2011. Non-balanced distribution into individual subgroups corresponds with the most often discussed disadvantages of used indexes, with the small part of patients meeting criteria for inclusion into the good prognosis subgroup [18]. Only 7%, 3% and 8% were assigned to the best prognostic subgroup in RPA, GPA and WBRT-30 scoring system, resp. However, calculated survival rates in each subgroup are well distributed ranging from 2.1 to 9.9, from 2.4 to 12.5 and from 1.8 to 7.5 months in RPA, GPA and WBRT-30, resp. Difference between adjacent subgroups (for example between RPA 1 and RPA 2 or between RPA 2 and RPA 3) is important for evaluation of impact of assigning to each subgroup. The most significant differences were observed using RPA system (relevant p-values are included in Fig. 2) favoring it over the others. In our cohort, RPA seems to be the best index for patient's stratification to identify patients who may benefit from more aggressive treatment. Two out of four patients with RPA 1 score who underwent WBRT exhibited extraordinary survival of 39.7 and 41.3 months and considering that they had one and two BM, more aggressive local treatment seems to be justified.

Tab. 2. Patients´ clinical and treatment characteristics.

Patients characteristics	**n = 121**
age	
mean (± SD)	60.3 (± 10.4)
sex	
male	53 (44%)
female	68 (56%)
Karnofsky performance status	
90%	34 (28%)
80%	34 (28%)
70%	29 (24%)
60%	16 (13%)
≤ 50%	8 (7%)
primary cancer type	
non-small cell lung cancer	30 (25%)
small cell lung cancer	16 (13%)
breast	20 (17%)
melanoma	16 (13%)
gastrointestinal cancer	4 (3%)
renal cell carcinoma	3 (2%)
others	32 (27%)
disease status	
extracranial metastases	85 (70%)
systemic treatment prior WBRT	90 (74%)
controlled primary tumor	55 (46%)
number of brain metastases	
> 3	74 (61%)
3	7 (6%)
2	10 (8%)
1	30 (25%)
RT technique	
WBRT	107 (88.3%)
WBRT + SIB	10 (8.2%)
SRS	3 (2.5%)
3D-CRT (5 fields)	1 (1)
RT dose	
5 × 4 Gy	47 (39%)
10 × 3 Gy	34 (28%)
10 × 3 Gy + SIB (à 4.0 Gy and à 4.3 Gy)	3 (2.5%) and 5 (4%)
1 × 18 Gy	1 (0.8%)
1 × 20 Gy	2 (1.6%)
single-fraction WBRT	10 (8.3%)
other	19 (15.8%)

SD – standard deviation, WBRT – whole brain radiotherapy, RT – radiotherapy, SIB – simultaneous integrated boost, 3D-CRT – 3-dimensional conformal radiotherapy

Tab. 3. Final OS in all subgroups calculated from both the time of the end of RT as well as from the time of RT indication.
P-values describe significance of different survival between each adjacent subgroups. Median OS are in months.

		Median OS				p (Log-Rank)
	n = 121	end of RT/indication	RPA [11], GPA [12]			end of RT/indication
RPA						overall 0.0008*/0.0005*
1	8 (7%)	8.4/9.9	7.1	–	–	} 0.06/0.056
2	89 (73%)	2.9/3.9	4.2	–	–	} 0.0021*/0.0015*
3	24 (20%)	1.4/2.1	2.3	–	–	
GPA						overall 0.01*/0.0087*
3.5–4.0	3 (3%)	11.5/12.5	11.0	–	–	} 0.38/0.44
3.0	9 (7%)	6.4/7.9	6.9	–	–	} 0.36/0.36
1.5–2.5	57 (47%)	3.5/4.9	3.8	–	–	} 0.02*/0.014*
0–1.0	52 (43%)	1.7/2.4	2.6	–	–	
				6-months survival		
				end of RT/indication	WBRT-30 [13]	
WBRT-30						overall 0.0001*/< 0.0001*
D: 19–18	10 (8%)	5.9/7.5	–	50/60%	93%	} –
C: 17–15	0	–	–	–	62%	} –
B: 14–10	88 (73%)	3.0/4.1	–	37.5/39.7%	29%	} 0.0002*/0.0001*
A: 9–6	23 (19%)	1.2/1.8	–	8.7/8.7%	4%	

RT – radiotherapy, OS – overall survival, RPA – Recursive partitioning analysis, GPA – Graded prognostic assessment, WBRT – whole brain radiotherapy

Tab. 4. Prognostic indexes for patients separated in accordance to RT techniques.

	WBRT, n = 107	WBRT + SIB, n = 10	SRS, n = 3
RPA 1	4/107 (4%)	3/10 (30%)	1/3 (33%)
RPA 2	80/107 (75%)	6/10 (60%)	2/3 (67%)
RPA 3	23/107 (21%)	1/10 (10%)	–
GPA 3.5–4.0	2/107 (2%)	1/10 (10%)	–
GPA 3.0	6/107 (5%)	2/10 (20%)	1/3 (33%)
GPA 1.5–2.5	48/107 (45%)	6/10 (60%)	2/3 (67%)
GPA 0–1.0	51/107 (48%)	1/10 (10%)	–
WBRT-30 D	5/107 (5%)	4/10 (40%)	1/3 (33%)
WBRT-30 C	–	–	–
WBRT-30 B	80/107 (75%)	5/10 (50%)	2/3 (67%)
WBRT-30 A	22/107 (20%)	1/10 (10%)	–

RT – radiotherapy, WBRT – whole brain radiotherapy, SIB – simultaneous integrated boost

Our study has several limitations. The retrospective nature of the study is self-limiting, especially in validity of reported patients performance status and the status of primary tumor control. Control status records of primary disease (important part of RPA scoring system) lack standardization and are not generally evaluated by use of the same criteria. Another limitation of this study is small sample size of selected patients. Limited number of patients leads to low statistical power to identify significant differences between each prognostic subgroup within prognostic index. Low sample size also precludes diagnosis specific evaluation and more patients will be required to evaluate for example disease specific GPA, which is currently considered as the potentially most widely used index in the future [16,19]. However, to test our spreadsheet tool for simple indexes calculation, selection

of patients within one year of clinical practice seems sufficient. Thus, sample extension is distinguished as a logical part of ongoing research.

In summary, our retrospective study proved feasibility of prognostic indexes evaluation for assessment of remaining lifetime in patients with brain metastases. Calculation is made much easier with prepared spreadsheet software which is now a standard part of computer equipment in all RT departments. Standard evaluation of prognostic indexes may increase probability that all suitable patients for more aggressive treatment will have an opportunity to get the best therapy. Future perspectives include incorporation of more iteration into our software tool for calculation of other prognostic indexes, enlarging sample size and identification of the best system for assessment of unselected patient's cohort.

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5. Chirurgická léčba mozkových metastáz

7.2 PUBLIKACE 4

Kazda T, Pospisil P, Dolezelova H, Slampa P. Whole brain radiotherapy: Consequences for personalized medicine. Rep Pract Oncol Radiother. 2013; 18(3): 133–138. doi: 10.1016/j.rpor.2013.03.002 (60)

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Anotace: Vzhledem k neustále narůstající incidenci a prevalenci onkologických onemocnění a díky zlepšení její terapie je stále více pacientů diagnostikováno s mozkovými metastázami. Za účelem dosažení nejlepší dostupné léčby se doporučuje individuální přístup při indikaci radioterapie, přičemž se bere v úvahu také paliativní záměr péče o pacienty s metastatickým onemocněním. Radioterapie včetně celomozkového ozařování patří do skupiny základních terapeutických metod v léčbě mozkových metastáz. Ve vztahu k personalizované indikaci celomozkového ozáření je důležité zodpovědět u každého jednotlivého pacienta následující otázky. Co očekáváme od léčby, zda je protinádorová léčba vůbec indikována. A pokud ano, která část mozku by měla být ozářena a jaká technika by měla být použita. Pro každého jednotlivého pacienta je důležité najít správné odpovědi, zejména ve vztahu ke kvalitě jeho zbývajícího života. Tento přehledový článek shrnuje doporučení týkající se celomozkového ozařování a poukazuje na další vývoj po roce 2013 v personalizované radioterapii mozkových metastáz.

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Review

Whole brain radiotherapy: Consequences for personalized medicine

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ABSTRACT

Several studies focusing on brain irradiation are in progress. Reflecting updates of relevant outcomes in palliative treatment of patients suffering from brain metastases, the primary objective of these studies is the evaluation of neurocognitive function and quality of life. Improvements of technology in radiation oncology allows us to spare the hippocampal region while appropriately irradiating other parts of brain tissue. Irradiation of the hippocampus region is likely to lead to manifestations of adverse events with a subsequent impact on patient's quality of life, which is in fact an improper approach in palliative medicine. Ongoing studies evaluate results of hippocampus avoiding radiotherapy compared to standard whole brain radiotherapy. Incorporation of neurocognitive function assessment may result in the confirmation of superiority of sparing the region of hippocampus and thus change current style of providing brain irradiation.

1. Background

Approximately 30% of patients develop brain metastases (BM) as a part of their cancer disease.[1] This number is expected to grow due to an increasing number of registered preparations from targeted therapy drugs, improvement of surgical and radiotherapy methods and an increased availability of better palliative and supportive care. Increasing incidence of BM is also due to improvements in imaging technologies and their higher availability.[2] Brain metastases are considered to be one of the most serious complications of cancer disease, which dramatically increase the morbidity and mortality. Their optimal treatment remains controversial, mainly with respect to the aim of provided medical care.[3] In most cases of patients with metastases (MTS) of any location, the treatment aim is not to destroy all cancer cells and cure the patient, but to reduce actual difficulties and prolong the overall survival with good quality of remaining life by achieving an appropriate reduction of symptoms and prevention of its further

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impairment.[4] Besides the reduction of symptoms, the goal of a good palliation is to minimize its side effects. In order to achieve this aim, it is important to determine appropriate end-points not only in relation to an individual patient, but also in relation to the ongoing randomized clinical trials (RCT) as resources for future treatment guidelines. Recently, more attention has been paid to symptom-related outcomes of care, especially to neurocognitive functions (NCF) and quality of life as the most frequently mentioned issues.[5]

One of the standard therapeutic methods of brain metastases is radiotherapy (RT), which offers several possibilities to influence further progression of disease. Apart from the basic technique, i.e. radiation of the whole brain (WBRT – whole brain radiotherapy), new treatment methods are being put into practice, such as stereotactic methods of intracranial radiosurgery or radiotherapy. These novel methods allow delivering higher doses of radiation into a small amount of tissue. However, these techniques remain available only for a small group of patients.[6] Recently, a lot of trials have been conducted to compare different radiotherapy techniques as separate methods of treatment to their combinations. Other studies deal with a combination of radiotherapy and neurosurgery.

In most patients the radiation of the whole brain is indicated because of numerous brain metastases present or because of unmanageable extracranial illness. Thus, attention must also be paid to the development of further improvements in providing WBRT, especially in the light of new knowledge about radiation brain injury mechanisms and in respect to the personalized palliative approach to each patient. In this article, we focus mainly on the whole brain radiotherapy.

In general, one of the main future directions in the treatment of cancer patients is the implementation of so called tailor-made personalized medicine into clinical practice. That means optimization of drug prescription based on patient's individual gene profile in a narrower sense. Although this concept applies particularly to systemic treatment with chemotherapeutic agents, some principles of this philosophy could be implemented into other areas of care for cancer patients, meaning the pursuit of individualized approach to the treatment. One of the basic principles of tailor-made personalized medicine is the usage of a specific procedure for the specific patient, in order to maximize, if possible, the therapeutic effect while avoiding side effects.

In relation to the facts mentioned above, it is necessary to take into account some patient-specific variables while making decisions about indications to cranial irradiation. At first, the question is if patient can realistically benefit from being provided such irradiation. In practice it is about responsible life expectancy estimation (for example expressed by the Karnofsky Performance Scale) and about considering all consequences relating to the actual possibilities to provide the care. If RT is indicated, the next question is what part of brain should be irradiated and how. Choosing the right procedure is important in relation to the assessment of all benefits and risks of our intervention. We summarize some recent recommendations in the use of WBRT and mention some future directions related to this issue.

2. Indications for WBRT

In daily radiotherapy practice, one of the most important factors in decision-making is the level of technical equipment in a particular radiotherapy department. Not all departments are able to provide their patients with the most advanced care, e.g. precise stereotactic radiosurgery (SRS), or WBRT with simultaneous integrated boost (SIB) to BM using volumetric modulated arc therapy delivered by helical tomotherapy or by linear accelerators (Rapid Arc, IMAT/VMAT therapy).[7] Thus, also because of this technical limitation, WBRT remains the most commonly radiotherapy method used in the treatment of patients with brain metastases.

When considering the best specific type of treatment it is important to compare all its pros and cons. In general, palliative treatment should be as undemanding as possible in order not to burden patients with long complex treatment. Cost of this care should be low or at least weighed against potential benefits in comparison with other lower or more expensive alternatives.[3]

Before starting treatment it is useful to recognize the number of BM – single lesion, oligometastatic (2–3) or multiple impairments. It is also very important to properly assess the general performance status and consider other specific clinical situations (presence or absence of extracranial metastases). These are the most common prognostic/predictive factors mentioned in recent guidelines. Karnofsky Performance Scale (KPS) is the most useful tool to estimate patient's ability to profit from any kind of treatment. Indeed, KPS is a part of all tools for stratification of patients into prognostic groups – Recursive Partitioning Analysis and Graded Prognostic Index (RPA and GPI score).[8,9] Patients with KPS of less than 70% (RPA group III) will benefit from WBRT compared to other type of brain radiotherapy regardless of the type of brain impairment.

Several studies have been performed to assess the importance of the implementation WBRT in combination with local treatment of brain metastases.[10–13] Abe et al.[14] reviewed these findings and concluded, that initial local brain radiotherapy without its whole irradiation does not influence overall survival, but results in a significant increase in brain tumor recurrence (BTR), while the inclusion of WBRT into the primary treatment prolongs time to recurrence and prevents neurologic death.[14]

Brain tumor recurrence means the clinical progression resulting in severe impact on patient's quality of life. BTR is the most important cause of additional deterioration of NCF. It seems that it is useful to stratify patients into the low and high risk group of BTR and hence determine the indication for WBRT.[11] Aoyama also evaluated the risk of developing brain metastases in breast cancer patients after up-front WBRT according to the risk of BTR. Patients in high BTR risk group (2 or more BM, presence of extracranial metastases) who underwent WBRT developed BTR in other site of brain in 21% at 6 months compared to 57% of patients without WBRT. Patients in the low BTR risk group (single BM, no extracranial metastases) with and without WBRT developed BTR at 6 months in 9%, vs. 31%, respectively.[15]

WBRT as a separate up-front treatment is a possible option for all prognostic groups in both most common scoring systems – RPA and GPA. That means that the choice of the type of radiotherapy offered to patients of the low risk group depends mostly on the technical equipment of the radiotherapy department. Patients with poor prognostic factors (RPA III group) benefit from WBRT alone the most.

3. Performing WBRT

In general, one of the most important outcomes in RCT is overall survival. Considering that most of patients presented with brain metastases die because of the progression of their extracranial disease, the overall survival seems not to be the best factor to assess during decision making for management of brain metastases. It is more important to consider the aim of our treatment and that is, as obvious in the palliative approach, symptoms relief, attempt to improve the overall survival while maintaining appropriate quality of life, in accordance with the general principle of "primum non nocere". This means maintaining good mental conditions, too. More recently, endpoints in brain tumor clinical trials have been refined, with emphasis put on the neurocognitive assessment and evaluation of the quality of life.[5,16]

Results of studies comparing different radiotherapy techniques report some changes in cognitive functions due to radiation.[17] The most serious cause of its alteration is a recurrence of cancer disease in brain; its risk might be assessed by BTR as mentioned above.[18] The risk of relapse is, however, smaller if aggressive therapy for brain metastases is used. It is essential to find a compromise between the benefits of such aggressive treatment in the sense of reducing the risk of later intracranial progression versus higher risk of iatrogenic alteration of cognitive functions and thus decrease in the quality of life, which is a very important endpoint for a good palliation. The impact of WBRT on reducing incidence of brain tumors relapse has been demonstrated in several RCTs. The omission of WBRT results in a relative increase of a BTR from 70% to 300% (calculated in the original article from absolute BTR risk with and without WBRT, which was 18% and 70%, respectively).[19]

Li et al.[20] confirmed that there is a correlation between tumor regression after WBRT and the improvement of some types of NCF. In contrast, memory-related NCF had a lower correlation with rated reduction of MTS deposits, suggesting different mechanisms of alteration of different kinds of NCF by cranial irradiation.[20] Nevertheless, it is clear, that WBRT plays an important role in protecting patients from decline in some types of NCF.

In fact, the development of brain metastases is based on hematogenous dissemination from primary or other sites. Impairment probability of certain parts of the brain depends also on its perfusion. 80% of all brain blood supply is deposited in the telencephalon, so it is the most frequently affected part.[21] But it is true that the whole brain can be seeded by BM, therefore, WBRT seems to be the best approach to control brain metastases.

The standard technique of WBRT involves the use of two opposed contralateral radiation fields with homogenous irradiation of the whole brain.[22] Shielding the eyes and other parts of splanchnocranium is performed using multileaf collimator at most. This technique requires only a simple planning with minimal personal and technical burden. The whole process of radiotherapy can be planned on the 2D X-ray simulator, so it is available also in the absence of the CT simulator. In this setting of WBRT, the whole brain is homogenously irradiated. The radiation dose is the same in areas of proven MTS as it is in areas without apparent MTS. However, it remains uncertain whether it is important to irradiate all parts of the brain, especially the region of the hippocampus. Provided that the hippocampus is unimpaired, it seems that benefits of its irradiation do not outweigh the potential risk of radiation injury. Alteration in the processes of learning or spatial memory processing is related to hippocampal injury.[23] The relationship between hippocampal radiation injury and alteration of NCF has been demonstrated also by Monje et al.[24,25] It is estimated, that only 3% of all BM are located in perihippocampal parts of the brain (within 5 mm of the hippocampus)[26]. New methods of WBRT have been developed in order to minimize the side effects resulting from irradiation of the hippocampal region.

4. Future directions

With a development of other therapeutic methods and with an increase in effectiveness of supportive and symptomatic treatment, the prolongation of overall survival in certain groups of patients is achieved after WBRT. These are mainly patients suffering from breast cancer.[27] We may expect the manifestation of long-term side effects of radiation to develop in these patients, including at most, the impairment of cognitive functions. Some degree of cognitive function alteration can be observed at baseline, due to the primary status of cancer disease and other factors.[28] In recent years, there has been a discussion on the significance of damage of neuronal stem cells due to ionizing radiation, with impact on changes of cognitive functions.[29] Neuronal stem cells are located in the hippocampal subgranular zone of the dentate gyrus. Their significance in relation to the process of learning and memory recall has been demonstrated in many studies.[30,31]

Nowadays, randomized clinical trials comparing the therapeutic results using different radiotherapy techniques are in progress, where the hippocampus region is protected in certain groups of patients.[32] Protecting of the hippocampus is ensured by using intensity modulated radiotherapy enabling high conformal radiotherapy with a steep dose gradient in locations with high priority of sparing. Providing this modern therapy places high demands on the accuracy of radiation and precision of planning. Despite RT techniques, the use of simple planning, as described above, is being developed.[33] The avoidance of the hippocampus in WBRT with evaluation memory delayed recall as a primary objective is a subject of ongoing prospective RTOG study (RTOG 0933).[34] Key studies and reviews reflecting preclinical and clinical evidence supporting performance of hippocampus-avoiding whole brain radiotherapy are summarized in Table 1.

The growing interest in optimizing care of patients with brain metastases is also reflected in the growing number of

Table 1 – Key studies and reviews demonstrating preclinical and clinical evidence supporting performing of hippocampus-avoiding whole brain radiotherapy.

Author	Year	Conclusion	Consequences
Abe[14]	2012	Omission of WBRT results in increasing of BTR	WBRT is still an important part of RT management of brain metastases. Importance of selective indications for local treatment only
Meyers[5]	2012	Quality of life optimization of brain tumor patients is essential while prolongation of overall survival is achieved	Emphasis on the neurocognitive assessment and evaluation of quality of life in ongoing trials
Bayer[35] and Eriksson[30]	1982 and 1998	New granule cells are generated from neuronal stem cells located in the dentate gyrus	Neuronal stem cells hypothesis approved
Collier[36]	1987	Memory function are associated with dentate gyrus of the hippocampus	Hippocampal damage will result in memory function decline
Mizumatsu[25]	2003	Pathogenesis of RT-induced NC deficit is in relation with NSC	CNS is not exclusively radio-resistant organ
Abayomi[23] and Jalali[37]	1996 and 2010	There is evidence in radiotherapy of brain and NC function impairment	Hippocampal sparing RT can reduce memory impairment after WBRT
Gondi[38]	2010	There is ability of modern RT techniques to spare region of hippocampus while delivering appropriate dose into the other parts of brain	Superiority of hippocampal - avoidance WBRT must be evaluated by a prospective clinical trial
Mehta[34], RTOG 0993 study	2012	A Phase II Trial of Hippocampal Avoidance During Whole Brain Radiotherapy for Brain Metastases	Prospectively evaluation of the NC benefit of hippocampal sparing during RT

WBRT, whole brain radiotherapy; BTR, brain tumor recurrence; RT, radiotherapy; NC, neurocognitive; NSC, neuronal stem cells; CNS, central nervous system.

studies and articles dealing with this subject. As showed in Fig. 1, there is a clear growth in publishing review articles on WBRT linked at MEDLINE PubMed. Current year's results are interpolated to 12 months to allow comparison with other years. Discussing of NCF is their part mainly at last 6 years. Standardized regular assessment of neurocognitive functions in patients with radiotherapy of brain is an essential step forward to implementation of modern radiotherapy methods into clinical practice.

If ongoing studies confirm that patients undergoing hippocampus-avoiding WBRT do not have increased risk of brain tumor recurrence while better preserving the neurocognitive function as a result of radiation to brain injury, providing hippocampus sparing radiotherapy will become the new method of choice. Then, it will be necessary to correctly estimate the risk of development of brain metastases in the perihippocampal region and to incorporate this factor into upgraded scoring systems.

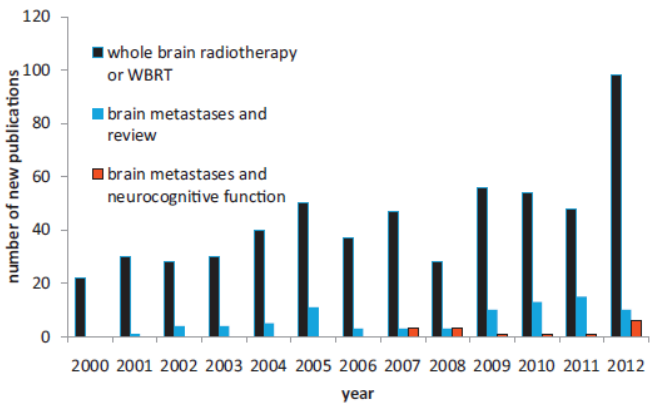

Fig. 1 – Number of new publications in PubMed database when entering given keywords as mentioned in graph.

It might be assumed that the withholding of WBRT will not be the subject of further research. As suggested in several studies (mentioned above) comparing the local treatment of brain metastases with WBRT, WBRT leads to a significant reduction in the risk of brain tumor recurrence and in the risk of neurological death. While providing the hippocampal sparing brain irradiation using modern radiotherapy techniques, it is also possible to increase the dose of radiation to areas of proven metastases (SIB). Combining these two approaches in a particular patient case, may improve the efficacy of radiation therapy while reducing the risk of late side effects. This means an individualized care as a type of personalized medicine in a wider sense.

Taking into account an increasing number of patients with brain metastases, studies dealing with this subject are becoming an important direction of further radiotherapy research. There is also an increasing number of diagnoses of early asymptomatic BM, because of examination of patients in relation to their enrollment into some clinical trials, where MRI of brain is performed as one of inclusion criteria. In these cases, a decision making is influenced by the consideration of specific trial enrollment criteria and by the fact, that these patients are often long survivals.

5. Summary

Several studies focusing on brain irradiation are in progress. Reflecting updates of relevant outcomes in palliative treatment of patients suffering from brain metastases, the primary

objective of these studies is the evaluation of neurocognitive function and quality of life. Improvements of technology in radiation oncology allows us to spare the hippocampal region while appropriately irradiating other parts of brain tissue. Irradiation of the hippocampus region is likely to lead to manifestations of adverse events with a subsequent impact on patient's quality of life, which is in fact an improper approach in palliative medicine. Ongoing studies evaluate results of hippocampus avoiding radiotherapy compared to standard whole brain radiotherapy. Incorporation of neurocognitive function assessment may result in the confirmation of superiority of sparing the region of hippocampus and thus change current style of providing brain irradiation.

Conflicts of interest

None declared.

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7.3 Hipokampus a jeho změny po radioterapii

Hipokampus je párová mozková struktura, která je umístěna ve ventromediální části temporálních laloků a leží laterálně od temporálního rohu postranních mozkových komor. Hipokampus anatomicky tvoří především gyrus dentatus a cornu ammonis a patří do limbického systému. Jeho hlavní funkcí je zapojení se do procesů učení, konsolidace a získávání informací a je také nezbytný pro vytváření nových vzpomínek (65). Je známo, že bilaterální a jednostranné poškození hipokampu mění učení a tvorbu paměti (66). Úplné patofyziologické vysvětlení všech těchto procesů stále chybí; nicméně úloha neurogeneze se zdá být jednou z nejpozoruhodnějších.

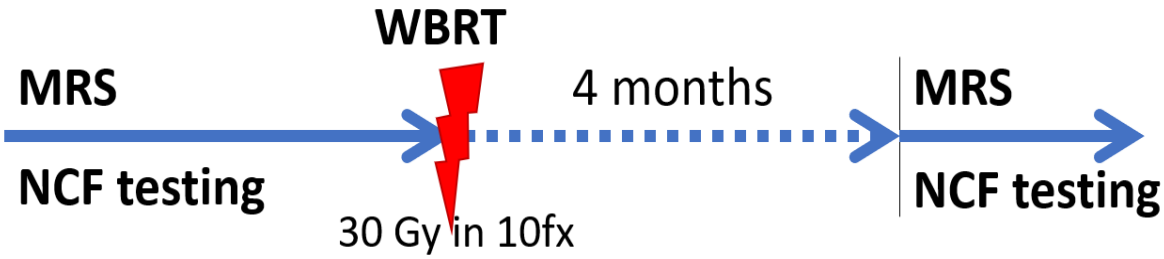
Mitoticky aktivní NSC jsou umístěny v různých částech mozku, především v subependymální zóně a v subgranulární zóně gyrus dentatus, odkud migrují do granulární buněčné vrstvy hipokampu (67). Hipokampální subgranulární zóna je kritickým neurologickým centrem pro učení a paměť. NSC mají typické vlastnosti kmenových buněk, jsou schopné jak sebeobnovy, tak generování nových diferencovaných buněk (68). Neurogeneze je komplikovaný proces s integrací mnoha regulačních buněk jako astrocytů nebo endoteliálních buněk s koordinovaným vývojem neurálních prekurzorových buněk ve specifickém neurogenním mikroprostředí zvaném „niche“ (68).

Vícero preklinických studií podporuje hypotézu kognitivní dysfunkce zprostředkované alterací na úrovni hipokampu (69)(70)(59). In vivo studie na zvířatech prokazují citlivost NSC na ionizující záření. Apoptóza NSC po ionizujícím záření byla nejprve popsána v subependymální zóně u mladých dospělých potkanů. Po jednorázových rentgenových dávkách 5 nebo 30 Gy dosáhla apoptóza vrcholu 6 hodin po ozáření (69)(70). Mizumatsu a kol. ozářil celý mozek experimentálních myší různými jednotlivými dávkami a detekoval apoptózu pomocí imunohistochemických analýz včetně hodnocení počtu proliferujících buněk a nezralých neuronů v subgranulární zóně hipokampálního gyrus dentatus (71). Byla pozorována na dávce závislá apoptóza, která dosáhla vrcholu 12 hodin po ozáření, po kterém následovalo snížení množství proliferujících buněk v subgranulární zóně (72). Změny v neurogenezi byly spojeny se zánětlivou odpovědí potvrzenou detekcí aktivovaných buněk mikroglie (72). V dalších studiích byly navíc popsány mírnější kognitivní poruchy vyvolané zářením u hlodavců doprovázené snížením počtu aktivovaných zánětlivých buněk v hipokampu po podání protizánětlivých látek, jako je ramipril a indometacin (73).

Údaje o odpovědi NSC na dávku ionizujícího záření in vivo nejsou k dispozici a ani se nepředpokládá z etického hlediska provedení takových experimentálních studií. V analýze QUANTEC (Quantitative Analyses of Normal Tissue Effects in the Clinic – základní radiobiologická analýza hodnotící rozdílné efekty radioterapie na jednotlivé tkáně) byla stanovena a/β (základní konstanta lineárně kvadratického modelu efektů radioterapie na nádorovou a normální okolní tkáň) hodnota mozku na 2,9 (74). Pro oblast hipokampu většina autorů používá poměr α / β v rozmezí od 2 do 3 (75)(59). Ostatní autoři však pracují s hodnotou a/β pro NSC kompartmenty a/β =10, přičemž používají obecnou hodnotu stanovenou pro kmenové buňky (76). Nicméně některé preklinické studie naznačují, že již tak nízké dávky jako 2 Gy mají za následek apoptózu neurogenních kmenových buněk (72)(77). Poradiační změny v oblasti hipokampu se tak podílejí na změnách NCF rezultujících v horší kvalitu života. Na druhou stranu kognitivní funkce a kvalita života je jistě komplexní fenomén, který je spoluutvářen mnoha faktory na straně pacienta, jeho okolí a také jeho nádorového onemocnění a předchozí léčbě. Typ radioterapie je pouze jednou proměnnou a k deterioraci celkového stavu a kognice daného pacienta může dojít i při vynechání léčby ionizujícím zářením, event. u ozařovacích technik šetřících oblasti hipokampu, jak je diskutováno dále.

V naší inovativní prospektivní studii jsme se zabývali poradiačními změnami mozku u pacientů indikovaných k celomozkovému ozařování, kteří byli léčení na Klinice radiační onkologie Masarykova onkologického ústavu mezi květnem 2013 a únorem 2015 (78)(79). Cílem bylo prospektivní hodnocení hipokampálních změn pomocí MR spektroskopie a korelace těchto změn s NCF a kvalitou života. Zařazeni byli pacienti s nově diagnostikovanými metastázami, včetně pacientů po metastazektomii, kteří byli indikováni, v souladu s tehdejšími doporučeními, k WBRT. Pacienti museli splňovat obecná kritéria k absolvování radioterapie (adekvátní spolupráce pacienta na ozařovnách, tolerance fixační masky), mít výkonnostní status alespoň Karnofsky index ≥ 70 % a příznivou prognózu přežití alespoň 4 měsíce dle GPA indexu (32) (prognostické indexy viz kapitola 4). Nevhodní byli pacienti s horší predikcí přežití a pacienti trpící jinými neurologickými nebo psychiatrickými chorobami nebo pacienti s radiologickou patologií v oblasti hipokampu nalezené během MR vyšetření před radioterapií. Všichni pacienti podepsali před zahájením studie informovaný souhlas. Schéma studie je na obrázku 5.

Obr. 5: Schéma prospektivní studie hodnotící poradiační změny hipokampu a korelaci k neurokognitivním funkcím. Pacienti na začátku absolvovali MR spektroskopické vyšetření hipokampu a testování neurokognitivních funkcí klinickým psychologem. Stejné testy a MR spektroskopie byly zopakovány 4 měsíce po celomozkovém ozáření



Zkratky: MRS: MR spektroskopie; NCF: neurokognitivní funkce; WBRT: celomozkové ozáření; Gy: Gray; fx: frakce.

U všech pacientů bylo provedeno vstupní multi-voxelové spektroskopické vyšetření s použitím GE Medical Systems Discovery MR 750 3T přístroje (sekvence PRESS-CSI s TE / TR = 135 ms / 1690 ms, FOV 120 × 120 mm^2). Oblast zájmu byla umístěna skrz celé temporální laloky s úpravou pozice voxelů dle lokalizace hipokampů, aby bylo možné vyšetřit MR spektroskopií celé hipokampy (velikost voxelu 10 x 10 x 15 mm) (80). Následné zpracování surových spektroskopických dat bylo provedeno pomocí LCModelu (81) pro výpočet absolutní koncentrace h-tNAA [hippocampal – total N-acetylaspartát; mM], který byl dále vizualizován a analyzován pomocí softwaru java Spectroscopic Imaging PROcessing (jSIPRO) (82) pro konečné výpočty průměrné koncentrace h-tNAA. Konečný výběr voxelů byl semiautomatický. V prvním kroku byly manuálně vybrány voxely, které alespoň ve 2/3 voxelu obsahovaly část hipokampu a ty s hodnotou spektrální chyby větší než 20 % byly následně automaticky vyloučeny. Tato chyba bere v úvahu poměr signál k šumu a šířku MRS křivky při maximu poloviny píku, dle metodiky hodnocení MRS dle Jiru et al. (82). Během celého procesu výběru voxelů nebyly viditelné konečné koncentrace metabolitů, což zvýšilo kredibilitu analýzy s redukcí selekčního bias voxelů. Pomocí softwaru jSIPRO pro reportování vypočtených MR spektroskopických map je možné vybrat všechny voxely uvnitř obou hipokampů na překryvném axiálním T2 váženém obrazu. Průměrně bylo analyzováno 9 voxelů na pravý a levý hipokampus. Variabilita počtu voxelů dostupných pro analýzu byla způsobena hlavně vyloučením některých voxelů z důvodu nízké kvality spektrálních dat

(vysoká hodnota chyb, šumu). MRS bylo provedeno před WBRT a opakováno o 4 měsíce později za použití stejné metodologie (78).

Vstupní a kontrolní (po 4 měsících po radioterapii) NCF byly hodnoceny klinickým psychologem v maximálním časovém intervalu 5 pracovních dnů kolem MRS. Byly hodnoceny standardizované testy zaměřené na paměť: AVLT (Auditory Verbal Learning Test) a BVMT-R (Brief Visuospatial Memory Test – Revised). AVLT zahrnuje zapamatování 15 slov pro 5 po sobě jdoucích pokusů (Total Recall, TR), jejich zopakování po 30 minutách (Delayed Recall, DR) a následná identifikace těchto slov ze seznamu souvisejících podobných slov (Recognition, R). Při následném kontrolním vyšetření se použila standardizovaná variace slov. BVMT-R zahrnuje zapamatování 6 geometrických obrazců pro 3 po sobě jdoucí pokusy (TR), které je zopakováno po 25 minutách (DR), a konečně je identifikuje mezi těmi, které jsou nabízeny v seznamu souvisejících obrázků (Recognition). Pro následné vyšetření byla použita standardizovaná alternativní forma BVMT-R. Krom těchto základních testů byly prováděny další NCF testy jako MMSE, Verbal fluency test, TMT A, B, Clock test a standardizované dotazníky kvality života EORTC QLQ-C30 a modul pro pacienty s mozkovými nádory QLQ-BN20 (dotazníky se standardizovaným překladem do češtiny).

WBRT bylo realizováno standardní zevní radioterapií založenou na dvou protilehlých laterolaterálních stejně váhovaných polích. Mnoholistový kolimátor byl použit k tvarování polí tak, že byl zahrnut celý mozek (předepsaná dávka v izocentru umístěnému uprostřed mozku). Ozáření bylo provedeno fotonovými paprsky lineárního urychlovače o energii 6 MV. Pacienti byli léčeni v poloze na zádech s hlavou imobilizovanou individuálně připravenými termoplastickými maskami. Cílový objem (mozkovna) byl definován pomocí 2D simulátoru (Varian Acuity iX), aby homogenně pokryl celý mozek s minimalizací dávky na oblast splanchnokrania. Předepsaná dávka byla stejná u všech pacientů: 30 Gy v 10 frakcích dodaných za 2 týdny. Získaná data byla statisticky zpracována tak, že každý pacient byl svou vlastní kontrolou. Relativní pokles koncentrací h-tNAA byl vyjádřen jako Δtest = (kontrolní test – vstupní test) ÷ vstupní test. U testů NCF byly hodnoceny absolutní změny jednotlivých skóre.

7.3.1 PUBLIKACE 5

Pospisil P, Kazda T, Bulik M, Dobiaskova M, Burkon P, Hynkova L, Slampa P, Jancalek R. Hippocampal proton MR spectroscopy as a novel approach in the assessment of radiation injury and the correlation to neurocognitive function impairment: initial experiences. Radiat Oncol. 2015; 10(1): 211 (78)

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IF_{2015} 2,466, ranking Q2 (43/124), RADIOLOGY, NUCLEAR MEDICINE AND MEDICAL IMAGING

Práce byla ohodnocena Chodounského cenou za 2. nejlepší publikaci v oboru Radiační onkologie v ČR za rok 2015.

Anotace: V této práci jsou publikovány pilotní výsledky prvních 10 hodnocených pacientů výše diskutované prospektivní studie hodnotící poradiační změny hipokampu a korelaci k neurokognitivním funkcím (predefinovaná interim analýza). V textu je především popisována metodika, která je shrnuta výše v samotném textu habilitační práce.

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RESEARCH Open Access

Hippocampal proton MR spectroscopy as a novel approach in the assessment of radiation injury and the correlation to neurocognitive function impairment: initial experiences

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Abstract

Background: The hippocampus is considered as the main radiosensitive brain structure responsible for postradiotherapy cognitive decline. We prospectively assessed correlation of memory change to hippocampal N-acetylaspartate (h-tNAA) concentration, a neuronal density and viability marker, by ^{1}H-MR spectroscopy focused on the hippocampus.

Methods: Patients with brain metastases underwent whole brain radiotherapy (WBRT) to a dose of 30 Gy in ten fractions daily. Pre-radiotherapy ^{1}H-MR spectroscopy focused on the h-tNAA concentration and memory testing was performed. Memory was evaluated by Auditory Verbal Learning Test (AVLT) and Brief Visuospatial Memory Test-Revised (BVMT-R). Total recall, recognition and delayed recall were reported. The both investigation procedures were repeated 4 months after WBRT and the h-tNAA and memory changes were correlated.

Results: Of the 20 patients, ten passed whole protocol. The h-tNAA concentration significantly decreased from pre-WBRT 8.9, 8.86 and 8.88 [mM] in the right, left and both hippocampi to 7.16, 7.65 and 7.4 after WBRT, respectively. In the memory tests a significant decrease was observed in AVLT total-recall, BVMT-R total-recall and BVMT-R delayed-recall. Weak to moderate correlations were observed between left h-tNAA and AVLT recognition and all BVMT-R subtests and between the right h-tNAA and AVLT total-recall.

Conclusions: A significant decrease in h-tNAA after WBRT was proven by ^{1}H-MR spectroscopy as a feasible method for the in vivo investigation of radiation injury. Continuing patient recruitment focusing on other cognitive tests and metabolites is needed.

Keywords: Hippocampus, Radiation injury, Neurocognitive function, Magnetic resonance spectroscopy

Background

Although the general improvement in the current management of cancer patients has led to an increase in the overall survival rate, more and more patients develop brain metastases (BM) [1]. Whole brain radiotherapy (WBRT) is a basic therapeutic approach used for its treatment. WBRT is, however, associated with adverse side effects leading to the possible worsening of the quality of life, particularly in relation to the worsening of neurocognitive function [2, 3]. Current clinical studies are providing increasing evidence of an association between a hippocampal radiotherapy (RT) dose and cognitive impairment [4, 5, 6]. Recently, new strategies have been investigated in order to minimize these adverse effects, particularly for patients with favorable prognostic factors [4, 7, 8]. One promising approach, enabling the preservation of neurocognitive functions (NCF) is hippocampal sparing during WBRT, as recently proven by phase II study [4] and currently being investigated in the ongoing phase III clinical trials (NCT01942980, NCT01780675, NRG CC001, NRG CC1432). However,

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further basic research is still necessary in order to provide a deeper insight into processes responsible for the hippocampal radiation injury.

Proton magnetic resonance spectroscopy (MRS) is a diagnostic and research method enabling an in-vivo examination of the spatial distribution of specific tissue metabolites concentration. Total N-acetylaspartate in the hippocampus (h-tNAA), including N-acetylaspartate together with N-acetylaspartylglutamate, is one commonly detectable brain tissue metabolite that is considered to be the marker of neuronal density and viability [9]. Although the process of hippocampal radiation injury is multifactorial [10], neuronal depletion by apoptosis is considered to be an essential process leading to NCF impairment [11, 12]. A detailed investigation of the metabolic response of hippocampus to irradiation reflecting possible neuronal depletion is still lacking.

Herein, with the first ten analyzable patients, we present our initial interim analysis providing an evaluation of the correlation between the h-tNAA concentration dynamics and the changes in NCF impairment in patients after WBRT. The primary endpoint of the study was to evaluate the post-WBRT decrease of the h-tNAA concentration measured by MRS. The secondary endpoint was the correlation between the h-tNAA concentration decrease and changes in memory function.

Methods

Patient selection

Patients with a current history of cancer disease and with either newly diagnosed BM or immediate postoperative radiotherapy after the surgical resection of a single metastasis that were referred for WBRT in the Department of Radiation Oncology, Faculty of Medicine, Masaryk University and Masaryk Memorial Cancer Institute between May 2013 and September 2014 were considered for study enrollment. Patients met inclusion criteria when having Karnofsky performance status ≥ 70 % and favorable survival prognosis of 4 months as predicted by a graded prognostic assessment [13] (index ≥ 1.5 is needed for prediction of survival higher than 3.8 months; age, Karnofsky status, number of brain metastases and presence of extracranial metasetases are used for index calculation). Patients with worse survival prediction and those suffering from other neurological or psychiatric diseases or patients with radiologic pathology in the hippocampus region found during pretreatment MRI were excluded. The study was approved by the Institutional Review Board and all of the patients provided their written informed consent before study enrollment.

MRS examination

A single slice multi-voxel spectroscopic examination was performed using GE Medical Systems Discovery MR 750 3 T (PRESS-CSI sequence with TE/TR =135 ms/1690 ms, 12 averages, FOV 120×120 mm^2) at the Department of Diagnostic Imaging, St. Anne's University Hospital Brno. The region of interest was placed through whole temporal lobi with the voxel layer position adjusted based on the localization of hippocampi in order to examine the whole hippocampi at long distance (voxel size set to $10 \times 10 \times 15$ mm^3) [14]. Postprocessing of raw spectroscopic data was performed using the LCModel [15] for the calculation of the h-tNAA absolute concentrate [mM] which were further visualized and analyzed by java Spectroscopic Imaging PROcessing software (jSIPRO) [16] for final reporting of the mean h-tNAA concentration. The final selection of voxels of interest was partially automated. In the first step, MRS voxels where hippocampus represented more that 2/3 of the covered tissue were manually selected and those with a spectral error value of greater than 20 % were subsequently automatically excluded. This error takes into account signal to noise ratio and full width at half peak maximum as proposed by Jiru et al. [17]. During the whole process of voxels selection, final metabolite concentrations were not visible ensuring blinding of analysis. By using jSIPRO software for reporting the calculated MR spectroscopic maps, it is possible to select all voxels within both hippocampi at an overlaid axial T2-weighted image. On average, nine voxels were analyzed per right and left hippocampus. The variability in the number of voxels available for analysis was mainly due to exclusion of some voxels because of low quality of spectral data (high error value). MRS was performed prior to WBRT and repeated 4 months later using the same methodology.

Neurocognitive function evaluation

NCF were examined by experienced psychologists at the maximum time interval of five working days around MRS. Standardized tests focusing on memory were assessed: AVLT (Auditory Verbal Learning Test) and BVMT-R (Brief Visuospatial Memory Test - Revised). The AVLT includes memorizing 15 words for five consecutive attempts (Total Recall, TR), recalling them after 30 min (Delayed Recall, DR) and subsequently identifying these words from a list of related words (Recognition, R). During the follow up examination, a standardized retest variation of words was used. The BVMT-R includes memorizing six geometric figures for three consecutive attempts (TR) and similarly as with the AVLT recalling them after 25 min (DR), and finally identifying them among those offered in the list of related figures (R). Standardized alternate form of BVMT-R was used for follow up examination.

Radiotherapy

WBRT was delivered by standard external beam radiotherapy based on two opposing laterolateral equally

weighted fields; the multi-leaf collimator was used to shape the fields in such a way that the whole brain was included (prescribed dose to the isocenter located in the middle of brain). Treatment was delivered with six megavoltage photon beams of linear accelerator. Patients were treated in a head-first supine position with the head immobilized by individually prepared thermoplastic masks. RT beams were defined in an RTG 2D simulator (Varian Acuity iX) to homogenously cover the whole brain while shielding the facial tissue. The prescribed dose was uniform in all patients: 30 Gy in ten fractions delivered in 2 weeks.

Data analysis

Obtained data were compared on a case-by-case basis where each patient was his or her own control. The relative decline in the h-tNAA concentrations was expressed as $\Delta test = (test\ control - test\ baseline) \div test\ baseline$. For NCF tests, absolute score changes were reported. Standard descriptive statistics were applied in the analysis; absolute and relative frequencies for categorical variables and mean supplemented by standard deviation and median with min-max range for quantitative variables. Wilcoxon's signed rank test was adopted for the computation of the statistical significance of differences in paired quantitative data. The relationship between quantitative variables was analyzed using the Spearman correlation coefficient and its statistical significance. The follow-up was calculated as the period from the date of the BM diagnosis to the death of the patient or the last contact with the patient; the overall survival time was analyzed using the Kaplan-Meier methodology. Statistical analysis was performed using JMP 10 Software (SAS Institute) and two-sided $\alpha = 0.05$ was taken as a level of statistical significance in all analyses.

Results

Patient's characteristics

A total of 20 patients with a median age of 60 years and a median 90 % Karnofsky performance status met the inclusion criteria. The majority of patients had lung cancer (six patients) and the median number of metastases was 1 (1–20). Ten (50 %) patients had already completed the planned control examination 4 months after the WBRT and were further analyzed (mean time to control 4.3 months ± 0.7 months). Their characteristics are summarized in Table 1. One (5 %) patient is still to take the control examination and nine (45 %) died or did not comply with the control examination (Fig. 1). The median overall survival was 11.9 months (95 % CI 7.5 to 13.9 months) for patients who underwent control examinations after 4 months and 9.2 months (95 % CI 3.5 to 13.9 months) for all 20 included patients.

Hippocampal MR spectroscopy

A post-WBRT decrease in the average h-tNAA concentration was consistent in all ten analyzable patients with minimal–5 % (patient number 1) and maximal–25 % (patient number 9) decrease (Table 2). Figure 2 displays pre-WBRT concentration of h-tNAA in the patient number five and its remarkable decrease after WBRT. No difference was observed in the h-tNAA concentration between the right and left hemisphere.

Table 1 Basic characteristics of ten analyzable patients

Patients characteristic					Pre-WBRT			MTS			Post-WBRT CHT	Time relapse to end of WBRT	
No	Sex	Age	Hand	Tumor	KPS	GPA [mo]	Surg	No	Location	Volume [ccm]		B [days]	F/U [mo]
1	M	57	r	NSCLC	90	6.9	Yes	2	r_F(1) + T(1)	4.2	Yes	16	5.1
2	M	53	r	RCC	90	3.8	No	1	r_P(1)	0.4	Yes	23	4.6
3	W	63	r	Breast	80	3.8	No	5	r_F(1) + P(2) + O(1) l_pons(1)	0.1	Yes	17	3.4
4	M	66	r	Occult	90	3.8	Yes	2	r_P(1), l_O(1)	0.05	Yes	34	3.7
5	W	47	r	Breast	90	3.8	No	20	r_F(3) + P(1) + O(1) l_F(6) + P(3) + T(1) + O(3) + Crbl(2)	15.5	Yes	20	3.5
6	M	69	r	GI	90	3.8	Yes	1	l_Crbl(1)	0	Yes	21	4.7
7	M	65	r	GI	90	6.9	Yes	1	l_F(1) + P(1)	0	No	17	3.4
8	M	63	r	RCC	90	6.9	No	1	r_Crbl(1)	0.1	Yes	17	4.7
9	W	58	r	Ovarian	100	11	Yes	1	r_Crbl(1)	0	No	24	4.6
10	W	48	r	Cervical	90	6.9	No	1	l_Crbl(1)	3.7	No	21	4.8

No number, *M* men, *W* women, *Dg* diagnosis, *NSCLC* non–small-cell lung cancer, *RCC* renal cell cancer, *GI* gastrointestinal cancer, *KPS* Karnofsky performance status, *MTS* metastases, *GPA* Graded Prognostic Assessment [13], *mo* months, *Surg* surgery, *r* right, *l* left, *F* frontal, *T* temporal, *P* parietal, *O* occipital, *Crbl* cerebellum, *CHT* chemotherapy, *B* baseline examination, *F/U* follow-up examination. Location: the number of metastases is mentioned in brackets

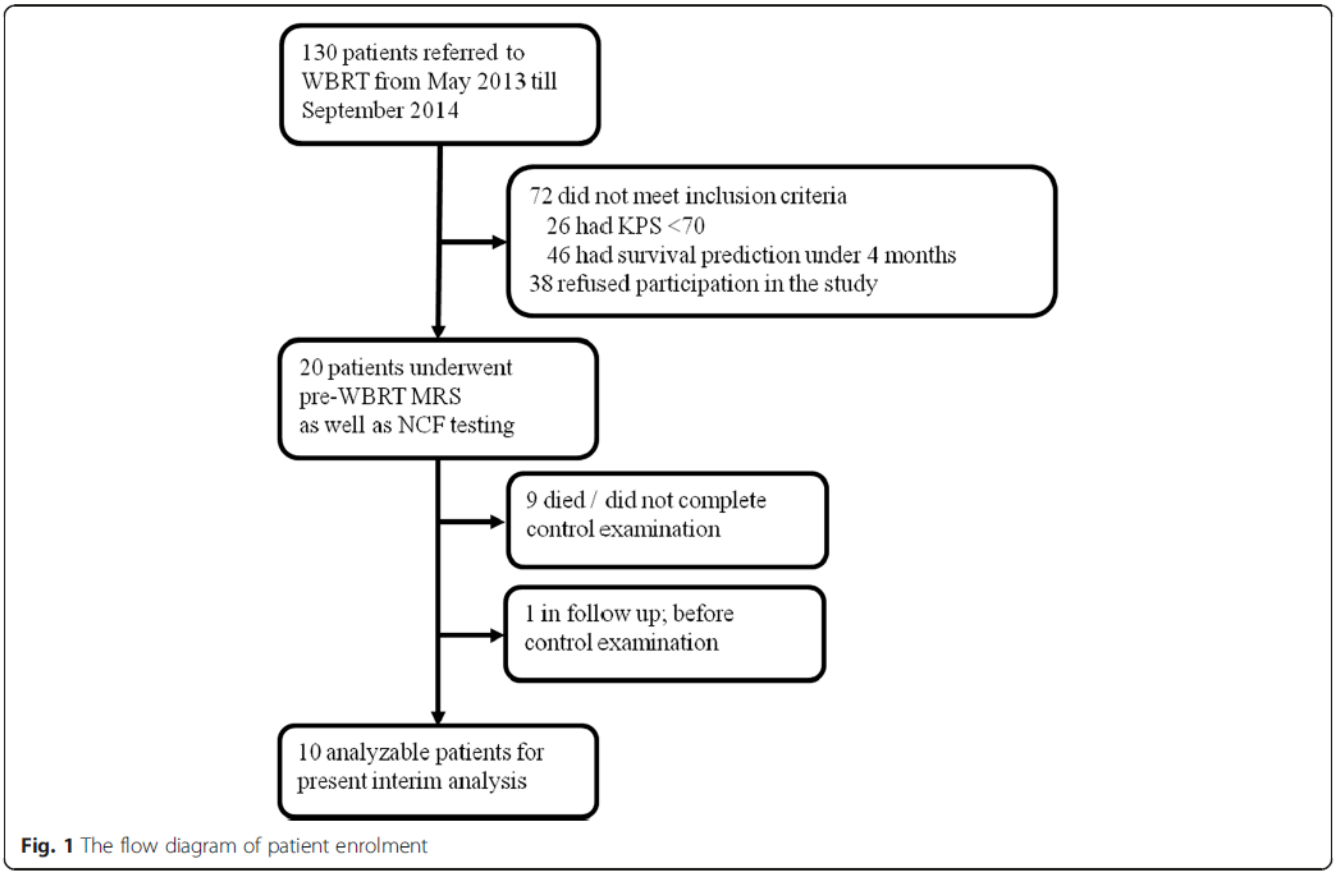

Fig. 1 The flow diagram of patient enrolment

Neurocognitive function analysis

All ten analyzable patients completed all of the tasks in the AVLT and BVMT-R tests. The relative declines in all tasks are summarized in Table 2 together with relative declines in the h-tNAA concentrations calculated using the same equation.

Table 2 Mean post-WBRT relative declines of the h-tNAA concentration and absolute changes in memory tests

No	h-tNAA			AVLT			BVMT-R		
	RH	LH	BH	TR	DR	R	TR	DR	R
1	−7 %	−3 %	−5 %	−12	−3	0	−19	−6	0
2	−14 %	−10 %	−12 %	−3	0	0	−2	−2	−1
3	−14 %	−19 %	−17 %	−16	−2	0	−8	−4	0
4	1 %	−14 %	−6 %	−11	+1	+2	−5	−1	−1
5	−28 %	−20 %	−24 %	−3	−2	+3	−4	−2	+1
6	−22 %	−21 %	−22 %	−10	−5	+1	0	−2	−1
7	−26 %	1 %	−13 %	−2	0	−1	−8	−3	−1
8	−27 %	−2 %	−15 %	−14	0	0	−4	−4	−3
9	−29 %	−22 %	−25 %	0	+2	−1	−18	−5	−1
10	−15 %	−22 %	−19 %	−13	−3	+3	0	+2	0

No patient's number, *h-tNAA* total N-acetylaspartate in the hippocampus, *RH* right hippocampus, *LH* left hippocampus, *BH* both hippocampi, *AVLT* Auditory Verbal Learning Test, *BVMT-R* Brief Visuospatial Memory Test-Revised, *TR* total recall, *DR* delayed recall, *R* recognition

In our group of patients in the AVLT_TR, the mean score decline (−8.4 points) was statistically significant in the control examination compared to pre-WBRT tests ($p = 0.0039$). In the corresponding BVMT-R_TR a significant decline was also observed (−6.8 points; $p = 0.008$). Moreover, the decline was also ascertained in the BVMT-R_DR (−2.7 points; $p = 0.001$). Mean differences between the baseline and control examination are summarized in Table 3.

No statistically significant strong correlation was observed between the decrease in the right, left and overall h-tNAA concentration and the decrease in the AVLT and BVMT-R subtests scores.

Weak positive correlation was observed between left h-tNAA concentration and AVLT_DR (Spearman correlation $r = 0.24$, $p = 0.5$). Weak to moderated negative correlation was observed between left h-tNAA and AVLT_R ($r = -0.47$, $p = 0.17$), BVMT-R_TR ($r = -0.36$, $p = 0.30$), BVMT-R_DR ($r = -0.36$, $p = 0.30$) and BVMT-R_R ($r = -0.39$, $p = 0.27$). For right h-tNAA concentration, the negative correlation was only to AVLT_TR ($r = -0.5$, $p = 0.14$).

Discussion

The personalized approach in medical care is increasingly discussed also in the management of patients

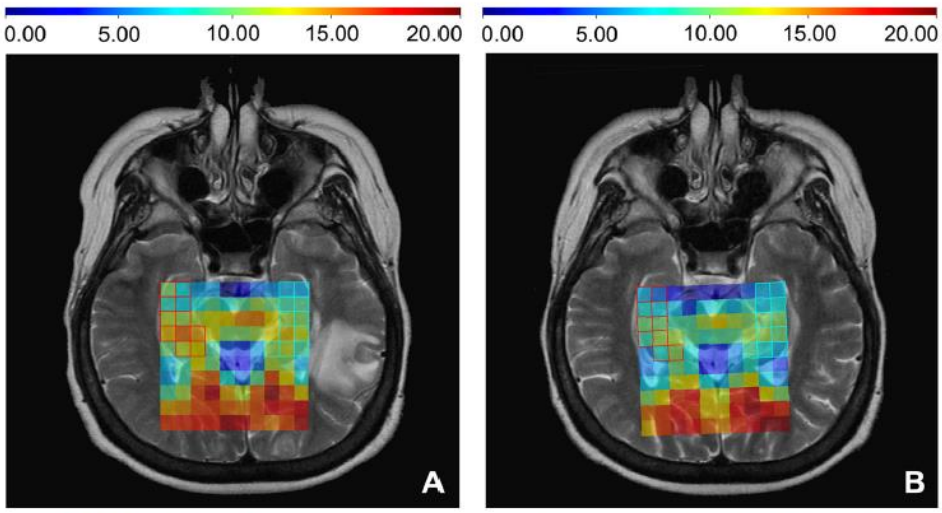

Fig. 2 Pre-WBRT (**a**) concentration of h-tNAA in the patient number 5 (11.29 mM in the right and 10.55 mM in the left hippocampus) and its decrease after WBRT (**b**) (8.14 mM in the right and 8.42 in the left hippocampus)

Table 3 Absolute mean differences between pre-WBRT and post-WBRT examination for the h-tNAA concentrations [mM] and all AVLT and BVMT-R subtests

	Pre-WBRT	Post-WBRT	Absolute mean difference		Relative mean difference [%]	
			(95 % CI)	*p*-value[+]	(95 % CI)	*p*-value[‡]
h-tNAA	[mM]	[mM]				
RH	8.9	7.16	−1.74	0.004*	−18.1	0.004*
			(−0.99 to −2.48)		(−11 to −25.2)	
LH	8.86	7.65	−1.21	0.004*	−13.4	0.004*
			(−0.56 to −1.86)		(−6.9 to −19.9)	
BH	8.88	7.401	−1.48	0.002*	−15.9	0.002*
			(−0.92 to −2.04)		(−10.9 to −20.9)	
AVLT						
TR	45.1	36.7	−8.4	0.004*		
			(−4.3 to −12.5)			
DR	7.3	6.1	−1.2	0.125		
			(0.33 to −2.7)			
R	12.8	13.5	0.7	0.250		
			(1.77 to −3.69)			
BVMT-R						
TR	22.6	15.8	−6.8	0.008*		
			(−1.96 to −11.6)			
DR	9.2	6.5	−2.7	0.001*		
			(−1.1 to −4.3)			
R	5.6	4.9	−0.7	0.109		
			(0.06 to −1.45)			

CI confidence interval, Asterisks denote statistical significance; cross denotes Wilcoxon signed test; double-cross denotes Wilcoxon signed rank test, hypothesized value 0; *h-tNAA* total N-acetylaspartate in the hippocampus, *RH* right hippocampus, *LH* left hippocampus, *BH* both hippocampi, *AVLT* Auditory Verbal Learning Test, *BVMT-R* Brief Visuospatial Memory Test-Revised, *TR* total recall, *DR* delayed recall, *R* recognition, *WBRT* whole brain radiotherapy

suffering from BM [18, 19]. Preserving neurocognitive functions and the quality of life is becoming an important target in clinical trials as well as in daily practice, especially after WBRT [20, 21]. Since even low dose radiation injury to the neural stem subgranular zone cells of the hippocampal dentate gyrus is related to early cognitive and memory decline [22], hippocampal sparing during WBRT seems to be the most promising approach [4, 23, 24] alongside pharmacological interventions [7, 25, 26]. Ongoing research which further ascertains processes responsible for hippocampal radiation injury may provide additional evidence supporting a particular personalized approach as well as revealing new strategies for mitigating the adverse neurocognitive effects of WBRT. However, additional factors, such as tumor-related morbidity, as well as the effects of surgery and chemotherapy may also contribute to final NCF impairment and must be taken into account.

In the present study, the post-WBRT neurocognitive decline was investigated in correlation to an innovative hippocampal examination by proton MR spectroscopy. To the best of our knowledge, this is the first in human study documenting the cognitive decline related to post-WBRT hippocampal metabolic changes as proven by noninvasive in vivo examination. Using hippocampal MRS is well established in cognitive disorder research particularly focusing on mild cognitive impairment (MCI), an early stage of dementia [27, 28]. NAA was found to be the most reliable marker of brain cognitive and memory dysfunction and MRS is presumed to be the predictor of the progression of MCI into Alzheimer dementia [29] as well as a predictor of the conversion of cognitively normal older adults into MCI [30].

Proton MR spectroscopy of the hippocampal region was also performed for the examination of postradiation metabolic changes in the brain, but only with limited regional differences in specific hippocampal evaluation [31–37]. The NAA reduction after radiotherapy was consistent throughout all mentioned studies, however, direct comparisons may be biased due to inconsistency in the use of the spectroscopy method (single voxel, single slice multivoxel, 3D echo planar spectroscopic imaging), target voxels placement, patient selection (primary or secondary brain tumors, therapeutic or prophylactic brain irradiation) as well as due to a lack of cognitive assessment with the exception of the Mini-Mental Status Examination evaluation in the Movsas et al. study [33], where no correlation to whole-brain decrease in NAA was observed 3–4 weeks after WBRT.

The feasibility of human quantitative spectroscopic measurement of radiation induced hippocampal brain injury was proven by investigators from the University of Pennsylvania who examined h-tNAA, creatine and choline as well as diffusion tensor imaging in seven patients 1 month after WBRT using 3D echo planar spectroscopic imaging. A trend towards a decrease in the ration of NAA and creatine was observed from the hippocampal region 1 month after radiation (1.48 ± 0.07 vs 1.27 ± 0.2, $p = 0.06$) [37]. In our study, a significant decrease of the h-tNAA spectra was observed in the both hippocampi as well as separately in the left and right hippocampus (single slice multi-voxel spectroscopic examination).

Functional magnetic resonance imaging can demonstrate the functional anatomy of cognitive and memory processes. Functional memory asymmetry is known mainly from epileptology where mapping the sites of memory function is important before neurosurgical planning for temporal lobe epilepsy. Left hippocampus is more related to verbal memory function comparing to visual memory connected more to the right one [38]. Similar asymmetry can be expected also in our cohort, since all analyzable patients were right handed. Although weak ($r = 0.24$), positive correlation was observed between decrease of left h-tNAA concentration and decrease in the AVLT_DR absolute score. This correlation may confirm the hypothesis that WBRT leads mainly to damage of relatively mitotically active neuronal stem cells which results in lower ability to maintain verbal memories.

The negative correlations between h-tNAA and NCF evaluated by both AVLT and BVMT-R (for example moderate negative correlation ($r = -0,5$) with trend to statistical significance ($p = 0,14$) between right h-tNAA and AVLT_TR) are probably biased by small sample size as well as selection bias of our patient cohort. However, consistent decrease in NAA concentrations and NCF test were observed in all patients. More analyzed patients are needed to provide some conclusions.

Altogether, it is too early to draw any clear conclusion with unequivocal explanation of observed correlations considering also potential effects of pre-WBRT neurocognitive dysfunction due to primary tumor-, patient- or chemotherapy-related effects or even gender [39, 40]. Indeed, some patients had relatively severe NCF decrease as proved by low scores in memory tests which may impact severity of post-WBRT changes. Nevertheless, results of presented interim analysis warrant continuing requirement in our ongoing study with other secondary analyses as evaluation of absolute NAA concentrations or hippocampal volumetry analyses. With more included patients, the true correlation may be discovered. The main advantage of the proposed research methodology is the non-invasive nature of the examination represented by advanced MR imaging which may be easily added to standard diagnostic imaging protocol. It may be assumed, that similar research may enhance pre-radiotherapy imaging description of hippocampal function in individual patient and guide asymmetric hippocampal avoiding

WBRT just as preoperative functional MRI has potential to predict postoperative verbal memory decline after anterior temporal lobe resection [41].

This small prospective clinical investigative study has numerous limitations. The Hopkins Verbal Learning Test - Revised (HVLT-R) is currently probably the most reliable test for the evaluation of radiation induced cognitive impairment [42]. However, proficiency in English is required and so its standardized Czech version was used in our study, which prevents a direct comparison with cited seminal randomized trials. The other limitation is seen in a narrowly focused MRS as well as NCF evaluation in this initial experience report. More metabolites (choline) as well as normalized concentrations with respect to creatine are among the most meaningful candidates for extended patient's requirements as well as for a retrospective analysis of already included patients.

Conclusion

A significant decrease in h-tNAA after WBRT was proven by ^{1}H-MR spectroscopy as a feasible method for the in vivo investigation of radiation injury. To definitely assess whether hippocampal avoiding RT approaches are worth the increased cost and effort of their performance, patients and tumor related biomarkers need to be established for the proper selection of suitable patients. Advanced MRI methods have the potential for the description of early adverse effects of brain irradiation long before standard white matter postradiation changes are visible with the time delay being beyond the average survival time of patients with BM. Studies similar to ours, where potential imaging biomarkers are correlated to prospectively evaluated neurocognitive changes, may identify which biomarker best correlates to the final affected treatment outcome and end point, i.e. an improvement in the quality of life of patients treated with palliative intent. Our promising results support continuing recruitment in ongoing studies focusing on other NCF tests as well as hippocampal metabolites.

Abbreviations

AVLT: Auditory verbal learning test; BM: Brain metastasis; BVMT-R: Brief visuospatial memory test-revised; DR: Delayed recall; h-tNAA: Total N-acetylaspartate in the hippocampus; HVLT-R: Hopkins verbal learning test-revised; MCI: Mild cognitive impairment; MR: Magnetic resonance; MRS: Magnetic resonance spectroscopy; NCF: Neurocognitive functions; R: Recognition; RT: Radiotherapy; TR: Total recall; WBRT: Whole brain radiotherapy.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

PP, TK, RJ, PS designed the study. PP and TK made the manuscript concept and drafted the article. RJ provided critical revision and was involved in drafting the manuscript. PB, LH, MD, MB performed the literature search and extracted relevant articles. PP, TK, MB, MD added important contents as pictures or tables and included data from their department. MB performed MR spectroscopy evaluation. MD performed cognitive tests. All authors participated revising of the manuscript. All authors read and approved the final manuscript.

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Ze 184 screenovaných pacientů splnilo vstupní kritéria celkem 84 pacientů, 49 z nich však účast ve studii odmítlo (nejčastěji z důvodu absence přímého benefitu ve smyslu prodloužení celkového přežití), zařazeno bylo tedy celkem 35 pacientů, kteří absolvovali vstupní MRS a NCF testování. Jde o soubor publikovaný v následujícím náhledu publikace 6 (7.3.2. Publikace 6 (79)). Před kontrolním vyšetřením 4 měsíce po radioterapii zemřelo 15 pacientů (43 % – odpovídá predikci z prognostických indexů, které poukazují na medián přežití, tedy 50 % pacientů s daným skóre se predikované doby dožije), dva další pacienti kontrolní testování odmítli. Zbývající výsledky jsou omezeny na 18 analyzovatelných pacientů, pro které byly k dispozici následné kontrolní zobrazovací a kognitivní vyhodnocení.

Průměrně bylo analyzováno 9 voxelů na pravý a levý hipokampus. Počet analyzovaných voxelů se lišil podle počtu voxelů, u nichž hodnota spektrální chyby byla větší než 20 %, protože tyto byly automaticky vyloučeny. Post-WBRT poklesy koncentrací h-tNAA a h-Cr (kreatinin) a také v poměru h-tNAA / Cr jsou uvedeny v tabulce prezentované v náhledu publikace 7.3.2. Publikace 6 (79). Statisticky významné snížení h-tNAA bylo pozorováno jak v pravém (-12,9 %), tak i levém (-12,0 %) hipokampu.

Statisticky významný pokles byl pozorován ve všech subtestech AVLT a BVMT-R s výjimkou AVLT_R. Pacienti vykazovali významný post-WBRT pokles v testu AVLT_DR s průměrným poklesem ze 7,4 na 5,6 bodů ($p = 0,01$), zatímco u MMSE nebyla pozorována žádná významná změna. Statisticky významná korelace byla nalezena mezi levým h-tNAA / Cr a BVMT-R_R (silný negativní korelační koeficient $r = -0,66$; $p = 0,008$). Byla pozorována pozitivní mírná korelace mezi poklesem levého h-tNAA a poklesem AVLT_TR ($r = + 0,32$; $p = 0,24$), stejně jako poklesem AVLT_DR ($r = + 0,33$; $p = 0,22$), ale výsledky nebyly statisticky významné. Významná korelace byla také pozorována mezi změnami v pravém h-tNAA / Cr a AVLT_DR ($r = -0,48$; $p = 0,061$). Celková subjektivní kvalita života (dotazníky) klesla po WBRT (průměrná změna -14,1 ± 20,3 bodů v transformované stupnici 0 až 100, $p = 0,018$). Analýza části dotazníků hodnotících kognitivní funkce popsala pokles z průměrných 86,5 na 80,2 bodů ($p = 0,059$), na hranici statistické významnosti. Ve sledovaném souboru nebyla nalezena korelace mezi koncentracemi metabolitů hipokampu a odpověďmi na otázky týkající se poklesu paměti.

Zajímavým zjištěním byl popis rozdílné reakce pravého a levého hipokampu na ozáření, kdy byla pozorována korelace mezi alterací paměti (paměť je nejdůležitější doménou NCF ve vztahu k radioterapii) a poklesem N-acetylaspartátu (markeru neuronů) v levém,

nikoliv však v pravém hipokampu. Některé ostatní práce také popisují rozdílné změny v pravé a levé hemisféře, naše práce byla první, která je přímo korelovala s prospektivně získanými daty popisujícími NCF (83)(84)(85).

7.3.2 PUBLIKACE 6

Pospisil P, Kazda T, Hynkova L, Bulik M, Dobiaskova M, Burkon P, Laack NN, Slampa P, Jancalek R. Post-WBRT cognitive impairment and hippocampal neuronal depletion measured by in vivo metabolic MR spectroscopy: Results of prospective investigational study. Radiother Oncol. 2017; 122(3): 373–379. (79)

Kategorie publikace: přehledová práce v časopise s IF

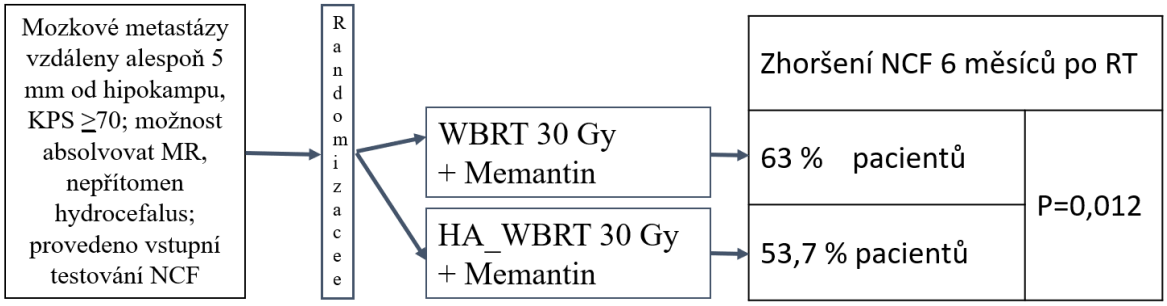
IF_{2017} 4,942, ranking Q1 (15/129) RADIOLOGY, NUCLEAR MEDICINE AND MEDICAL IMAGING, Q1 (51/223) ONCOLOGY

Práce byla ohodnocena Chodounského cenou za nejlepší publikaci v oboru Radiační onkologie v ČR za rok 2017.

Anotace: Jedná se o hlavní publikaci reportující výsledky grantového projektu prospektivně hodnotícího změny hipokampu po celomozkovém ozáření pomocí inovativního přístupu s využitím MR spektroskopie. Výsledky jsou diskutovány na předchozích stranách habilitační práce. V rámci oboru radiační onkologie se jedná o unikátní publikaci v hlavním časopise evropské radioterapeutické společnosti.

7.4 Strategie k minimalizaci nežádoucích účinků RT mozku

Obr. 6: Schéma NRG-CC001 studie a hlavní výsledek (88)(89)



7.4.1 PUBLIKACE 7

Kazda T, Jancalek R, Pospisil P, Sevela O, Prochazka T, Vrzal M, Burkon P, Slavik M, Hynkova L, Slampa P, Laack NN: Why and how to spare the hippocampus during brain radiotherapy: the developing role of hippocampal avoidance in cranial radiotherapy. Radiat Oncol 2014; Jun 16; 9: 139 (59)

Kategorie publikace: přehledová práce v časopise s IF

IF_{2014} 2,546, ranking Q2 (40/125) RADIOLOGY, NUCLEAR MEDICINE AND MEDICAL IMAGING

Práce byla ohodnocena Chodounského cenou za nejlepší publikaci v oboru Radiační onkologie v ČR za rok 2014.

Anotace: V této přehledové práci jsou shrnuty mechanismy poradiačního poškození hipokampu a navazující klinická evidence šetření této oblasti v průběhu ozařování primárních i sekundárních mozkových nádorů. Následně jsou shrnuty jednotlivé plánovací studie prokazující možnost šetření hipokampů při radioterapii CNS, stává se tak vodítkem pro radiologické fyziky připravující ozařovací plány s šetřením oblasti hipokampu. Toto potřebné know-how bylo nutnou prerekvizitou pro další studie zabývající se touto problematikou, které probíhají na našem pracovišti. Na závěr přehledového článku jsou diskutovány četné kontroverzní otázky těchto radioterapeutických technik.

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Why and how to spare the hippocampus during brain radiotherapy: the developing role of hippocampal avoidance in cranial radiotherapy

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Abstract

The goal of this review is to summarize the rationale for and feasibility of hippocampal sparing techniques during brain irradiation. Radiotherapy is the most effective non-surgical treatment of brain tumors and with the improvement in overall survival for these patients over the last few decades, there is an effort to minimize potential adverse effects leading to possible worsening in quality of life, especially worsening of neurocognitive function. The hippocampus and associated limbic system have long been known to be important in memory formation and pre-clinical models show loss of hippocampal stem cells with radiation as well as changes in architecture and function of mature neurons. Cognitive outcomes in clinical studies are beginning to provide evidence of cognitive effects associated with hippocampal dose and the cognitive benefits of hippocampal sparing. Numerous feasibility planning studies support the feasibility of using modern radiotherapy systems for hippocampal sparing during brain irradiation. Although results of the ongoing phase II and phase III studies are needed to confirm the benefit of hippocampal sparing brain radiotherapy on neurocognitive function, it is now technically and dosimetrically feasible to create hippocampal sparing treatment plans with appropriate irradiation of target volumes. The purpose of this review is to provide a brief overview of studies that provide a rationale for hippocampal avoidance and provide summary of published feasibility studies in order to help clinicians prepare for clinical usage of these complex and challenging techniques.

Keywords: Hippocampus, Hippocampal sparing, Hippocampal avoiding radiotherapy, Brain radiotherapy, Feasibility study, Planning study

Background

Both primary and secondary brain tumors (BT) represent a significant public health problem. An increasing incidence in primary brain tumors (PBT) as well as brain metastasis (BM) has been documented over recent years. In 2014, more than 24,000 new PBT are estimated to be diagnosed in the United States [1]. Moreover, about 1,4 million new solid tumor cases of all histological origin are diagnosed each year in the United States and approximately 30% of them develop BM [1]. Therefore, management of BT is an increasingly important component of cancer therapy [2].

Radiotherapy is an important modality in the treatment of BT. Radiotherapy remains the standard treatment for vast majority of high-grade or malignant brain tumors and plays an integral role in treatment of many low-grade and benign primary brain tumors. However, concerns regarding neurocognitive toxicity after radiotherapy in patients with benign or low-grade tumors make the timing of treatment controversial [3].

Historically, radiotherapy was also a mainstay of treatment for BM. With improved survival and increased awareness of the cognitive effects of WBRT, the role of WBRT in BM has come under question [4]. Because of these concerns there has been a trend towards increased reliance on focal treatments such surgery and stereotactic

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radiosurgery (SRS) [5]. However, achieving whole brain control is associated with improved survival and preserved neurocognitive domains with exception of memory function, especially recall and delayed recall [6]. Thus, understanding the risk of brain tumor recurrence at distant sites of brain is important in counseling patients regarding the risks and benefits of WBRT. Patients with single BM and no extracranial metastases are at low risk for in-brain recurrence and omitting early WBRT because of the risk of intermediate and late adverse effects (AE) can be safely done as long as the patient commits to regular imaging [7]. Conversely, patients with progressive systemic disease are at a higher risk for distant brain failure and likely benefit from the addition of WBRT despite possible late complications [8].

For most malignant adult PBT and BM, radiotherapy prolongs survival but is rarely curative. Thus, emphasis on minimizing the AE of treatment is becoming one of the most important factors in the treatment. Recently, more attention has been paid to symptom related outcomes of care, especially to neurocognitive function (NCF) and quality of life (QoL) [9-11]. With improvements in radiotherapy systems technology, it is now possible to modify treatment plans to selectively spare structures that may contribute to decreased QoL and NCF. In order to achieve this aim, it is important to determine appropriate end-points primarily in relation to the ongoing randomized clinical trials as resources for future treatment guidelines [12].

Decline in NCF as an iatrogenic side effect of brain irradiation is well-known [13]. The mechanism of radiation injury is complex and multi-factorial. In the past, cognitive decline after radiotherapy was believed to be a late effect of treatment mediated through microvascular changes and neuroglial loss. However, there is increasing evidence for acute and subacute cognitive changes after radiotherapy that appear to be mediated through the neurogenic zones including the hippocampus. Preclinical evidence supports the concept of hippocampal radiation injury as a mediator of subsequent AE, most notably in memory-related domains of neurocognition [14]. Retrospective clinical reports as well as early results of prospective trials support the role of hippocampus in early changes in cognitive function after radiotherapy [11]. The purpose of this review is to provide a brief overview of studies that provide a rationale for hippocampal avoidance (HA) and provide summary of published feasibility studies in order to help clinicians prepare for clinical usage of these complex and challenging techniques.

Hippocampus and radiation injury

The hippocampus is a paired brain structure, located in the ventromedial part of the temporal lobes, laying lateral to the temporal horn of the lateral ventricle. The hippocampus is composed of the dentate gyrus and the cornu ammonis regions and belongs to the limbic system. Its main role in brain function is cooperation in learning, consolidation and retrieval of information and it is also essential for formation of new memories [15]. Bilateral and unilateral radiation injury of the hippocampus is known to alter learning and memory formation [16]. Complete pathophysiologic explanation of all these processes is still lacking; nevertheless, the role of neurogenesis seems to be one of the most compelling [17].

Mitotically active neural stem cells (NSCs) are located in different parts of brain, namely in the subependymal zone and in the subgranular zone of the dentate gyrus, wherefrom they migrate into the granular cell layer of hippocampus [18]. The hippocampal subgranular zone is a critical neurologic center for learning and memory [19]. NSCs have typical features of the stem cells. They are capable of both self-renewal and generating new differentiated cells [20]. Neurogenesis is a complicated process with integration of many regulatory cells as astrocytes or endothelial cells with coordinate evolution of neural precursor cells together with each other in a specific neurogenic microenvironment called "niche" [21,22].

Multiple preclinical studies support the hypothesis of hippocampus-mediated cognitive dysfunction [23-30]. In vivo animal studies demonstrate sensitivity of these NSCs to ionizing radiation. Apoptosis of NSCs after ionizing radiation was first described in the subependymal zone in the young adult rat. After single x-ray doses of 5 or 30 Gy, apoptosis peaked 6 hours after irradiation [23]. Several years later, postradiation apoptosis was observed also in the rats' dentate gyrus after exposure to single 10 Gy dose [24]. Decline in neurogenesis was associated with cognitive impairment in rodent models for both single and fractionated brain irradiation [14,25]. Mizumatsu et al. irradiated the whole brain of experimental mice with various single doses and used immunohistochemical staining methods for detection of apoptosis as well as numbers of proliferating cells and immature neurons in the subgranular zone of the hippocampal dentate gyrus. Dose-dependent apoptosis was observed and peaked 12 hours after irradiation followed by subsequent reduction in amount of proliferating cells in subgranular zone [27]. Changes in neurogenesis were associated with an inflammatory response as validated by detection of activated microglia cells [29]. Moreover, administration of anti-inflammatory agents such as ramipril and indomethacin can mitigate radiation-induced cognitive impairment in rodents suggesting the inflammatory response is important in mediating the effects of radiotherapy [30].

However, these and other mechanisms of radiation effects on neurogenesis do not completely describe the radiobiology of the hippocampus [31]. More recent in vitro and in vivo research reveals other important radiation induced

hippocampal changes which may also influence cognition [32]. Investigators at University of California at Irvine, CA, USA have optimized a SYBR green based assay to study the effects of low dose RT before changes are visible radiographically. Even a dose of 2 Gy delivered to human NSCs leads to decreased numbers of cells undergoing neuronal differentiation after irradiation [33]. Additional work from the same group suggests the mechanism of radiation-induced inhibition of neurogenesis may be mediated through oxidative stress [34].

Although significant pre-clinical data supports a decrease in NSC number and function after radiotherapy, changes in neuronal architecture, as recently described by Parihar and Limoli in measurements of micromorphometric parameters in mice following cranial irradiation by 1 and 10 Gy, may also be important in mediating the effects of radiotherapy [35]. Dose-dependent reduction of dendritic branching, length and area were described as well as the reduction of immature filopodia as compared with mature spine morphology of dendritic segments. These postradiation changes correlated with alterations in synaptic protein production that were noted up to 1 month after brain irradiation [35]. These types of changes are likely to be equally important as disruption of neurogenesis in eliciting cognitive decline after radiotherapy.

Recent studies provide dose–response data and estimation of clonogenic survival fraction of human NSCs after brain irradiation. This data is important from a radiation oncology point of view primarily for determination of pertinent treatment planning recommended dose constraints.

In QUANTEC analysis, the normal brain α/β value has been established to be 2.9 [36]. For the hippocampal region, most authors use the α/β ratio in range from 2 to 3 [37]. However, other authors work with the α/β value for NSCs compartments equal to 10 [38,39] using a general value established for stem cells [40]. Some authors use α/β ratio 10 for the true hippocampus and an α/β value 2 for the whole hippocampus planning-at-risk volume illustrating the lack of consensus regarding the optimal model of radiation sensitivity. However, preclinical evidence suggests doses as low as 2 Gy to result in apoptosis of neurogenic stem cells supporting a no-shoulder dose-response [29,33]. Several other studies have measured altered survival and proliferation using a range of metabolic and SYBR green based assays. These studies revealed that doses of as low as 2 Gy reduced survival by over 50% [33]. Thus, accumulating preclinical data indicate that neurocognitive dysfunction manifests at much lower doses (<10 Gy) than previously expected [34].

Clinical evidence for hippocampal sparing

In addition to preclinical evidence, retrospective clinical reports also suggest the hippocampal region may play a role in NCF decline after radiotherapy. Children with brain tumors treated on prospective clinical trials that included planned neurocognitive assessments were evaluated with neurocognitive studies up to 5 years after radiotherapy. Mean doses of 45 Gy or higher to the left temporal lobes were associated with significant declines in longitudinal IQ [41,42]. The relationship between hippocampal dose level and the risk of subsequent NCF impairment was described in the group of patients with adult low-grade gliomas; NCF was assessed at the baseline and at 18 months follow-up for conventionally treated patients. Biologically equivalent dose greater than 7.3 Gy (equivalent dose in 2-Gy fractions) applied to 40% of hippocampal volume was associated with long-term NCF impairment, especially in list-learning delayed recall [43]. Recently, results of the first prospective phase II study (RTOG 0933) of HA in BM patients suggest a reduction in risk of cognitive dysfunction with HA [11]. Primary cognitive outcome was delayed recall at 4 months as measured by the Hopkins Verbal Learning Test for patients with WBRT comparing with those with HA WBRT. Results were compared to historical control group. Only 7% of patients experienced decline in memory compared to 30% of patients in the historical cohort ($p = 0.0003$). QoL was evaluated as well and was preserved up to 6 months follow-up. Based on these results, RTOG is planning a phase III randomized trial of prophylactic cranial irradiation with or without hippocampal sparing for small cell lung cancer patients (RTOG 1317).

Hippocampus-sparing: feasibility studies

Although evidence is mounting in regards to the importance of the hippocampus in mediating cognitive changes after radiotherapy, it has only been with recent technologic advances that the feasibility of a meaningful reduction in hippocampal dose while maintaining acceptable tumor control probability has been established. Below we review the feasibility studies evaluating HA for PBT and BM (Figure 1).

Primary brain tumors: HA feasibility studies

Complex intensity modulated radiotherapy (IMRT) plans were developed to evaluate the feasibility of sparing contralateral and bilateral hippocampi in glioma patients [38]. In "sparing" plans for the hemispheric HGG cases, it was possible to reduce the mean physical dose to the contralateral hippocampus planning-at-risk volume by 56.8% compared to standard treatment plan prepared without prospective sparing of the hippocampus (15.8 Gy vs. 36.6 Gy). In addition, more central location of PBT enables sparing of both hippocampi as documented by mean physical dose reduction by more than a third (16.8 Gy in sparing vs. 25.6 Gy in standard plan) [38]. Based on previous preclinical data, even low doses can result in NSCs apoptosis, but assuming that hippocampus is

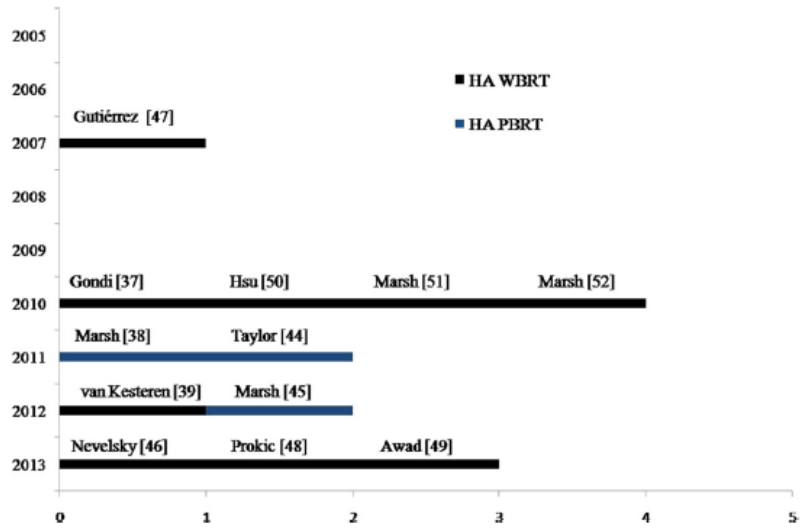

Figure 1 Overview of recently published radiotherapy planning studies dealing with hippocampal avoidance. Only studies with more than 9 patients included [44].

more parallel than serial organ, a reduction of median hippocampal dose may reduce NCF impairment even if no unequivocal cut-off dose threshold is known. Unfortunately, reported dose reduction is related to hippocampal planning-at-risk volumes, which were created by 3 mm expansion of hippocampi, so it is not possible to compare these results with other published studies.

PBT are frequent diagnosis in children in whom minimization of subsequent late AE is even more important. In a evaluating HA in pediatric gliomas, the NSCs compartments, the limbic circuit and the whole hippocampus were recognized as organ at risk (OARs) and included in experimental treatment plans [45]. For each RT plan the biological equivalent doses were calculated providing more radiobiologically exact comparison of doses in OARs. In all cases (10 different PBT), experimental plans significantly reduce both mean physical dose (by 56.0%) and mean biological equivalent doses (by 52.1%) delivered to the study OARs in comparison to plans without any effort to spare these structures. As might be expected, greatest hippocampal sparing was seen in hemispheric gliomas whereas worse results were observed for diffuse tumors where whole ventricular RT was indicated.

Brain metastases: HA feasibility studies

Many planning studies have shown the dosimetric feasibility of HA WBRT using different radiotherapy systems as linear accelerator (LINAC) based IMRT, helical tomotherapy or volumetric modulated arc therapy (VMAT). In addition, HA brain irradiation is also possible using Elekta IMRT step and shoot systems [46].

The pioneer study was performed in 2007 by Gutiérrez et al., who tested feasibility of HA WBRT with simultaneous integrated boost (SIB) to BM in experimental radiotherapy plans using helical tomotherapy [47]. Regardless a different setting of treatment plans (pitch and field width), they described no significant difference in hippocampal doses. Authors concluded that it is possible to create combined plans with homogeneous whole brain dose distribution equivalent to conventional WBRT, while conformal HA and radiosurgically equivalent dose boosting to individual metastases.

Mean dose guidelines for HA WBRT were first published by Gondi [37]. HA plans were compared with standard WBRT ones where a homogenous dose 30 Gy was applied to the whole brain including hippocampus. For HA plans, the median hippocampal dose was achieved 5.5 Gy (D_{max} 12.8 Gy) and 7.8 Gy (D_{max} 15.3 Gy) for helical tomotherapy and LINAC based RT, respectively. These dose reductions have been considered a reference for other subsequent planning studies.

Because of higher availability of stereotactic systems, recent trends are to combine WBRT with stereotactic boosting to BM and thus improve local control. Also in this sequential concept, it is possible to spare hippocampus in both parts of treatment: HA WBRT and subsequent HA SRS boost. Moreover, using IMRT, it is possible to integrate boosting into the first WBRT part in concept of SIB. Comparing this approach with classical sequential concept (WBRT + stereotactic radiotherapy), the SIB is more effective in lowering doses to the hippocampus for patients with up to 8 metastases [48].

Although multiple techniques allow HA WBRT, treatment time can vary significantly depending on the technique. Using VMAT for HA WBRT with SIB for melanoma brain metastases, the average beam-on time was achieved 3.6 min while abide the RTOG 0933 feasibility DV constraints [49]. Arc based delivery times are generally faster

than conventional IMRT. VMAT was 3.5 times faster than classical IMRT techniques as discussed in other one planning study focused on HA WBRT published last year [46,50].

Similarly as for BM treatment, HA WBRT technique can be used for prophylactic cranial irradiation (PCI) where are NCF preserving approaches even more justified. Comparisons of limbic sparing experimental plans were conducted in 11 patients indicated for WBRT and for PCI. Similar reduction of hippocampal biological equivalent doses was achieved for both of these clinical situations [51,52]. These results are not surprising considering the fact, that PCI differ from WBRT only in terms of fractionation and that the standard radiotherapy technique is similar.

Comparison of treatment planning results with other studies is summarized in Table 1.

How to spare hippocampus

Because of hippocampal anatomic shape and central brain location, it can be a challenge to create appropriate HA treatment plan for irradiation of both PBT and BM. Nevertheless, modern IMRT techniques such as helical tomotherapy or VMAT are able to achieve HA with acceptable target volume coverage and dose homogeneity. Although a variety of treatment techniques are available for HA WBRT, the ability to achieve OAR dose goals varies by technique. In general, helical tomotherapy offered significantly better HA compared to LINAC based IMRT in terms of the mean normalized tissue dose, as well as the median and maximal hippocampal dose. However, despite different technical capabilities of mentioned radiotherapy systems, it can be concluded, that using either helical tomotherapy or LINAC based IMRT is sufficient for sparing not only traditional OARs but also the hippocampus [37]. An effort to minimize hippocampal dose must not lead to irradiation of other brain OARs. This is important especially for gliomas treated by overall higher doses compared with treatment of BM.

In addition, dose constraints are expected to be different for HA WBRT and HA PBRT. For BM, it is possible to sufficiently spare both hippocampi, and dose-volume constraints used in representative HA WBRT planning studies were summarized in Table 1. On the other hand, for HA PBRT, especially in the treatment of hemispheric gliomas, ipsilateral hippocampus is often included in target volumes (and considering much larger doses compared with WBRT). Thus, it is not possible to achieve appropriate dose reduction for ipsilateral hippocampus and only contralateral hippocampus could be considered as OAR. As an example, for HGG the following constraints criteria have been proposed: 0% of the hippocampal volume cannot receive more than 8 Gy in the first phase of treatment (up to 46 Gy) and no more than 4 Gy in the final phase (next 14 Gy to the target volume) [38].

Contouring of target volumes is, as a potential source for systematic error, one of the most important parts of whole radiotherapy planning process. Structure contouring for radiotherapy purpose is sometimes slightly different process comparing with the other medical discipline.

Table 1 Hippocampal dose-volume constraints and achieved doses in representative HA WBRT planning studies

Author, year	Clinical situation	RT system	No.	Fractionation	Hippocampal constraints		Hippocampal doses			α/β
					D_{max}		D_{max}	D_{mean}	D_{median}	
Gutierrez, 2007 [47]	WBRT	HT	10	15 × 2.15 Gy	6 Gy		-	5.86 Gy_2	5.34 Gy_2	2
Gondi, 2010 [37]	WBRT	HT	5	10 × 3.0 Gy	6 Gy	3 Gy ≤ 20%	12.8 Gy	-	5.5 Gy	2
		LINAC			11 Gy	9 Gy ≤ 40%	15.3 Gy		7.8 Gy	2
Hsu, 2010 [50]	WBRT + SIB	LINAC	10	15 × 2.15 Gy (SIB á 4.2 Gy)	-	D_{mean} < 6 Gy_2	-	5.23 Gy_2	-	2
Marsh, 2010 [51]	PCI	HT	11	15 × 2.0 Gy	15 Gy		-	12.5 Gy	-	-
	WBRT		11	14 × 2.5 Gy	15 Gy			14.3 Gy		
Marsh, 2010 [52]	PCI	HT	10	15 × 2.0 Gy			-	11.5 Gy	-	-
	WBRT		10	14 × 2.5 Gy	-	-	-	11.8 Gy	-	-
Van Kesteren, 2012 [39]	WBRT	LINAC 3D-CRT	10	12 × 2.5 Gy			13.5 Gy	6Gy	-	10
Nevelsky, 2013 [46]	WBRT	LINAC IMRT	10	10 × 3.0 Gy	16 Gy	$D_{100\%}$ < 9 Gy	14.35 Gy	-	-	-
Awad, 2013 [49]	WBRT + SIB	VMAT RA	30	5-15fx	-		32.2 Gy	20.4 Gy	21.9 Gy	-
Prokic, 2013 [48]	WBRT + SIB	VMAT RA	10	12 × 2.5 Gy BM 12 × 4.25	-		12.33 Gy ($D_{2\%}$)	7.55 Gy	7.15 Gy	H 2 BM 10
	WBRT + FSRT	VMAT RA	10	12 × 2.5 Gy + FSRT 2 × 9 Gy	-		15.82 Gy ($D_{2\%}$)	9.8 Gy	9.34 Gy	H 2 BM 10

3D-CRT: three dimensional conformal radiotherapy; RA: Rapid Arc; HT: helical tomotherapy; FSRT: fractionated stereotactic radiotherapy; D_{max}: maximal dose; D_{mean}: mean dose; $D_{100\%}$: dose in 100% of volume; $D_{2\%}$: dose in 2% of volume; D_{median}: median dose; H: hippocampus.

Exact volumetric assessing of the whole hippocampus is important especially in basic neurological research [53] as well as in research dealing with diseases connected to hippocampal impairment [54]. On the other hand, only some HA radiotherapy feasibility planning studies defined in detail the process of contouring, almost exclusively with reference to the Radiation Therapy Oncology Group online contouring atlas [55]. Authors of this atlas do not contour the entire hippocampus, but are focusing mostly on the subgranular zone as a place of NSCs occurrence. This approach is suggested as a standard for HA WBRT. On the other hand, for HA PBRT, where only the contralateral hippocampus is often spared, it is possible to contour the whole hippocampus irrespective of its NSCs rich part according to a radiation oncologist's guide to contouring the hippocampus proposed by Chera et al. [56]. Moreover, considering an attempt to spare NCF during brain irradiation, some studies defined OARs even more comprehensively including the whole limbic circuit (whole hippocampus; the rest of limbic circuit comprising the amygdalar complex, the fornix, the cingulum, the cingulated gyrus, and the mammillary bodies) [38,51].

Physician's requirements expressed in terms of dose-volume constraints are best achievable using inverse planning, which enables to set different priority points to different OARs and target volumes and thus it is possible to find compromise in dose coverage for all important treatment structures. As an example, in Table 1 were described parameters for both helical tomotherapy and LINAC based IMRT as presented in a seminal planning study [37]. These set of dose-volume constraints have been used in RTOG 0933 study, a first HA WBRT clinical trial which results were mentioned above [11]. Although methodology of the study enables differences in radiotherapy systems for preparation of a particular treatment plan, plans have to meet the required dosimetric constraints prior to approval for clinical use. Table 2 presents acceptable and unacceptable variations from "per protocol planning" for including particular IMRT treatment plan into RTOG 0933 trial. In our HA planning study, we compare different Arc radiotherapy techniques in order to achieve mentioned constraints. In the setting of non-coplanar beams arrangement, we have observed even higher hippocampal preservation compared to classical coplanar irradiation (not published data) (Figure 2).

In addition to the recent sophisticated methods enabling HA during brain irradiation, a simpler technique using two opposing laterolateral fields with central leaf shielding for appropriate HA has also been discussed [39]. The simplicity of this technique could enable radiotherapy departments that are not equipped with the latest technology to still offer HA radiotherapy. This technique is simple reproducible, as demonstrated by one experimental plan from our department (Figure 3).

Controversies

There are several medical and ethical controversies especially about the indications for HA brain irradiation. Providing of hippocampal sparing techniques is difficult and expensive. Thus, responsible decision must be made with respect to selection of appropriate patients especially in terms of probability of long term survival and QoL. The difference in the cost of basic 3D-CRT and advanced radiotherapeutic methods needed for HA brain irradiation is probably the most important controversy. Unfortunately, in many departments, especially in low-income countries, IMRT techniques are not widely available even for curative treatment (head and neck or prostate cancer). And even in large centers, it is not clear, whether implementation of more expensive RT technique is worthwhile to prevent probable mild neurocognitive decline. Only well designed randomized trials and cost-effective analysis can evaluate whether, or not these approaches should be incorporated into general practice. On the other

Table 2 Acceptable and unacceptable variations from per protocol IMRT treatment planning according to RTOG 0933 trial [11]

Treatment component	Parameter	Per protocol	Variation acceptable	Unacceptable deviation
MRI/CT Fusion and Contouring	MRI-CT fusion	No corrections to MRI/CT fusion requested	No corrections to MRI/CT fusion requested	Corrections to MRI/CT fusion requested
	Hippocampal Contouring	≤ 2 mm deviation using the Hausdorff distance*	> 2 and ≤ 7 mm deviation using the Hausdorff distance*	> 7 mm using the Hausdorff distance*
HA WBRT IMRT Planning	PTV	$D_{2\%} \leq 37.5$ Gy	$D_{2\%} > 37.5$ Gy ≤ 40 Gy	$V_{30} < 90\%$
		$D_{98\%} \geq 25$ Gy	$D_{98\%} < 25$ Gy	$D_{2\%} > 40$ Gy
	Hippocampus	$D_{100\%} \leq 9$ Gy	$D_{100\%} \leq 10$ Gy	$D_{100\%} > 10$ Gy
		$D_{max} \leq 16$Gy	$D_{max} \leq 17$ Gy	$D_{max} > 17$ Gy
OARs constraints	Optic nerves and chiasm	$D_{max} \leq 37.5$ Gy	$D_{max} \leq 37.5$ Gy	$D_{max} > 37.5$ Gy
Unscheduled break days	-	0 break days	1–3 break days	> 3 break days

*according to comparison with contours prepared by co-principal investigators.
PTV: planning target volume; $D_{2\%}$: dose in 2% of volume; $D_{98\%}$: dose in 98% of volume; $D_{100\%}$: dose in 100% of volume; D_{max}: maximal dose; V_{30}: volume irradiated by 30 Gy.

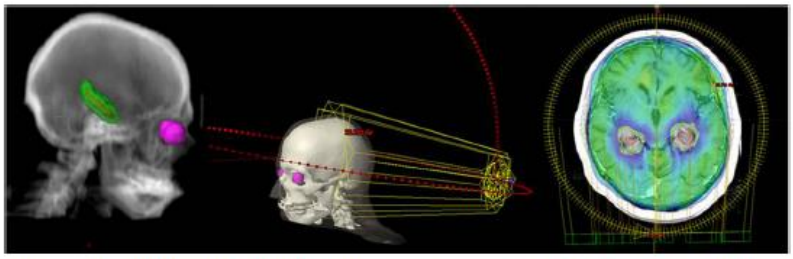

Figure 2 Examples of non-coplanar Arc treatment plan with hippocampal sparing and homogenous dose coverage in the rest of the brain.

hand, if IMRT is indicated for another reason, the hippocampus can be considered as other OAR assuming that no other standard OAR will receive more radiation.

Especially for patients with PCI or for children, it is important consider potential AE of some techniques using for hippocampal sparing such as helical tomotherapy for example. In an effort to minimize dose in hippocampus, there is a risk of overtreatment of other parts of the brain and surrounding structures with increased risk of induced secondary malignancies. To assess this potential disadvantage of helical tomotherapy, one study measured integral doses in uninvolved brain regions of HGG patients for both conventional IMRT and helical tomotherapy techniques [57]. The results proved reduction of brain integral dose in average by 23% after IMRT compared with tomotherapy in all tested treatment plans. Despite a theoretical risk of local overtreatment, integral dose delivered by any technique has been surprisingly lower in sparing plans compared with non-sparing ones. From this point of view, usage of traditional IMRT techniques is considered as optimal way how to spare hippocampus. Another approach reducing brain integral dose would be the proton therapy [58].

Considering sparing of some part of brain during WBRT in BM treatment as well as in prophylactic situation, a worry of subsequent increase risk of intracranial disease progression in spared regions is justified. However, many imaging studies described overall low number of metastases in the hippocampus as well as in other parts of the limbic circuit [59-62]. For example, on study evaluated 697 BM in 107 patients, only one of 53 oligometastatic patients (1.9%) had hippocampal metastases (that is 0.97% of all their metastases). In the group of non-oligometastatic patients, in hippocampus was presented only 2.29% of BM [59]. Moreover, other study with 371 patients and 1133 BM localize 8.6% of them into the HA region (hippocampus plus 5 mm margin); however, no metastasis was presented in the hippocampus itself [60]. It can be concluded, that sparing of hippocampus would likely not significantly increase the risk of treatment failure.

On the other hand, others have hypothesized, that neurogenic niches may not only harbor normal NSC but

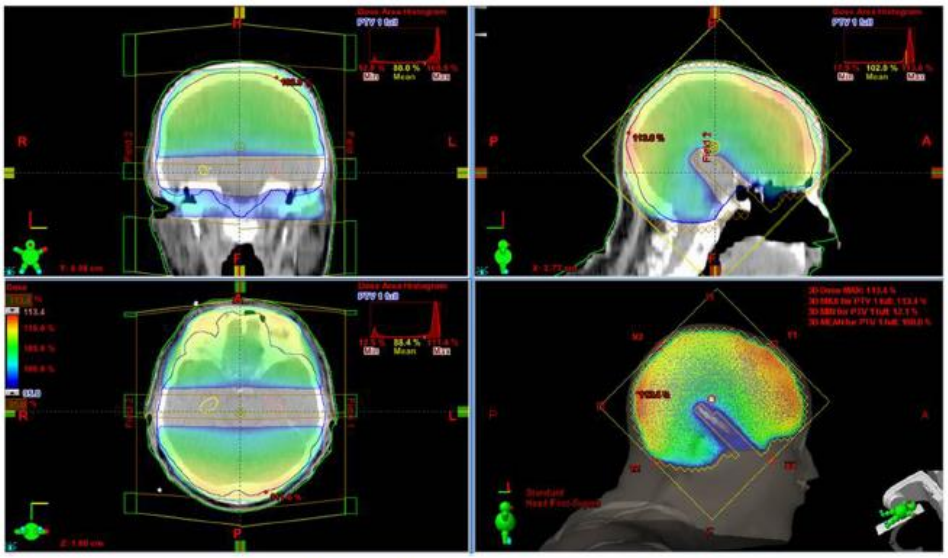

Figure 3 Simple RT technique using 2 laterolateral brain fields with 2 leafs positioned to block the hippocampus.

also cancer stem cells responsible for late recurrence. In a retrospective analysis of dose coverage of neurogenic niches in patients with malignant gliomas performed by Evers et al., dose to subventricular zone greater than 43 Gy was associated with a significant improvement in progression free survival compared to those with lower dose (15.0 vs. 7.2 months PFS; $P = 0.028$) [63]. Interestingly, similar analysis of dose delivered to the hippocampal formation did not yield statistically significant results which confirm the complexity of radiation effects on neurogenic niches [63]. These results highlight the need for well-designed clinical trials as well as continued pre-clinical research to evaluate beneficial or detrimental effects of hippocampal sparing.

The most important treatment related controversy is inconsistency in recommended dose reduction. At this time there is no level I evidence to conclusively support a particular recommendation. Preclinical studies indicate probable no-shoulder dose–response [29]. On the other hand, retrospective clinical studies suggest that biological equivalent dose greater than 7.3 Gy EQD_2 applied to 40% of hippocampus was associated with worse NCF outcomes [43]. Ongoing phase III trials evaluating NCF function will provide more possible dose-volume constraints associated with possible milder NCF impairment. Because of cost of advanced radiotherapy techniques, it is controversial whether apply intensity modulated plan in some particular patients which will be not able to achieve assumed dose goals especially in situation of standard three dimensional conformal plan would be originally considered. Based on the recently reported phase II trial [11], a dosimetric recommendation for HA WBRT ($D_{median} < 7.8$ Gy, D100% < 10 Gy and $D_{max} < 15.3$ Gy) can be recommended for patients with brain metastasis and expected survival greater than 6 months.

Future directions

Although HA appears to be promising in reducing cognitive affects after RT, ongoing studies and other clinical research are needed to determine the optimal dose and volume constraints. It is not clear based on radiobiology of neural stem cell response to radiation whether it is possible to define specific threshold values in terms of recommended target doses. Even if the nature of radiation injury of hippocampus is same in all patients, the different target doses that can reasonably be achieved in different clinical situations vary with prescribed doses and different clinical target volumes i.e. partial vs. whole brain irradiation or in therapeutic vs. prophylactic indication or in adults vs. children brain tumors. The role of HA in PCI and children has also not been established and is an area of future investigation. Optimal NCF evaluation tools to measure specific effects on hippocampus, as opposed to other etiologies of cognitive dysfunction, and optimal timing of administration is still largely unknown. To be able to compare results from different studies it is necessary to standardize process of NCF testing. However, the ideal tools to measure early changes in cognitive function as compared to late effects of treatment may not be the same. In addition, the testing must be feasible to administer in a busy clinical practice. Ongoing research on pathophysiology of brain irradiation injury may reveal other possible important brain structures whose sparing can contribute to better preservation of NCF, or further analysis of hippocampal subregion (cornu ammonis for example) may demonstrate avoidance region with higher priority for dose sparing. Development of cost-effectiveness analysis will be probably one of the most important steps forward to implementation of this advanced radiotherapy technique especially in low and middle income countries. Comparing cost of standard 3D-CRT (classical 2 latero-lateral fields for WBRT for example) and cost of VMAT or helical tomotherapy systems for example poses important questions whether consequent increase in costs offset theoretical mitigation of neurocognitive decline related to brain irradiation. Especially in situation where are presented many other different sources of cognition impairment in patients suffering from advanced cancer.

Conclusion

In summary, it is now technically and dosimetrically feasible to implement HA approaches into clinical practice. Furthermore, taking into account very low beam-on time of modern RT systems, it is ethically justifiable to use these techniques also in the palliative indications for patients with BM as well as HGG. As regards boosting of BM, comprehensive techniques with SIB provide tumor doses comparable with sequential approach of classical WBRT + SRS which require even 2 planning procedures which can result in such dosimetric inaccuracies. Moreover, HA WBRT with SIB provides better hippocampal sparing and this treatment approach seems to be the most promising to implement into clinical practice after confirmation of better cognitive outcomes after sparing of hippocampus in ongoing clinical trials.

Recently, first phase II clinical trial with prospectively measured NCF while providing HA WBRT showed significantly better outcomes for patients treated with hippocampal sparing in terms of better cognitive functions as well as quality of life. Conventional techniques of WBRT are now still recommended as standard approach for patients with multiple brain metastases and hippocampal sparing is generally not used outside of the context of clinical trials. Phase III studies are now ongoing and further implementation will depend on the results of these trials. For treatment of PBT, especially in its hemispherical location, it is reasonable to include contralateral hippocampus

into the OARs assuming that no other organ at risks or target volumes would be over/under irradiated. Ongoing phase III trials will definitely prove the clinical significance of this developing approach.

Abbreviations

BT: Brain tumors; PBT: Primary brain tumors; BM: Brain metastasis; PBRT: Partial brain irradiation; HGG: High-grade gliomas; WBRT: Whole brain radiotherapy; SRS: Stereotactic radiosurgery; AE: Adverse effects; NCF: Neurocognitive functions; PCI: Prophylactic cranial irradiation; HA: Hippocampal avoidance; IMRT: Intensity modulated radiotherapy; NSCs: Neural stem cells; OARs: Organs at risks; LINAC: Linear accelerator; VMAT: Volumetric modulated arc therapy; SIB: Simultaneous integrated boost.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

TK, PP, PS designed the study. TK made the manuscript concept and drafted the artide. RJ and NNL provided critical revision and were involved in drafting the manuscript. PB, MS, LH performed the literature search and extracted relevant articles. OS, TP, MV added important content as pictures or tables and included data from their department. All authors participated on revising of the manuscript. All authors read and approved the final manuscript.

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7.4.2 PUBLIKACE 8

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Práce byla ohodnocena Chodounského cenou za 2. nejlepší publikaci v oboru Radiační onkologie v ČR za rok 2018.

Úvod: Hipokampus šetřící WBRT je široce diskutovaná metoda radioterapie v léčbě pacientů s mnohočetnými mozkovými metastázami, jejímž cílem je zmírnění zhoršení především verbální paměti jakožto přímého důsledku ozáření oblastí hipokampu. Některá data naznačují rozdílné post-radiační změny v levém a pravém hipokampu, přičemž se dá hypotetizovat, že za alteraci NCF jsou více zodpovědné změny v levém hipokampu vedoucí k teoretickému návrhu pouze jednostranného (dominantního – levého) šetření hipokampu během WBRT.Metoda: Cílem této retrospektivní studie je popsat prostorové rozložení mozkových metastáz na v kohortě 260 pacientů (2 595 metastáz) a zhodnotit distribuci metastáz samostatně v levém a pravém hipokampu a v příslušných perihipokampálních zónách (HAZ), včetně vyhodnocení lokalizace centra jednotlivých metastáz.

Výsledek: Medián počtu metastáz v mozku byl tři, přičemž nejčastějším typem primárního nádoru byl bronchogenní karcinom; 36 % mělo jednu metastázu. Téměř 8 % pacientů mělo metastázy v hipokampu (1,1 % všech metastáz) a 18,1 % pacientů v HAZ (3,3 % všech metastáz). Nebyl pozorován žádný statisticky významný rozdíl v lateralitě hipokampálního postižení, a to ani při analýze umístění centra metastáz. Více pacientů, u kterých bylo centrum metastáz v HA zóně vlevo (15) vs. vpravo (6) HAZ, se přibližovalo k hranici statistické významnosti.

Závěr: Nebyl pozorován žádný významný rozdíl v lateralitě uložení mozkových metastáz v hipokampálních strukturách. Hypotetizovaná technika jednostranného šetření hipokampu v průběhu WBRT by měla, za předpokladu adekvátní preservace NCF, teoretickou výhodu v přibližně 50% snížení rizika následné recidivy v podzářených oblastech.

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Research Article

Incidence of Hippocampal Metastases: Laterality and Implications for Unilateral Hippocampal Avoiding Whole Brain Radiotherapy

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Introduction. Hippocampi sparing whole brain radiotherapy (WBRT) is an evolving approach in the treatment of patients with multiple brain metastases, pursuing mitigation of verbal memory decline as a consequence of hippocampal radiation injury. Accumulating data are showing different postradiotherapy changes in the left and right hippocampus with a theoretical proposal of only unilateral (dominant, left) hippocampal sparing during WBRT. *Method*. The aim of this retrospective study is to describe spatial distribution of brain metastases on MRI in a cohort of 260 patients (2595 metastases) and to evaluate distribution separately in the left and right hippocampus and in respective hippocampal avoiding zones (HAZ, region with subtherapeutic radiation dose), including evaluation of location of metastatic mass centre. *Results*. The median number of brain metastases was three, with lung cancer being the most common type of primary tumour; 36% had single metastasis. Almost 8% of patients had metastasis within hippocampus (1.1% of all metastases) and 18.1% of patients within HAZ (3.3% of all metastases). No statistically significant difference was observed in the laterality of hippocampal involvement, also when the location of centre of metastases was analyzed. There were more patients presenting the centre of metastasis within left (15) versus right (6) HAZ approaching the borderline of statistical significance. *Conclusion*. No significant difference in the laterality of BM seeding within hippocampal structures was observed. The hypothesized unilateral sparing WBRT would have theoretical advantage in about 50% reduction in the risk of subsequent recurrence within spared regions.

1. Introduction

The paradigm of palliative radiotherapy of brain metastases (BM) has been recently shifting towards strengthen the quality of life (QoL), especially neurocognitive functions [1, 2]. For better preservation of neurocognition, stereotactic radiotherapy has become the currently recommended approach both in upfront treatment of limited brain metastases [3, 4] as well as in postoperative adjuvant radiotherapy [5, 6]. Apart from local stereotactic radiotherapy, many other strategies, including administration of N-methyl-D-aspartate receptor antagonist memantine, are being investigated in order to mitigate the well-known adverse iatrogenic effects of classical whole brain radiotherapy (WBRT), which has been utilized for decades as a simple, cheap, and widely available treatment of BM [7–10]. Hippocampal sparing during WBRT is a recent modification of radiotherapy that provides a low risk of adverse events with appropriate local and distal brain control [11].

Radiation injury (radioinjury) of the hippocampus is a phenomenon described from preclinical experiments and clinical observations, with radiotherapy doses as low as 2 Gy leading to changes in neural progenitor cells residing within hippocampal neurogenic niches and being involved in memory formation [11–14]. Following promising results from the single-arm phase II clinical trial RTOG 0933, in which conformal avoidance of both hippocampi during WBRT was associated with preservation of memory and QoL compared to historical controls [14], the randomized phase III trial of WBRT combined with memantine and with or without hippocampal sparing is currently evaluating the potential of hippocampal sparing for patients with brain metastases (NRG CC001-NCT02360215).

What is missing is a clear understanding of eventual laterality of hippocampal radioinjury. Some preliminary evidence, however, suggests differential changes in the left and in the right hippocampus after radiotherapy or surgery [15–20]. In our previous prospective study, we observed a correlation between post-WBRT verbal memory impairment and changes in the left hippocampus measured by *in vivo* magnetic resonance spectroscopy, whereas no such correlation was observed in the right hippocampus [19]. In another recent study focused on hippocampal radiation dose volume effects and memory deficits, in which combined data from another three prospective studies were analyzes, the left hippocampus appeared more sensitive to radiation than the right one [20]. For example, a 20% risk of decline in verbal memory was associated with the maximal delivered dose of 28.8 Gy to the right hippocampus, but with only 23.7 Gy to the left one. Considering that post WBRT cognitive impairment (represented mainly by verbal memory deficits) would have been associated predominantly with unilateral hippocampal radioinjury, only unilateral (left) sparing during WBRT may be judged. This novel approach of unilateral hippocampus sparing WBRT would be associated with reduced concern regarding subtherapeutic dose in spared regions and with the possibility of improved sparing of single hippocampus. In our pilot dosimetric study, left unilateral sparing yielded lower doses in spared hippocampus with a more homogenous irradiation of the remaining brain [21]. To justify clinical testing of this radiotherapy technique, it would be useful to evaluate whether there is some difference in the incidence of BM within left versus right hippocampus; however, no prior study has assessed the laterality of hippocampal BM seeding.

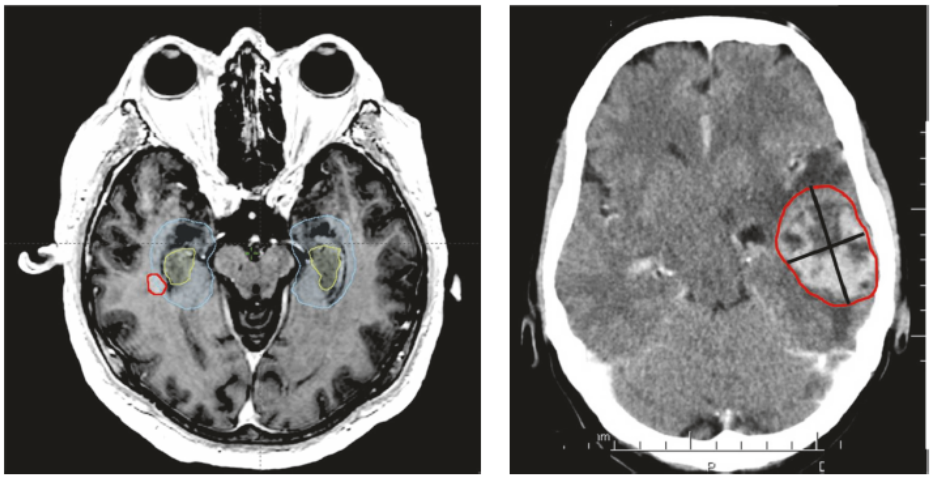
The aim of this retrospective study is to describe spatial distribution of BM in a cohort of 260 consecutive patients with a total of 2595 BM, evaluating distribution separately in the left and the right hippocampus and in respective hippocampal avoiding zones (HAZ).

2. Material and Methods

2.1. Patients and Image Selection. Consecutive patients with newly diagnosed BM referred between 1.1.2011 and 31.12.2014 to radiotherapy at Masaryk Memorial Cancer Institute in Brno, Czech Republic, were included in this retrospective study. Patients with available MRI scan that revealed first BM were eligible for further analysis. This MRI was used to describe spatial distribution of BM in order to avoid bias of previous local treatment of BM in estimation of incidence of hippocampal BM. Basic clinical data was obtained from electronic medical records. All patients signed the informed consent allowing usage of their clinical and imaging data for research purposes in an anonymous form.

2.2. Image Analysis. The location of BM was described in the first instance as temporal, occipital, parietal, frontal, or other (cerebellum, brain stem, diencephalon, or leptomeningeal BM) and BM were subsequently quantified within each region. MRI scans (T1 weighted sequence with intravenous administration of contrast agent) were transferred and imported into Eclipse™ radiotherapy treatment planning system (Varian Medical Systems, Palo Alto, CA), which enables smart contouring tools such as individual structures segmentation, isotropic expansions, and several Boolean operations. Left (LH) and right hippocampi (RH) were separately contoured in all patients referring to RTOG contouring atlas (Hippocampal contouring: a contouring Atlas for RTOG 0933) [22]. An expansion of 5 mm was performed to create left and right HAZ [14, 23]. All BM in the proximity of HAZ were manually contoured. The centre of all metastases (as the initial focal point of metastatic settlement) was also spatially correlated to both hippocampi and HAZ. All structures were double-checked and approved by experienced radiologists. Intersections of contoured BM and LH, RH, and pertinent HAZ were analyzed using Boolean operators (Figure 1).

2.3. Statistical Analysis. Basic statistics were employed to describe initial patients' characteristics. Binominal test was used for the calculation of the difference between BM occurrence within LH, RH, and pertinent HAZ. The evaluation of different number of metastases in the right and left hippocampus (or HAZ) required a comparison of patients who had more metastases in the right and in the left side.



(a) (b)

FIGURE 1: Illustrative cases of contouring and evaluation of hippocampal metastasis (a). Large metastasis (b) touching the hippocampus at the border illustrates the need for an analysis of the centre of the mass to enable a valid assessment of spatial relationships to potentially undertreated perihippocampal zones.

All significance testing was performed at the 0.05 level; R software version 3.2.4. was used for all analyses.

3. Results

3.1. Patient Characteristics. A total of 495 patients were screened for eligibility; 260 (55%) had available MRI and were eligible for further BM analysis (total number of 2595 BM). The median number of BM was 3 with lung cancer being the most common type of primary tumour (120/260 patients; 46.2%). Thirty-six percent had single lesion. The other basic clinical characteristics are summarized in Table 1.

3.2. Spatial Distribution of Brain Metastases and Relation to Hippocampi. Spatial distribution of BM is summarized in Table 2. Most patients presented with frontal lobe BM (154/260 patients; 59.2%). The most common localization of BM was also frontal lobe with mean 6.25 BM and median 2 BM within frontal lobes. Within left and right temporal lobes, there was a mean of 1.48 and 2.57 BM and median of 1 and 1 BM. Eight percent of patients (20/260 patients) had BM within hippocampi and 18% of patients (47/260 patients) within HAZ. There was no statistically significant difference in the number of patients who had more BM in the right (9 patients) versus the left (8 patients) hippocampus. Similarly, no significant difference was observed in the number of patients with involvement of right (20 patients) versus left (22 patients) HAZ ($p = 0.88$). There was also no difference in the number of BM within right and left hippocampus ($p = 0.57$) or within right and left HAZ ($p = 0.91$).

Furthermore, the presence of centre of a mass of BM within hippocampi and HAZ was evaluated. Five patients (5/260; 1.9%) developed BM whose centre was located within hippocampus and 9.6% of patients (25/260 patients) within HAZ. Higher number of patients developed more metastases whose centre was within left HAZ (15 patients) comparing to right HAZ (6 patients), approaching the borderline of statistical significance with $p = 0.07$. Four patients had the same number of metastases within left and right HAZ. Further details are summarized in Table 3.

TABLE 1: Basic clinical characteristics of included patients.

Characteristic	N = 260
Age (mean; years)	57.8
Sex (men; %)	125 (48.1%)
Primary diagnosis	
NSCLC	79 (30.4%)
SCLC	34 (13.1%)
Lung-not verified	7 (2.7%)
Breast	48 (18.5%)
Melanoma	30 (11.5%)
GYN	13 (5.0%)
Unknown origin	11 (4.2%)
RCC	11 (4.2%)
GI	9 (3.5%)
GU	5 (1.9%)
others	13 (5.0%)
Initially disseminated	96 (36.9%)
Number of MTS	
Mean	10.0
Median	3
IQR (25-75 %)	1-7

MTS: metastasis, NSCLC: non-small-cell lung cancer, SCLC: small-cell lung cancer, GI: gastrointestinal, GYN: gynecology, RCC: renal cell carcinoma, GU: genitourinal, and IQR: interquartile range

4. Discussion

No significant difference in the laterality of BM seeding within hippocampus was observed in this large retrospective

Table 2: Spatial distribution of brain metastases.

Location of metastasis	N= 260 patients N= 2595 metastases
Temporal – No. of patients	95 (36.5%)
Left	61 (23.5%)
Right	62 (23.9%)
Temporal – No. of metastases	310 (11.9%)
Mean/ Median/ IQR (25-75 %)	3.26/1/1-2.5
Left/Right	
Mean	2.48/2.57
Median	1/1
IQR (25-75 %)	1-2/1-2
Occipital – No. of patients	101 (38.9%)
Left	73 (28.1%)
Right	57 (21.9%)
Occipital – No. of metastases	288 (11.1%)
Mean/ Median/ IQR (25-75%)	2.85/1/1-2
Left/Right	
Mean	1.95/2.56
Median	1/1
IQR (25-75 %)	1-2/1-3
Parietal – No. of patients	128 (49.2%)
Left	85 (32.7%)
Right	83 (31.9%)
Parietal – No. of metastases	397 (15.3%)
Mean/ Median/ IQR (25-75 %)	3.10/1/1-2
Left/Right	
Mean	2.55/2.17
Median	1/1
IQR (25-75 %)	1-2/1-2
Frontal – No. of patients	154 (59.2%)
Left	121 (46.5%)
Right	98 (37.7%)
Frontal – No. of metastases	962 (37.1%)
Mean/ Median/ IQR (25-75 %)	6.25/2/1-4
Left/Right	
Mean	4.02/4.86
Median	1/2
IQR (25-75 %)	1-2/1-4
Other locations – No. of patients	29 (11.2%)
Other locations – No. of metastases	638 (24.6%)

Abbreviations: No.- number, MTS- metastasis, IQR-interquartile range

study. Nevertheless, normative standards are not known and, thus, before the start of this study, it was not possible to estimate the sample size needed to reach statistical significance with sufficient power. However, we believe that the lack of significance that we observed in the analysis of 260 patients indicates that there is truly no difference in the laterality of hippocampal BM involvement.

Several previous retrospective studies described perihippocampal incidence of BM [24–30]. Earlier studies focused on a general estimation of perihippocampal BM incidence, while further trials aimed at assessing some specific aspect such as the measurement of the distance of BM from hippocampi in Harth *et al.* [28] or the determination of the number of brain metastases in patients with melanoma [29] or breast cancer [30]. Nevertheless, no studies have specified laterality of BM location. Data from all previous studies indicate that hippocampi are a rare site of BM and that hippocampus avoiding WBRT is a safe procedure with low risk of undertreatment in hippocampi or HAZ. A construction of HAZ during radiotherapy planning is needed to generate a dose gradient fallout from the surrounding brain (irradiated to the full prescribed dose), but delivered dose within HAZ might be insufficient to control micrometastases.

The ideal methodology for assessing this risk of hippocampal (or HAZ) metastases would be a close observation of patients with BM treated with HA-WBRT and followed with regular imaging. Considering the relatively low incidence of hippocampal metastases in general, a high number of patients treated by this complex RT technique would be needed to report data with sufficient power. Even more patients would be needed considering the aim of our study to describe the potential difference in laterality of hippocampal metastatic seeding (what means to divide enrolled patients into cohorts). Given the current absence of such a dataset in available literature before ongoing trials will be published, the retrospective review of large cohort of radiotherapy-naïve patients was chosen as the best possible approach currently to estimate the hippocampal and HAZ metastases incidence before eventual initiation of trials of unilateral hippocampal sparing. This approach of using treated patient data retrospectively for an analysis also seems to be ethically preferable comparing to the straightforward treatment of patients with unilateral hippocampal sparing WBRT and the evaluation of the development of BM in spared region in follow-up. With this retrospective description of the distribution of metastases, it can be at least estimated what is the risk of hippocampal (or HAZ) failure after HA-WBRT. Recently, in a pooled analysis of available data, we summarized the incidence of BM in 1557 patients from listed studies [24–30] and calculated that BM is present within hippocampi in 1.6% of patients and within HAZ in 9%, representing 0.6% and 2.8% of all BM, respectively [31]. In comparison to this pooled analysis, we observed in the current study a much higher incidence of BM within hippocampus (in 7.7% patients representing 1.1% of all BM) as well as in HAZ (in 18.1% of patients representing 3.3% of all BM). This higher incidence observed in our unselected real-practice cohort may be explained by a relatively high mean number of BM (mean number of 10 BM compared to a mean of 4.5 BM in pooled analysis) with many patients presented initially with multiple BM disease. In another recent descriptive analysis of consecutive series of 2419 patients with BM treated at the Medical University of Vienna between 1990 and 2011, 48.7% of patients presented with a singular BM, 27.7% with 2–3, and 23.5% with >3 BM [32]. The corresponding percentages in our current study are as follows: 36%, 22%, and 42%, respectively. Some patients are referred to our radiotherapy department from relatively distant tertiary outpatient oncology practices, some with less availability and throughput of MRI devices,

Table 3: Presence of brain metastases (or their centre) within right and left hippocampus and hippocampal avoiding zones and laterality of hippocampal involvement.

	within H	within left H	within right H	P value	within HAZ	within left HAZ	within right HAZ	P value
Patients (n=260) with edge of MTS	20 (7.7%)	12 (4.6%)	12 (4.6%)		47 (18.1%)	30 (11.5%)	27 (10.4%)	
Patients (n=260) with *more* MTS		8	9	NS		22	20	p = 0.88
Patients (n=260) with centre of MTS	5 (1.9%)	3 (1.2%)	3 (1.2%)		25 (9.6%)	19 (7.3%)	12 (4.6%)	
Patients (n=260) with *more* centre of MTS		2	2	NS		15	6	p = 0.07
Number of MTS (n=2595) with edge	28 (1.1%)	12 (0.5%)	16 (0.6%)	p = 0.57	86 (3.3%)	42 (1.6%)	44 (1.7%)	p = 0.91
Number of MTS (n=2595) with centre of MTS	7 (0.3%)	3 (0.1%)	4 (0.1%)	NS	41 (1.6%)	25 (0.9%)	16 (0.6%)	p = 0.21

MTS: metastasis, H: hippocampus, HAZ: hippocampus avoiding zone, NS: not specified, and p value close to 1.

potentially explaining the lower number of limited brain disease in our cohort that contributed to relatively higher hippocampal involvement. Regardless of a possibly high incidence of BM observed in our study, progression in the HAZ area was very rare in patients from the prospective RTOG 0933 trial, which reported progression within HAZ in only 3 out of 67 progressed patients (4.5%) after a radiotherapy performed with sparing of both hippocampi [14]. Altogether, despite these promising safety profile of RTOG 0933 and despite reported cases of advantageous usage of hippocampal sparing in real clinical practice, some controversy remains, especially regarding the safety of this method with concerns about undertreatment of HA regions [33, 34]. The superiority of HA-WBRT in the management of patients with BM and the potential update in current standards of care will need to be confirmed within prospective randomized trials, most notably in the above-mentioned NRG CC001-NCT02360215 trial or NRG-CC003-NCT02635009 (A Randomized Phase II/III Trial of Prophylactic Cranial Irradiation with or without Hippocampal Avoidance for Small Cell Lung Cancer). In the meantime, this approach should be considered experimental and utilized only in individually selected cases with a required planning MRI for hippocampi contouring as well as for the exclusion of potential small BM within hippocampi or HAZ [34].

The analysis presented here is the first large study focused on the laterality of hippocampal BM involvement. It contributes to the field by providing important knowledge needed before initiating programs of unilateral (left) hippocampus sparing during WBRT, which may be sufficient to preserve verbal memory, the most commonly affected neurocognitive domain following brain irradiation. Of course, evaluation of general QoL and of another neurocognitive domains related to the right (nondominant) side of brain would be needed in the trial where bilateral versus unilateral hippocampal sparing during WBRT would be tested. With the hypothesized noninferiority of unilateral sparing, there would be a possible advantage of about 50% reduction in the risk of subsequent recurrence within spared regions based on our current observation of no significant difference in the laterality of BM seeding. Moreover, unilateral hippocampal avoiding leads to dosimetrically increased sparing of preserved hippocampus [21].

We acknowledge several limitations of our study apart from its self-limiting retrospective nature, disallowing for example standardization of MRI, which should be ideally volumetric and standardized at baseline in order not to miss small lesion. The other limitations are mitigated by the analysis of location of centre of BM. With the generally spherical shape of BM, the centre of BM represents the site of initial focal growth of a micrometastasis. Whether this centre is placed within hippocampi or HAZ, in this particular patient, the focal point of metastatic settlement is inside the part of brain which would be spared in HA treatment approach (for example in previous HA prophylactic brain irradiation). On the other hand, the patient with a large metastasis within the left temporal lobe presented in the Figure 1 would be also classified as hippocampal since the border of BM touches the edge of the hippocampus. However, the spot where its centre is located is clearly outside the eventually undertreated HAZ and would receive a full dose of radiation (for example in previous HA prophylactic brain irradiation). Metastases in both outlined cases can be labelled as "hippocampal" but with different consequences behind, resolved by the analysis of the location of centres of metastases. Thus, discrimination between the centre of a mass and the border of a mass is necessary to comprehensively assess the risk of undertreating patients with HA-WBRT and would provide additional information in other ongoing trials as well. In our analysis of centres of BM, we observed interesting difference in patients with different number of centres of MTS in the right and left sides, where more patients presented with the centre of BM within left versus right HAZ (15 versus 6 patients; p = 0.07). These patients warrant further study including the analysis of potential changes in cerebral blood supply. Thus, the most reliable feature of our study is probably this analysis of the centre of BM mass.

In conclusion, a relatively high incidence of perihippocampal BM was observed in our large retrospective study with no clear difference in the laterality of BM seeding within the hippocampus. Spatial patterns of failure in ongoing phase III trials, where the role of hippocampal avoiding WBRT is being assessed, may reveal true laterality of hippocampal recurrence rate and further support the proposed testing of unilateral hippocampal sparing during WBRT.

Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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7.4.3 PUBLIKACE 9

Lakomy R, Hynkova L, Pospisil P, Burkon P, Slavik M, Slampa P, Jancalek R, Kazda T.* Patterns of failure after brain metastases radiotherapy: reflections on the importance for treatment and clinical trials reporting. Neoplasma. 2017; 64(3): 329–337. doi: 10.4149/neo_2017_302. (102)

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Anotace: Prostorové vyhodnocení recidiv mozkových nádorů po radioterapii je důležité také v případě mozkových metastáz. V tomto review jsou shrnuty nejdůležitější klinické studie determinující jednotlivé základní léčebné postupy (operace ± adjuvantní radioterapie, stereotaktická radioterapie ± celomozkové ozáření, nebo celomozkové ozáření – WBRT samotné) s důrazem na význam hodnocení prostorového vztahu recidivy k absolvované léčbě. Zvlášť jsou diskutovány nové léčebné postupy jako stereotaktická radiochirurgie a radioterapie lůžka po resekci metastázy nebo WBRT se šetřením oblasti hipokampů. Tak například v případě tohoto postupu je nutné odlišit, zda k následné nové progresi došlo v oblasti přilehlé k hipokampu, v hipokampu samotném, nebo v oblasti ozářené plnou terapeutickou dávkou záření. V přehledovém článku je zdůrazněna nutnost hodnocení charakteru recidiv ve všech probíhajících studiích testujících nové léčebné algoritmy u pacientů s mozkovými metastázami.

7.4.4 PUBLIKACE 10

Kazda T, Vrzal M, Prochazka T, Dvoracek P, Burkon P, Pospisil P, Dziacky A, Nikl T, Jancalek R, Slampa P, Lakomy R. Left hippocampus sparing whole brain radiotherapy (WBRT): a planning study. Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub. 2017; 161(4): 397–402. doi: 10.5507/bp.2017.031. (103)

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Práce byla ohodnocena Chodounského cenou za 2. nejlepší publikaci v oboru Radiační onkologie v ČR za rok 2017.

Úvod: Jednostranné šetření dominantního (levého) hipokampu v průběhu WBRT by mohlo zmírnit kognitivní pokles, zejména verbální paměť, ve stejném rozsahu jako HA-WBRT. Cílem této radioterapeutické (RT) plánovací studie je dozimetrické srovnání HA-WBRT s RT plány šetřící pouze levý hipokampus (LHA-WBRT).

Metody: HA-WBRT plány byly retrospektivně připraveny pro 10 pacientů v souladu se studií RTOG 0933 a sloužily jako výchozí pro následné srovnání s několika připravenými plány LHA-WBRT: 1) se snahou zachovat stejné podzáření levého hipokampu, a tím vyhodnotit potenciál zlepšení prozáření mozkovny („BEST PTV“) a 2) se snahou zachovat stejnou dozimetrii při plánování cílového objemu PTV jako v HA-WBRT („BEST LH“), a tím vyhodnotit potenciál dalšího snížení dávky v levém hipokampu.

Výsledek: Všechny plány HA-WBRT splňovaly kritéria protokolu RTOG 0933 s průměrným indexem konformity 1,09 a průměrným indexem homogenity (HI) 0,21. Střední hodnota D100% pravého a levého hipokampu byla 7,8 Gy a 8,5 Gy a průměrná D_{max} 14,0 Gy, resp. 13,8 Gy. Plány „BEST PTV“ snížily HI o 31,2 % (P = 0,005), což se projeví nižším PTV_ D2% (-0,8 Gy, P = 0,005) a vyšším PTV_D98% (+1,3 Gy, P = 0,005) a dále bylo možné snížení dávky na optiky a chiasma D_{max} o 1 Gy. V „BEST LH“ byly průměrné D100% a D_{max} pro levý hipokampus významně sníženy o 11,2 % (P = 0,005) a 10,9 % (P = 0,005).

Závěry: Technika LHA-WBRT by mohla zlepšit pokrytí PTV a/nebo další snížení dávky ušetřeného hipokampu. Budoucí klinické studie musí potvrdit, zda je statisticky významné snížení dávky v levém hipokampu také klinicky významné, a samozřejmě potvrdit hypotézu dostatečnosti pouze levostranné hipokampální preservace pro dosažení šetření NCF.

Left hippocampus sparing whole brain radiotherapy (WBRT): A planning study

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Aims. Unilateral sparing of the dominant (left) hippocampus during whole brain radiotherapy (WBRT) could mitigate cognitive decline, especially verbal memory, similar to the widely investigated bilateral hippocampus avoidance (HA-WBRT). The aim of this planning study is dosimetrical comparison of HA-WBRT with only left hippocampus sparing (LHA-WBRT) plans.
Methods. HA-WBRT plans for 10 patients were prepared in accordance with RTOG 0933 trial and served as baseline for comparisons with several LHA-WBRT plans prepared with an effort: 1) to maintain the same left hippocampus dosimetry ("BEST PTV") and 2) to maintain same dosimetry in planning target volume as in HA-WBRT ("BEST LH").
Results. All HA-WBRT plans met RTOG 0933 protocol criteria with a mean Conformity index 1.09 and mean Homogeneity index (HI) 0.21. Mean right and left hippocampal D100 % was 7.8 Gy and 8.5 Gy and mean Dmax 14.0 Gy and 13.8 Gy, respectively. "BEST PTV" plans reduced HI by 31.2 % (P=0.005) which is mirrored by lower PTV_D2% (-0.8 Gy, P=0.005) and higher PTV_D98% (+1.3 Gy, P=0.005) as well as decreased optic pathway's Dmax by 1 Gy. In "BEST LH", mean D100% and Dmax for the left hippocampus were significantly reduced by 11.2 % (P=0.005) and 10.9 % (P=0.005) respectively.
Conclusions. LHA-WBRT could improve target coverage and/or further decrease in dose to spared hippocampus. Future clinical trials must confirm whether statistically significant reduction in left hippocampal dose is also clinically significant.

Key words: brain metastases, hippocampus, memory, cognition, HA WBRT

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INTRODUCTION

Hippocampal sparing during whole brain radiotherapy (WBRT) in an effort to preserve cognitive function is a currently widely investigated approach in palliative irradiation in patients with brain metastases unsuitable for local treatment[1]. Many planning studies have shown the dosimetric feasibility of hippocampus avoiding (HA) WBRT in different clinical situations using many different radiotherapy systems and techniques[2-5]. However, these studies must be considered as experimental until well designed clinical trials with appropriate endpoints definitely reveal the significant clinical benefit of these novel approaches[2,6]. Further, some reports suggest different post radiotherapy and/or post surgery changes in the two hippocampi. As a result, unilateral hippocampal sparing has been proposed[7-11].

The most important neurocognitive domain affected by WBRT is memory. Radio-injury of the left, usually dominant, hippocampus may affect the formation of memory to a greater extent, in particular verbal memory[9,11]. Dosimetric consequences of potential unilateral (left) hippocampus sparing during WBRT are not known. We hypothesize that left hippocampal avoiding (LHA) during WBRT can possibly reduce the dose within the spared hippocampus as well as improve dose coverage of the remaining brain including the right hippocampus. Minimizing the dose to the least possible level is of high clinical relevance since higher hippocampal $D_{100\%}$ was shown to predict greater decline in some memory tests over time[12,13]. Also, the dose-response relationship between equivalent dose in 2-Gy fractions to 40% of the bilateral hippocampi ($EQD_{2Gy}40\%$) and impairment in delayed recall at 18 months was described after fractionated stereotactic radiotherapy for benign or low-grade brain tumors[12]. The aim of this planning study was to compare HA-WBRT with LHA-WBRT treatment plans, paying particular attention to left hippocampal dosimetry and quantitatively describe the potential benefit of only one-sided hippocampal sparing. To the best our knowledge, this is the first report of the practical consequences of LHA-WBRT.

MATERIALS AND METHODS

Patients and contouring

This retrospective planning study included ten consecutive patients with brain metastases and with available planning CT and MRI scans (9 women, mean age 54 years, 5/10 with lung cancer). Left and right hippocampi were separately contoured using the free available online RTOG contouring atlas as a reference[14]. A five millimeter margin around each hippocampus was created for the planning at risk volume (PRV) (ref.[15]). Other organs at risk (optic nerves, chiasm and lenses) were segmented according to recent contouring guidelines[16]. Planning target volume (PTV) contained the whole brain with 5 mm expansion to accommodate random setup uncertainty.

Three different treatment plans were created for each patient as described below (Fig. 1):

1) "standard" HA-WBRT serving as the baseline plan, 2) LHA-WBRT maintaining the same left hippocampal dosimetry as in the baseline plan (labeled as "BEST PTV") and 3) LHA-WBRT maintaining the same baseline plan's PTV's dosimetry (labeled as "BEST LH"). For "standard" HA-WBRT, both hippocampi_PRV were cropped out, while only the left hippocampus_PRV was cropped out for LHA-WBRT plans. Thus, these experimental plans included the entire right hippocampus within PTV.

Experimental treatment plans

All treatment plans were created utilizing Eclipse™ treatment planning system (Varian Medical Systems, Palo Alto, CA). The dose calculation was performed using the Anisotropic Analytical Algorithm (v11, Varian Medical Systems, Palo Alto, CA) with a 2.5 mm grid size and with the heterogeneity correction turned on. VMAT treatment plans were created for a TrueBeam STX with HD120 MLC (2.5 mm leaf width at isocenter). The 6 MV photon beam model were used in all plans. The CT images which were used for planning were 3 mm slices.

Baseline plans for bilateral hippocampus sparing WBRT were created in accordance with online available RTOG 0933 (phase II trial assessing bilateral HA WBRT) study protocol criteria as follows: 90 % of PTV receiving 10 x 3 Gy; PTV_$D_{2\,\%}$ ≤ 37.5 Gy, PTV_$D_{98\,\%}$ ≥ 25 Gy; D_{max} of optic nerves or optic chiasm ≤ 37.5 Gy, Hippocampal $D_{100\,\%}$ ≤ 9 Gy and Hippocampal D_{max} ≤ 16 Gy) (ref.[13,15]). $D_{x\%}$ represents the dose received by x % of specified structure. All treatment plans utilized three coplanar full arcs and one non-coplanar semi arc (couch angle 90 degrees and partial non-coplanar arc spanning 194 degrees (from 345 to 179 degrees)) in order to meet planning constraints criteria as much as possible.

Dosimetric analysis

The following parameters were reported for PTV: $V_{100\%}$, PTV_$D_{2\%}$, PTV_$D_{98\%}$, conformity index (CI) and homogeneity index (HI). CI was calculated based on the formula: ($V_{95\%Rx}/V_{PTV}$), where $V_{95\%Rx}$ is the volume encompassed by 95% of the prescription isodose surface. This definition of CI is not strictly as in ICRU 62, since the entire PTV is not always totally encompassed by the 95 % isodose. Nevertheless, it remains a useful measure of the conformality of the proposed treatments[17].

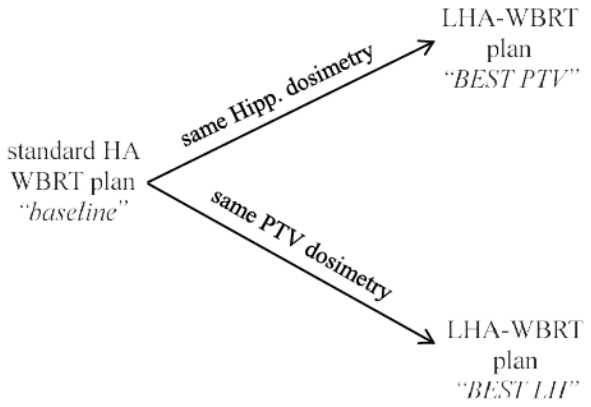

Fig. 1. Diagram of development of experimental treatment plans.

HI was calculated based on the formula: (($D_{2\%}$-$D_{98\%}$)/D_{median}) with zero indicating the ideal homogeneity since $D_{2\%}$ and $D_{98\%}$ are equal. D_{max} was reported for optic structures. $D_{40\%}$ for the left hippocampus, converted to biologically equivalent doses in 2-Gy fractions (EQD2) assuming an α/β ratio of 2 Gy, was recorded (EQD_2^{2Gy} 40 %) (ref.[12]). All pertinent values were extracted from dose-volume histograms using an in house developed data mining software. Basic statistical methods including the Wilcoxon signed-rank test were used to obtain mean values and relative as well as absolute differences between HA-WBRT and experimental plans.

RESULTS

Hippocampus avoiding-WBRT ("baseline") treatment plans

HA-WBRT plans' characteristics are summarized in Table 1. All treatment plans met RTOG 0933 "per protocol criteria" for PTV coverage with mean CI 1.09 (range 1.08 - 1.1) and mean HI 0.21 (range 0.19 – 0.23). Mean value of near maximal dose in PTV was $D_{2\%}$ = 33 Gy (RTOG 0933 limit is ≤ 37.5 Gy) with mean near minimal dose in PTV $D_{98\%}$ = 26.4 Gy (RTOG 0933 limit is ≥ 25 Gy). All hippocampal dose-volume constraints were met ("per protocol criteria") with an exception in one patient where right as well as left hippocampal $D_{100\%}$ exceeded limit of 9 Gy (9.34 Gy and 10.07 Gy, respectively). The isodose treatment plan for one representative patient is presented in Fig. 2.

Left HA-WBRT ("BEST LH") treatment plans

For these experimental treatment plans, inverse planning was tailored to achieve the same PTV dosimetry as in "baseline" HA-WBRT. Resultant dosimetric characteristics are listed in table 2 along with absolute and relative differences between these data and mean parameters in "baseline" HA-WBRT. The right hippocampus is intentionally not spared leading to mean $D_{100\%}$ = 30.1 Gy. Mean

Table 1. Summary of treatment characteristics of HA-WBRT plans (effort to meet RTOG 0933 "per protocol" criteria).

Target / organ at risk	Mean (SD) "baseline"	RTOG 0933 criteria
PTV		
$V_{100\%}$	90 % (0)	90 %
$D_{2\%}$	33 Gy (0.08)	≤ 37.5 Gy
$D_{98\%}$	26.4 Gy (0.29)	≥ 25 Gy
CI	1.09 (0.007)	
HI	0.21 (0.01)	
Optic nerves and chiasm		
D_{max}	33.7 Gy (0.48)	≤ 37.5 Gy
Hippocampus_right		
$D_{100\%}$	7.8 Gy (0.56)	≤ 9 Gy
D_{max}	14 Gy (0.37)	≤ 16 Gy
Hippocampus_left		
$D_{100\%}$	8.5 Gy (0.57)	≤ 9 Gy
D_{max}	13.8 Gy (0.21)	≤ 16 Gy
EQD_2^{2Gy} 40%	8.24 Gy (0.4)	

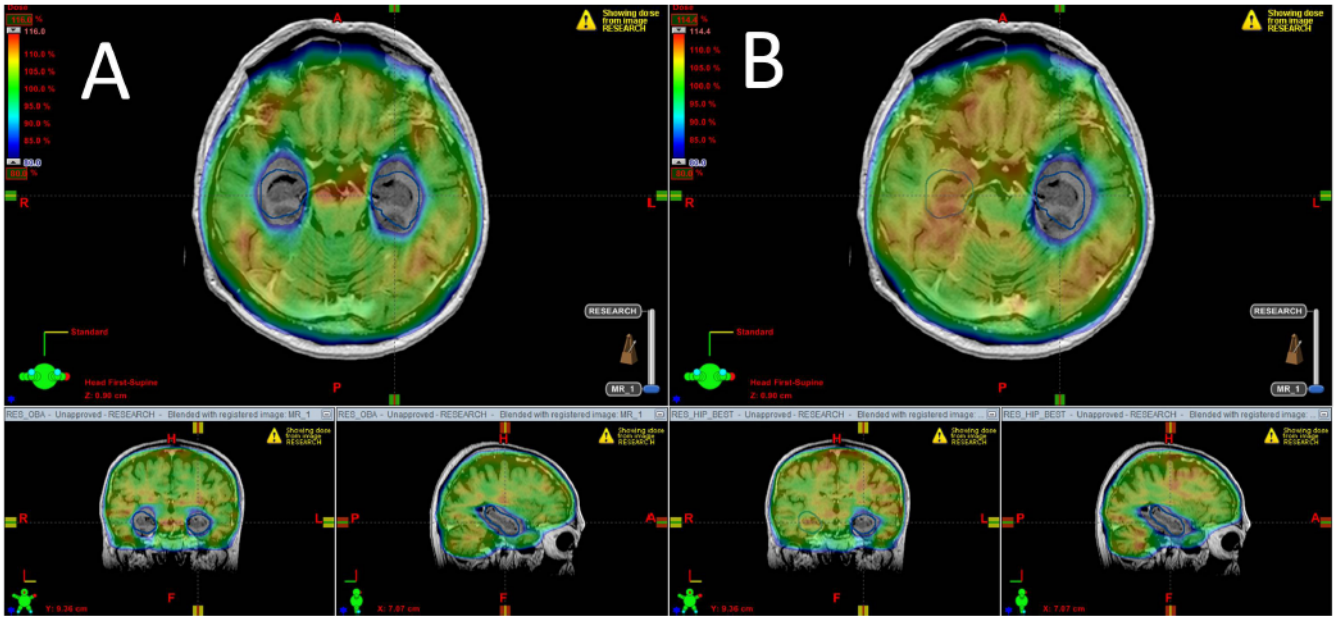

Fig. 2. Isodose treatment plan of representative HA-WBRT (A) and LHA WBRT ("BEST LH") for the same patient (B). Dose is displayed in color wash with minimal dose of 80 % from prescribed dose.

$D_{100\%}$ and D_{max} for the left hippocampus were significantly reduced by 11.2 % (P=0.005) and 10.9 % (P=0.005) respectively. Moreover, left hippocampal EQD_2^{2Gy} 40 % was significantly reduced from a mean value 8.24 Gy in "baseline" to the mean value of 6.82 Gy in "BEST LH" experimental plan (P=0.005). The isodose treatment plan for one representative patient is shown in Fig. 2.

Left HA-WBRT ("BEST PTV") treatment plans

For these experimental treatment plans, inverse planning was tailored to achieve the same left hippocampus dosimetry as in "baseline" HA-WBRT. Resultant dosimetric characteristics are listed in table 3 along with absolute and relative differences between these results and mean parameters in "baseline" HA-WBRT. Homogeneity of PTV irradiation was significantly improved with the same left hippocampal $D_{100\%}$ (P=0.92) and D_{max} (P=0.39) as in "baseline" plans. HI was reduced by 31.2 % (P=0.005) mirrored by lower PTV_$D_{2\%}$ (-0.8 Gy, P=0.005) and higher PTV_$D_{98\%}$ (+1.3 Gy, P=0.005). No difference was observed in conformity index.

DISCUSSION

The potential of further decrease of hippocampal irradiation during unilateral hippocampal sparing WBRT is described in this planning study. This concept makes it possible to significantly reduce unilateral hippocampal $D_{100\%}$, D_{max} and EQD_2^{2Gy} 40% with comparable target coverage as in "standard" HA-WBRT. Vice versa, it is possible to significantly improve target coverage with ac-

Table 2. Summary of treatment characteristics of Left HA-WBRT ("BEST LH") treatment plans.

Target / organ at risk	Mean (SD) "BEST LH"	Absolute (relative) difference to "baseline" HA-WBRT
PTV		
$V_{100\%}$	90 % (0)	0 (0 %)
$D_{2\%}$	32.9 Gy (0.08)	-0.1 Gy (-0.2 %)
$D_{98\%}$	27.1 Gy (0.49)	+0.7 Gy (+2.7 %)
CI	1.1 (0.004)	+0.01 (-0.7 %)
HI	0.2 (0.02)	-0.03 (-12.0 %)
Optic nerves and chiasm		
D_{max}	33.3 Gy (0.37)	-0.5 Gy (-1.4 %)
Hippocampus_right		
$D_{100\%}$	30.1 Gy (0.34)	+22.3 Gy (+286.8 %)
D_{max}	32.9 Gy (0.39)	+19 Gy (+136 %)
Hippocampus_left		
$D_{100\%}$	7.6 Gy (0.68)	-0.9 Gy (-11.2 %)
D_{max}	12.3 Gy (0.19)	-1.5 Gy (-10.9 %)
EQD_2^{2Gy} 40%	6.82 Gy (0.54)	-1.43 Gy (-17.4 %)

Table 3. Summary of treatment characteristics of Left HA-WBRT ("BEST PTV") treatment plans.

Target / organ at risk	Mean (SD) "BEST PTV"	Absolute (relative) difference to "baseline" HA-WBRT
PTV		
$V_{100\%}$	90 % (0)	0 (0 %)
$D_{2\%}$	32 Gy (0.07)	-0.8 Gy (-2.4 %)
$D_{98\%}$	27.8 Gy (0.42)	+1.3 Gy (+5 %)
CI	1.09 (0.008)	+0.01 (+0.55 %)
HI	0.15 (0.02)	-0.07 (-31.2 %)
Optic nerves and chiasm		
D_{max}	32.7 Gy (0.39)	-1 Gy (-3 %)
Hippocampus_right		
$D_{100\%}$	29.6 Gy (0.29)	+21.8 Gy (+280.7 %)
D_{max}	32.2 Gy (0.27)	+18.3 Gy (+131.1 %)
Hippocampus_left		
$D_{100\%}$	8.5 Gy (0.54)	+0.01 Gy (+0,2 %)
D_{max}	13.7 Gy (0.33)	-0.1 Gy (-0,8 %)
EQD_2^{2Gy} 40%	8.22 Gy (0.53)	-0.02 Gy (-0.3 %)

ceptance of the same unilateral hippocampal dosage as in "standard" HA-WBRT. Decreasing the hippocampal dose ($D_{100\%}$) to as low as possible was shown to predict less decline in some memory tests over time in patients irradiated for brain metastases[12,13]. More recently, white matter damage as well as thinning of the cerebral cortex after brain irradiation proved to be highly dose-dependent[18,19]. Hippocampus itself demonstrates radiation dose-dependent atrophy after treatment for brain tumors[20,21]. These dose-dependent brain changes are predicted to influence cognition and memory. Altogether, minimizing the dose within this critical part of the brain may be of high clinical relevance[22]. The risk of recurrence of brain metastases in undertreated regions is a reasonable trade-off especially in palliative irradiation.

Our previous study described significant decreases in hippocampal N-acetylaspartate concentration (marker of neuronal density and viability) following WBRT (ref.[10]). However, only changes in the left hippocampus positively correlated with the decline in memory function[11]. Another recent study of predictors for late neurocognitive dysfunction showed correlations of vascular dose-response in the left hippocampus in females with changes in memory function after radiotherapy[9]. Is it possible that only unilateral hippocampal radio-injury is responsible for subsequent neurocognitive decline? The functional anatomy of the cognitive domains suggests that verbal memory, the gold standard in evaluation of post radiotherapy cognitive impairment, often localize to the dominant hippocampus[7]. Nevertheless, it would be useful to at first know, whether and to what extent this radiotherapy approach translates into improvement in radiotherapy treatment plans.

In order to demonstrate the potential of LHA-WBRT, we created two types of experimental plans with different optimalization intent. "BEST LH" treatment plans'

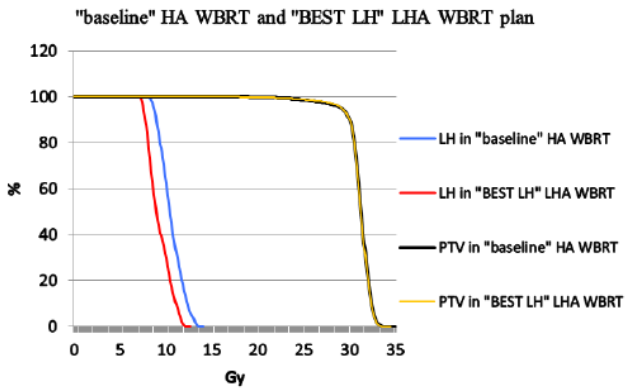

Fig. 3. Averaged dose-volume histogram from all patients presenting differences between "baseline" HA WBRT and "BEST LH" left hippocampus sparing WBRT treatment plans.

potential to further decrease left hippocampal dose with the same target coverage is showed in Fig. 3. The left hippocampal EQD_2^{2Gy} 40% was significantly reduced from a mean value 8.24 Gy in "baseline" to mean 6.82 Gy in "BEST LH" experimental plan. This dosimetric parameter for both hippocampi was established by Gondi et al. with a threshold of 7.3 Gy; irradiation surpassing this value is associated with long-term impairment in list-learning delayed verbal recall in patients with benign or low-grade adult gliomas[12]. "BEST LH" treatment optimization successfully undershot this threshold value. Although, we only assumed that the threshold value can be used for patients with brain metastases and for unilateral hippocampal sparing. Nevertheless, the slope of dose-response curve for EQD_2^{2Gy} 40% suggests that doses of around 6 to 8 Gy are highly clinically important[12]. For this reason, the decrease from 8.24 Gy to 6.82 Gy as observed in our planning study may be clinically relevant. Altogether, even if this reduction would not further decrease cognitive impairment (suggesting the dominant role of left hippocampus), with full irradiation of right hippocampus, the risk of subsequent development of hippocampal or perihippocampal metastases is reduced by one half. This risk is generally considered low because only 1.6% of brain metastasis extend to the hippocampus itself[23].

There are several limitations in our study, which are mainly related to the nature of planning studies in general. Among others, comparison of PTV dosimetry between "baseline" HA-WBRT plan and two experimental LHA-WBRT plans is biased due to different definition of PTV. This is because in LHA-WBRT plans, the right hippocampus was integrated to PTV. Another already mentioned limitation is in adaptation of hippocampal dose-volume constraints from studies of primary gliomas (EQD_2^{2Gy} 40%).

The inherent limitation may be the fundamental question whether there is a role for WBRT in up-to-date treatment of brain metastases and with higher availability of systems for stereotactic radiosurgery[24-26]. From one perspective, the best technique for sparing the hippocampus is avoidance of WBRT itself and proceeding with stereotactic radiotherapy. Clearly, the role of WBRT is changing and more data from ongoing clinical trials are needed to establish the best treatment recommendations for defined subsets of patients[27].

CONCLUSION

Unilateral hippocampal sparing during WBRT could improve target coverage and/or further reduce the dose to the spared hippocampus. Whether reduction in left hippocampus dosage as described in our planning study would further reduce post radiotherapy side effects warrants further research. Only future clinical trials can confirm whether statistically significant reduction in left hippocampal dose is also clinically significant.

ABBREVIATIONS

WBRT: whole brain radiotherapy; HA-WBRT: hippocampus avoiding whole brain radiotherapy; LHA-WBRT: left hippocampus avoiding whole brain radiotherapy; PTV: planning target volume; MRI magnetic resonance imaging; PRV planning organ at risk volume; VMAT: volumetric arc therapy.

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Author contributions: TK, MV, PP, RL: development of methodology and genereal research concept, plans evaluation, statistical analysis, manuscript writing; PD, TP: preparation of experimental treatment plan and cross approval; PB, AD, TN: contouring and evaluation of treatment plans, statistical analysis; RJ, PS: collaboration on manuscript writing, literature search and data interpretation. All authors contributed on the first draft's preparation and read and approved the final manuscript.
Conflict of interest statement: The authors state that there are no conflicts of interest regarding the publication of this article.

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6. Radioterapie v pooperační terapii mozkových metastáz

7. Závěr

Lze uzavřít, že v současné době již není v případě pacientů s mozkovými metastázami místo pro dříve občas vídaný nihilismus a že individualizovaná léčba může pacientům přinést výrazný benefit, jako v případě prezentované pacientky, která je nyní 2,5 let po léčbě zjevně velmi agresivní mozkové metastázy (opakované rychlé progrese s meningeálním postižením v horizontu měsíců), přesněji 2,5 let bez rizika známých nežádoucích účinků spojených s dříve prakticky jedinou léčebnou možností – celomozkovým ozářením. Současné portfolio radioterapeutických technik pro individualizovanou radioterapii mozkových metastáz zahrnuje cílenou stereotaktickou radiochirurgii a frakcionovanou radioterapii, celomozkové ozáření a jeho modifikace (hipokampus šetřící techniky, simultánní integrovaný boost na oblast makrometastáz), případně radioterapii oblasti lůžka po metastazektomii. V dané oblasti jsme přispěli především rozšířením poznání iatrogenní alterace na úrovni hipokampu, pravděpodobně nejdůležitější struktury CNS ve vztahu k poradiační toxicitě. S využitím MR spektroskopie jsme, in vivo, popsali signifikantní úbytek koncentrace N-acetylaspartátu, jakožto markeru viability a počtu neuronů. Zpracováním metodiky unilaterálního šetření hipokampu a analýzou distribuce mozkových metastáz ve vztahu k lateralitě postižení jsme přispěli k dalšímu vývoji speciálních radioterapeutických postupů, jako je možnost unilaterálního šetření levého, dominantního hipokampu. Komplexní onkologická léčba pacientů s mozkovými metastázami zahrnující kromě protinádorové léčby také léčbu podpůrnou a symptomatickou je cestou k dalšímu zlepšování léčebných výsledků včetně na pacienta orientovaných parametrů, jako je kvalita života a neurokognitivní funkce.

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11. Seznam zkratek

ADC	aparentní difúzní koeficient
ALK	anaplastická lymfomová kináza
ASCO	American Society of Clinical Oncology
ASTRO	American Society for Radiation Oncology
AVLT	Auditory Verbal Learning Test
BVMT-R	Brief Visuospatial Memory Test - Revised
CBCT	cone beam CT
CNS	centrální nervový systém
CT	výpočetní tomografie
CTV	clinical target volume

DR	Delayed Recall
DS-GPA	disease specific - graded prognostic assessment
EGFR	receptor epidermálního růstového faktoru
EORTC	European Organisation for the Research and Treatment of Cancer
FDA	Food and Drug Administration
FDOPA	6-[18F]-L-fluoro-L-3, 4-dihydroxyphenylalanine
FET	18F-fluoro-ethyl-l-tyrosine
FLAIR	Fluid-attenuated inversion recovery
FSRT	Fractionated stereotactic radiotherapy
fx	frakce
GPA	Graded Prognostic Assessment
GTV	gross tumor volume
Gy	Gray
HA-WBRT	Hippocampus avoiding - WBRT
HA-WBRT_SIB	Hippocampus avoiding - WBRT a simultánní integrovaný boost
HAZ	Hippocampus avoiding zone
HDR	high dose-rate
HER	receptor lidského epidermálního růstového faktoru
HI	index homogenity
h-Cr	hippocampal - kreatin
h-tNAA	hippocampal - total N-acetylaspartát
IF	impact factor
IgG1	imunoglobulin G1
IGRT	image guided RT
IMRT	radioterapie s modulovanou intenzitou svazku
jSIPRO	java Spectroscopic Imaging PROcessing
KPS	výkonnostní stav dle Karnofského indexu
LH	levý hipokampus
LHA-WBRT	Left hippocampus avoiding - WBRT
MMSE	Mini Mental State Exam
MR	magnetická rezonance
MRS	MR spektroskopie
NCF	neurokognitivní funkce

NCCTG	North Central Cancer Treatment Group
NMDA	N-methyl-D-aspartát
NSC	neuronální kmenové buňky
NTRK	neurotrophic receptor tyrosine kinase
OS	celkové přežití
PET	pozitronová emisní tomografie
PFS	progression free survival
PTV	planning target volume
QALY	quality adjusted life years
QANTEC	Quantitative Analyses of Normal Tissue Effects in the Clinic
R	Recognition
RANO	Response Assessment in Neuro-Oncology
RANO-BM	Response Assessment in Neuro-Oncology Brain Metastases
RECIST	Response Evaluation Criteria in Solid Tumors
RPA	Recursive Partitioning Analysis
RTOG	Radiation Therapy Oncology Group
SIR index	Score Index for Radiosurgery
SRS	Stereotactic radiosurgery
tCho	koncentrace celkového cholinu
tNAA	celková koncentrace N-acetylaspartátu
TMT	Trail Making Test
TR	Total Recall
TRK	kinázy tropomyosinových receptorů
VMAT	pohybová objemově modulovaná radioterapie
WBRT	whole brain radiotherapy, celomozkové ozáření
WBRT_SIB	WBRT a simultánní integrovaný boost
WHO	Světová zdravotnická organizace

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