Aus der Klinik für Strahlentherapie
der Universität zu Lübeck
Direktor: Prof. Dr. med. Dirk Rades

Entwicklung einer innovativen Methode zur Schonung der Hypothalamus-Hypophysen-Achse bei Ganzhirnbestrahlungen

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Preena Mehta
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1. Berichterstatter: Herr PD Dr. med. Stefan Janssen

2. Berichterstatter: Herr Prof. Dr. med. Norbert Brüggemann

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Gender-Hinweis

Aus Gründen der besseren Lesbarkeit wird in dieser kumulativen Dissertation auf die gleichzeitige Verwendung der Sprachformen männlich, weiblich und divers (m/w/d) verzichtet und stattdessen die Sprachform des generischen Maskulinums angewendet. Es wird an dieser Stelle darauf hingewiesen, dass sämtliche Personenbezeichnungen gleichermaßen für alle Geschlechter gelten.

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Abkürzungsverzeichnis

AAA	*Anisotropic Analytical Algorithm*
ACTH	*adrenocorticotropic hormone*, Adrenocorticotropes Hormon
CN	*conformality index or conformation number*, Konformitätsindex
CRH	*corticotropin-releasing hormone*, Corticotropin-Releasing Hormon
cRT	*cranial radiotherapy*, kraniale Bestrahlung
CT	*computed tomography*, Computertomographie
ds-GPA	*disease-specific graded prognostic assessment*, primärturmorspezifischer Score
FSH	*follicle-stimulating hormone*, follikelstimulierendes Hormon
fT4	*free tetraiodothyronine*, freies Tetrajodthyronin
GH	*growth hormone*, Wachstumshormon
HI	*homogeneity index*, Homogenitätsindex
HT-P	*hypothalamic-pituitary*, Hypothalamus-Hypophyse
IGF-1	*insulin-like growth factor,* Insulin-ähnliches Wachstums-Faktor
IMRT	*intensity-modulated radiotherapy*, intensitätsmodulierte Strahlentherapie
LH	*luteinizing hormone*, luteinisierendes Hormon
KPS	*Karnofsky performance status*, Karnofsky-Allgemeinzustand
MLC	m*ultileaf-collimator*, Multilamellen-Kollimator
MRT	*magnetic resonance tomography*, Magnetresonanztomographie
NCCN	*National Comprehensive Cancer Network*
NSCLC	*non-small cell lung cacner,* nicht-kleinzelliger Lungentumor
OAR	*organs at risk*, Risikoorgane
PCI	*prophylactic cranial irradiation*, prophylaktische Hirnbestrahlung
PRL	*prolactin*, Prolaktin
PRV	*planning risk volume*, geplantes Risikovolumen
PTV	*planning target volume*, geplantes Zielvolumen
RPA	*recursive partition analysis*, rekursive Partitions-Analyse
RTOG	*Radiation Therapy Oncology Group*
SCLC	*small cell lung cancer*, kleinzelliger Lungentumor
SHBG	*sexual hormone-binding globulin*, Sexualhormon-bindendes Globulin
SIB	*simultaneous integrated boost*, simultan integrierter Boost
SRS	*stereotactic radiosurgery,* stereotaktische Radiochirurgie

TC	*target coverage*, Zielvolumenabdeckung
TPS	*treatment planning system*, Bestrahlungsplanungssystem
TSH	*thyroid-stimulating hormone*, Thyreoidea-stimulierendes Hormon
UKSH	Universitätsklinikum Schleswig-Holstein
VMAT	*volumetric modulated arc therapy*, volumenmodulierte Rotationsbestrahlung
WBRT	*whole brain radiotherapy*, Ganzhirnbestrahlung

1 Einleitung und Fragestellung

Krebserkrankungen sind die zweithäufigste Todesursache weltweit (Yusuf et al., 2019). In den letzten Jahrzehnten haben sich die Überlebensraten vieler Tumorpatienten aufgrund neuer Behandlungsansätze und optimierter Früherkennung deutlich verbessert (Quaresma et al., 2015). Als Folge dessen können sich gerade bei Langzeitüberlebenden therapiebedingte chronische Langzeitnebenwirkungen von onkologischen Therapien manifestieren. Endokrine Dysfunktionen zählen dabei zu den häufigsten Langzeitnebenwirkungen der Krebstherapie und wurden in bis zu 50 % der Fälle bei Tumorpatienten beschrieben, die im Kindesalter behandelt wurden (Gebauer et al., 2018). Entsprechend wurden dezidierte Leitlinien für die Nachsorge pädiatrischer Patienten publiziert, die das Ziel haben, mögliche endokrine Fehlfunktionen möglichst frühzeitig zu erkennen und zu behandeln (Sklar et al., 2018). Nur wenige Studien untersuchten dabei die Folgen für erwachsene Krebspatienten und für die meisten Tumorentitäten existieren solche Nachsorge-Schemata nicht (Gebauer et al., 2018). Aber auch bei erwachsenen Tumorpatienten, die eine zerebrale Strahlentherapie erhalten haben, kann es zu nicht unerheblichen Veränderungen des Hormonhaushalts kommen (Kyriakakis et al., 2016). Diese Veränderungen sind dosisabhängig und treten schon ab Bestrahlungsdosen von 18 Gy (Darzy et al., 2009) auf. Besonders relevant sind endokrine Dysfunktionen bei Langzeitüberlebenden mit einem guten Allgemeinzustand oder Patienten mit einer prophylaktischen Ganzhirnbestrahlung (*prophylactic cranial irradiation*, PCI). Dabei können alle Hormone der verschiedenen Hypothalamus-Hypophysen-Achsen betroffen sein. Dysfunktionen gehen beispielsweise mit einer Fatigue-Symptomatik und verschlechterten Lebensqualität einher und zählen damit zu den häufigsten endokrinen Spätfolgen einer zerebralen Strahlentherapie (Murray et al., 2002; Darzy et al., 2009). Für Patienten, deren Überlebenszeit limitiert ist, erscheint eine dezidierte Nachsorge ebenfalls sinnvoll, da endokrine Dysfunktionen bereits kurzzeitig zu einer verminderten Lebensqualität führen können. Informationen zu Hormonveränderungen nach zerebraler Bestrahlung basieren bislang jedoch im Wesentlichen auf Patientenkollektiven, die an Nasopharynxkarzinomen oder nicht-hypophysären Hirntumoren bestrahlt wurden, nicht aber auf Daten von Patienten, die bei Hirnmetastasen strahlentherapeutisch behandelt wurden.

Hirnmetastasen stellen die häufigste intrakranielle Tumormanifestation dar. 10 bis 30 % aller Krebspatienten entwickeln innerhalb ihres Krankheitsverlaufes Hirnmetastasen (Khuntia et al., 2006). Trotz innovativer Entwicklungen und der Zunahme von Hochpräzisionsbestrahlungen bleibt die Ganzhirnbestrahlung (*whole brain radiotherapy,* WBRT) eine häufige Therapie bei Patienten mit multiplen Hirnmetastasen. Darüber hinaus kann eine prophylaktische Ganzhirnbestrahlung bei Patienten mit kleinzelligem Lungenkarzinom (*small cell lung cancer*, SCLC) indiziert sein (Simone et al., 2020) (S3-Leitlinie: Prävention, Diagnostik, Therapie und Nachsorge des Lungenkarzinoms). Ganzhirnbestrahlungen können allerdings mit Nebenwirkungen, wie etwa Einschränkungen der neurokognitiven Leistung, assoziiert sein (Appelman-Dijkstra et al., 2011). Dabei scheinen vor allem die neuronalen Stammzellen des Hippocampus bei Gedächtnisveränderungen eine Rolle zu spielen. Die Arbeitsgruppe um Gondi et al. hat in einer Phase-II-Studie gezeigt, dass eine Schonung (d. h. geringere Dosis im Vergleich zum restlichen Hirngewebe) der Hippocampus-Region während einer Ganzhirnbestrahlung zu einer verbesserten kognitiven Leistung und Lebensqualität führt (Gondi et al., 2014). Ein allgemein etablierter Schwellenwert, ab dem eine mögliche Schädigung der Stammzellen im Bereich des Hippocampus auftritt, existiert jedoch nicht. Um die onkologische Sicherheit bei zeitgleicher Dosisreduktion in der Hippocampus-Region während einer Ganzhirnbestrahlung zu gewährleisten, haben Gondi et al. zunächst die Befallswahrscheinlichkeit für Metastasen in diesem Bereich untersucht. Bei einem geschätzten Risiko von 8,6 % sahen die Autoren den klinischen Einsatz einer Schonung dieses Areals als onkologisch sicher an (Gondi et al., 2010). Die Möglichkeiten einer technischen Umsetzung der Hippocampus-Schonung wurden daraufhin von mehreren Arbeitsgruppen untersucht (Gondi et al., 2010b; Pokhrel et al., 2015; Lee et al., 2015; Sood et al., 2018; Wang et al., 2016). Dazu wurden Bestrahlungspläne mit verschiedenen modernen Bestrahlungstechniken, wie die helikale Tomotherapie, volumenmodulierte Rotationsbestrahlung (*volumetric modulated arc therapy*, VMAT) und intensitätsmodulierter Strahlentherapie (*intensity-modulated radiotherapy*, IMRT), erstellt, um die bestmögliche Abdeckung des Zielvolumens bei zeitgleicher Schonung der Hippocampus-Region und der Risikostrukturen zu erhalten. So konnten Gondi et al. die mittlere Dosis im Bereich des Hippocampus bei einer Ganzhirnbestrahlung mit einer Gesamtdosis von 30 Gy

auf 9 Gy reduzieren und damit verbesserte neurokognitive Ergebnisse erzielen (Gondi et al., 2014).

Nach der von Gondi et al. veröffentlichten *Radiation Therapy Oncology Group* (RTOG) -Studie in 2014 wurde der Ansatz der Hippocampus-Schonung zunehmend in die klinische Routine implementiert. Infolgedessen und in Anbetracht der auftretenden endokrinen Dysfunktionen bei den therapierten Patienten sowie den daraus folgenden Einschränkungen der Lebensqualität stellt sich weiterhin die Frage, ob eine Schonung der Hypothalamus-Hypophysen-Achse analog zur Schonung der Hippocampus-Region gerechtfertigt und klinisch umsetzbar wäre. Dafür müsste ein Dosisschwellenwert ermittelt werden, ab dem mit einer erhöhten Wahrscheinlichkeit endokrine Defizite auftreten. Generell scheint eine Dosisreduktion im Rahmen der Ganzhirnbestrahlung von zumeist 30 Gy vorteilhaft, da hormonelle Dysfunktionen bereits ab 18 Gy auftreten können (Appelman-Dijkstra et al., 2011). Darüber hinaus ist das Wissen der generellen Befallswahrscheinlichkeit für Metastasen im Bereich des Hypothalamus und der Hypophyse begrenzt. Nur bei einer geringen quantitativen Beteiligung dieser Strukturen, wäre ein innovativer Schonungsansatz der Hypothalamus-Hypophysen Region onkologisch überhaupt vertretbar. Abschließend müsste die technische Umsetzbarkeit eines solchen Schonungsansatzes, für die in der Literatur bislang nur wenige Fallbeschreibungen existieren, evaluiert werden.

Basierend auf diesen Vorüberlegungen sollen in der vorliegenden, kumulativen Dissertation folgende Fragestellungen adressiert werden:

1. Gibt es einen Dosisschwellenwert und einen Zeitpunkt, ab dem Hormonveränderungen nach einer zerebralen Bestrahlung häufig auftreten? Sind Hormonveränderungen nach einer Ganzhirnbestrahlung in der Literatur beschrieben?
2. Wie hoch ist die Rate an Hormonveränderungen nach einer Ganzhirnbestrahlung? Welche Hormone unterliegen einer Veränderung?
3. Welche Befallswahrscheinlichkeit von Hirnmetastasen gibt es im Bereich der Hypothalamus-Hypophysen-Region?
4. Wie ist eine Schonung der Hypothalamus-Hypophysen-Region während einer Ganzhirnbestrahlung technisch umsetzbar?

2 Übersicht der Publikationen der Dissertation

Mehta P, Fahlbusch FB, Rades D, Schmid SM, Gebauer J, Janssen S. Are Hypothalamic-Pituitary (HP) Axis Deficiencies after Whole Brain Radiotherapy (WBRT) of Relevance for Adult Cancer Patients? - A Systematic Review of the Literature. BMC Cancer. 2019 Dec 12; 19(1):1213. **[Impact Factor = 4,430]**

Gebauer J, Mehta P, Fahlbusch FB, Schmid SM, Rades D, Janssen S. Hypothalamic-Pituitary Axis Dysfunction after Whole Brain Radiotherapy - A Cohort Study. Anticancer Res. 2020 Oct; 40(10):5787–5792. **[Impact Factor = 2,480]**

Mehta P, Janssen S, Bartscht T, Schmid SM, Fahlbusch FB, Rades D. Prevalence of Metastases within the Hypothalamic-Pituitary Area in Patients with Brain Metastases. Radiat Oncol. 2019 Aug 27; 14(1):152. **[Impact Factor = 3,481]**

Mehta P, Janssen S, Fahlbusch FB, Schmid SM, Gebauer J, Cremers F, Ziemann C, Tartz M, Rades D. Sparing the Hippocampus and the Hypothalamic-Pituitary Region during Whole Brain Radiotherapy: A Volumetric-Modulated Arc Therapy Planning Study. BMC Cancer. 2020 Jun 30; 20(1):610. **[Impact Factor = 4,430]**

3 Zusammenfassungen der Publikationen

3.1 Sind Defizite der Hypophysen-Hypothalamus-Achse nach einer Ganzhirnbestrahlung für erwachsene Krebspatienten relevant? Eine systematische Bewertung der Literatur.

Mehta P, Fahlbusch FB, Rades D, Schmid SM, Gebauer J, Janssen S. Are Hypothalamic-Pituitary (HP) Axis Deficiencies after Whole Brain Radiotherapy (WBRT) of Relevance for Adult Cancer Patients? - A Systematic Review of the Literature. BMC Cancer. 2019 Dec 12; 19(1):1213.

Das Ziel der ersten Arbeit ist eine strukturelle Erfassung möglicher hormoneller Defizite nach Bestrahlungen von erwachsenen Krebspatienten im Bereich der Hypothalamus-Hypophysen-Region mit speziellem Fokus auf Daten zu Patienten mit Hirnmetastasen und Ganzhirnbestrahlungen gewesen.
Die systematische Literaturrecherche erfolgte mit der Suche nach den folgenden Begriffen: „kraniale Strahlentherapie“ (engl. ‚cranial radiotherapy‘) ODER „kraniale Bestrahlung“ (engl. ‚cranial irradiation‘) ODER „hormonelle Veränderungen“ (engl. ‚hormonal changes‘) ODER „hormonelle Beeinträchtigung“ (engl. ‚hormonal impairment‘) ODER „hormonelle Mängel“ (engl. ‚hormonal deficiencies'). Es wurden nur Studien in englischer Sprache mit erwachsenen Patienten berücksichtigt, bei denen Informationen zu ihrer endokrinologischen Funktion nach einer kranialen Bestrahlung vorlagen. Die initiale Recherche wurde durch die manuelle Suche innerhalb der Referenzlisten sowie Querverweise ergänzt.
Die initiale Recherche ergab 889 Zitate. Durch die Elimination der Duplikate und Studien mit Patienten im Kindesalter verblieben 286 Arbeiten. Nach Durchsicht der Titel und Zusammenfassungen wurden 28 Originalarbeiten mit insgesamt 1728 Patienten in die Analyse eingeschlossen. 15 Studien thematisierten dabei die Bestrahlung bei Patienten mit Nasopharynx-/Schädelbasis-Tumoren, während sich 13 Studien mit (nicht hypophysären-)Hirntumoren befassten. In keiner Studie wurden Patienten mit Hirnmetastasen eingeschlossen, die eine Ganzhirnbestrahlung erhalten hatten. Die Prävalenz einer Hypophyseninsuffizienz reichte von 20 bis 90 %

[Wachstumshormon (*growth hormone*, GH): 19–100 %, Adrenocortikotropes Hormon (*adrenocorticotropic Hormone*, ACTH): 4–73 %, Thyreoidea-stimulierendes Hormon (*thyroid-stimulating hormone*, TSH): 4–70 %, Luteinisierendes- und Follikelstimulierendes Hormon (*luteinizing hormone*, LH; *follicle-stimulating hormone*, FSH): 0–55 % und Prolaktin (*Prolactin*, PRL): 7–100 %]. Das Zeitintervall zwischen der kranialen Bestrahlung (*cranial radiotherapy*, cRT) und der endokrinen Untersuchung lag zwischen drei Monaten und 25,6 Jahren. In 13 Studien wurde nach drei Jahren (im Median) mit der Nachuntersuchung begonnen. Die Gesamtdosis im Hypothalamus-Hypophysen-Bereich lag zwischen 4 Gy bis 97 Gy, wobei in acht Studien keine Dosisangaben beschrieben wurden.

3.2 Veränderungen der Hypophysen-Hypothalamus-Achse nach einer Ganzhirnbestrahlung – eine Kohortenstudie.

Gebauer J, Mehta P, Fahlbusch FB, Schmid SM, Rades D, Janssen S. Hypothalamic-Pituitary Axis Dysfunction after Whole Brain Radiotherapy - A Cohort Study. Anticancer Res. 2020 Oct; 40(10):5787–5792.

Das Ausmaß endokriner Veränderungen der Hypophysen-Hypothalamus-Achse von erwachsenen Krebspatienten, die als Teil ihrer Krebstherapie eine Ganzhirnbestrahlung erhalten hatten, wurde in der zweiten Arbeit quantifiziert. Dabei wurden die Daten von Patienten verwendet, die in den Jahren 2007 bis 2018 in der Klinik für Strahlentherapie, Universitätsklinikum Schleswig-Holstein (UKSH) Campus Lübeck eine Bestrahlung erhalten hatten. Die Ethikkommission der Universität zu Lübeck hat gemäß der Deklaration von Helsinki das Protokoll dieser Studie genehmigt (Aktenzeichen: 19-409A).
In die Studie eingeschlossen wurden Patienten mit einer Nachbeobachtungszeit von mindestens 6 Monaten und ohne Anzeichen eines intrakraniellen Progresses. Sie erhielten eine aktuelle endokrinologische Untersuchung inkl. der Parameter der Hypothalamus-Hypophysen (*hypothalamic-pituitary*, HT-P) -Funktion. Diese wurde in Übereinstimmung mit der publizierten Leitlinie für Langzeitüberlebende, die im Kindesalter an einem Tumor behandelt wurden, durchgeführt. Die Untersuchung beinhaltete eine früh morgendliche Messung der folgenden Hormone: Inulin-ähnlicher Wachstumsfaktor (*insulin-like growth factor*, IGF-1), LH, FSH, Testosteron und Sexualhormon-bindendes Globulin (*sexual hormone-binding globulin*, SHBG) (Männer) oder 17 Beta-Östradiol (Frauen), PRL, TSH, freies Tetrajodthyronin (*free tetraiodothyronine*, fT4), Cortisol und ACTH. Ergänzt wurden die Laboruntersuchungen durch eine klinische Untersuchung und Anamnese mit Erfassung des Allgemeinzustandes (Karnofsky-Allgemeinzustand, *Karnofsky performance status*, KPS), des Fatigue-Werts (Skala: 1–10) und des Distress Thermometers (Skala: 1–10) vom *National Comprehensive Cancer Network* (NCCN) (Holland et al., 2013). Basierend auf den endokrinen Veränderungen wurden Alter, bestrahlte Dosis, das Zeitintervall zwischen der Ganzhirnbestrahlung bis zur endokrinologischen Untersuchung und die zuvor genannten Scores je nach Gruppe mithilfe des nicht-parametrischen Mann-Whitney U-Verfahrens (IBM SPSS, Statistics

software for Windows, Version 25.0; BM Corp., Armonk, NY, USA) verglichen. Die Korrelationen wurden mithilfe des nicht-parametrischen Rho Tests von Spearman analysiert.

Insgesamt wurden 26 Patienten in die retrospektive Analyse eingeschlossen: 16 Frauen (61,5 %) und 10 Männer (38,5 %). Das mediane Alter zum Zeitpunkt der WBRT lag bei 58 Jahren (Spannweite: 36–81 Jahre) und zum Zeitpunkt der endokrinologischen Bewertung bei 60 Jahren (Spannweite: 37–90 Jahre). Die WBRT-Behandlungsschemata der Patienten wurden in zwei allgemeine Kategorien unterteilt: Patienten mit einem kleinzelligen Lungentumor nach einer prophylaktischen Therapie und Patienten mit Hirnmetastasen und therapeutischer Ganzhirnbestrahlung. 12 Patienten erhielten eine PCI mit einer prophylaktischen Gesamtdosis von 30 Gy (15 × 2 Gy); 14 Patienten erhielten bei Vorhandensein von Hirnmetastasen eine WBRT mit einer therapeutischen Gesamtdosis von 36 Gy (18 × 2 Gy). Das mediane Intervall vom Zeitpunkt der Bestrahlung zur endokrinologischen Untersuchung betrug 20,5 Monate (Spannweite: 6–151 Monate).

Bei 50 % aller Patienten wurden Einschränkungen in der HT-P-Funktion beobachtet. Patienten mit einer HT-P-Dysfunktion zeigten einen Trend zu kürzeren Intervallzeiten vom Zeitpunkt der Bestrahlung zur endokrinologischen Untersuchung mit einem medianen Intervallzeitraum von 15 Monaten (Spannbreite: 6–132 Monate). Davon hatten 34,6 % eine Dysfunktion einer HT-P-Achse und jeweils 7,7 % der Patienten hatten Dysfunktionen zweier oder dreier Achsen vorzuweisen. Eine Veränderung des Wachstumshormons trat bei 8 % der Patienten auf; ein LH/FSH-Mangel wurde bei 37,5 % nachgewiesen. Eine Hyperprolaktinämie konnte bei 26,9 % der Patienten festgestellt werden. Bei einem Patienten konnte ein TSH-Defizit nachgewiesen werden. Sechs Patienten mit bekannter Einnahme von L-Thyroxin bei Hypothyreose wurden von der Analyse ausgeschlossen. Ein Patient erhielt bei signifikant reduziertem morgendlichem Cortison Level die Diagnose einer ACTH-Defizienz und es wurde umgehend eine Hydrocortisontherapie eingeleitet. Die Diagnose wurde mittels zwei konsekutiver Corticotropin-Releasing-Hormon-Stimulationstests (*corticotropin-releasing hormone-Test*, CRH-Test) bestätigt.

Zum Zeitpunkt der endokrinen Nachsorge lag der mediane Karnofsky-Allgemeinzustand bei 80 % (Spannweite: 50–100 %), der mediane Fatigue-Wert sowie das NCCN Distress Thermometer lagen bei 6 (Spannweite: 0–10 bzw. 2–10).

Es wurde kein signifikanter Unterschied bei Patienten mit oder ohne endokrinen Defiziten in den oben genannten Parametern beobachtet. Zudem ergab sich insgesamt keine Korrelation zwischen den oben genannten Scores, der applizierten Dosis, dem Alter sowie dem Intervall zwischen WBRT und endokriner Testung mit dem Vorhandensein von endokrinen Dysfunktionen.

3.3 Prävalenz von Metastasen im Bereich der Hypophyse und des Hypothalamus bei Patienten mit Hirnmetastasen

Mehta P, Janssen S, Bartscht T, Schmid SM, Fahlbusch FB, Rades D. Prevalence of Metastases within the Hypothalamic-Pituitary Area in Patients with Brain Metastases. Radiat Oncol. 2019 Aug 27; 14(1):152.

Das Ziel der dritten Arbeit ist die Bestimmung der Befallswahrscheinlichkeit von Hirnmetastasen im Bereich der Hypophyse und des Hypothalamus gewesen, um die onkologische Sicherheit einer möglichen Schonung dieses Bereiches während einer Ganzhirnbestrahlung zu evaluieren.
Mithilfe von Datensätzen von Gadolinium-kontrastverstärkten T1-gewichteten Magnetresonanztomographie (*magnetic resonance tomography*, MRT) -Aufnahmen (Feldstärke min. 1,5 Tesla, Schichtdicke: max. 1,5 mm) von 865 Patienten mit Hirnmetastasen, behandelt in den Jahren 2014–2018 an der Klinik für Strahlentherapie UKSH, Campus Lübeck, wurden die Hypophyse, der Hypothalamus und der Hippocampus in die transversalen Schichten von fusionierten Computertomographie (*computed tomography*, CT) -Datensätzen konturiert (Fan et al., 2018; Scoccianti et al., 2015). Ein Sicherheitssaum von 5 mm wurde jeweils um den Hypothalamus und die Hypophyse addiert. MRT-Untersuchungen, die nicht den erforderlichen Anforderungen entsprachen (z.B. fehlende T1-gewichtete Sequenzen, größere Schichtdicke, fehlendes Kontrastmittel oder Bewegungsartefakte), wurden nicht berücksichtigt. Es wurden die folgenden Daten für jeden Patienten dokumentiert: Primärtumorentität, Alter bei der Diagnose der Hirnmetastasen, Geschlecht, maximale Größe der Hirnmetastasen und die Gesamtzahl der Hirnmetastasen. Dabei sind Patienten mit 30 oder mehr Hirnmetastasen der Kohorte „= 30“ zugeordnet worden, da bei über 30 Läsionen eine weitere Zählung einzelner Herde nicht sinnvoll bzw. in den allermeisten Fällen gar nicht realisierbar ist. Patienten mit zerebraler Vorbestrahlung sowie mit leptomeningealer Metastasierung wurden ausgeschlossen. Analog zu den Arbeiten mit dem Ziel Hippocampus-Schonung wurde die Anzahl der Metastasen innerhalb des Hypothalamus-Hypophysen-Areals (Strukturen + 5 mm Saum) dokumentiert und mit den oben genannten Variablen korreliert. Es wurde ein binäres, logistisches Regressionsmodell entwickelt. Ein p-Wert von $< 0,05$ wurde als statistisch signifikant erachtet. Für die

logistische Regressionsanalyse der Anzahl der Hirnmetastasen wurde die Analyse n = 1 bis 3 vs. n = 10 verwendet, da zahlreiche Studien den Einsatz einer Radiochirurgie bei 1 bis 3 Hirnmetastasen unterstützten. Die Ethikkommission der Universität zu Lübeck hat das Protokoll dieser retrospektiven Studie genehmigt (Aktenzeichen: 19-075A).

Es wurde eine Gesamtzahl von 4280 Hirnmetastasen bei 865 Patienten identifiziert, woraus sich ein Durchschnitt von etwa 5 Hirnmetastasen (Spannweite: 1–30 Metastasen; Patienten mit mehr als 30 Hirnmetastasen sind inbegriffen) pro Patient ergab. Die Größe einer einzelnen Metastase reichte von 0,2 bis 11 cm (Median: 1,8 cm). Das Durchschnittsalter der Patienten lag bei 64 Jahren (Spannweite: 29–60 Jahre). Die Primärtumorentitäten waren wie folgt verteilt: 46 % nicht-kleinzellige Lungentumoren (*non small cell lung cancer*, NSCLC), 14 % SCLC, 12 % Mammakarzinome, 7 % Melanome, 4 % kolorektale Karzinome, 3 % Nierentumoren und 13 % andere Tumorentitäten. Bei 26 Patienten befanden sich Metastasen innerhalb des Hypothalamus bzw. in dessen nächster Umgebung (+ 5 mm); dies entspricht etwa 3 % aller Patienten bzw. etwa 1 % aller Metastasen. Eine Lokalisation von Metastasen innerhalb der Hypophysen-Region (Hypophyse + 5 mm Saum) wurde bei 9 Patienten festgestellt, was etwa 1 % aller Patienten bzw. <1% aller Metastasen entspricht. Der einzige statistisch signifikante Faktor für einen Befall der Hypothalamus-Region (Hypothalamus + 5 mm Saum) war das Vorhandensein von > 10 Metastasen. Im Gegensatz dazu gab es keinerlei statistisch signifikante Korrelation der oben genannten Variablen mit einem Metastasenbefall im Bereich der Hypophyse.

3.4 Eine VMAT-Planungsstudie zur Schonung des Hippocampus und der Hypophysen-Hypothalamus-Achse während einer Ganzhirnbestrahlung

Mehta P, Janssen S, Fahlbusch FB, Schmid SM, Gebauer J, Cremers F, Ziemann C, Tartz M, Rades D. Sparing the Hippocampus and the Hypothalamic-Pituitary Region during Whole Brain Radiotherapy: A Volumetric-Modulated Arc Therapy Planning Study. BMC Cancer. 2020 Jun 30; 20(1):610.

Um die Hypothese eines Vorteils der HT-P-Schonung während einer Ganzhirnbestrahlung langfristig in einer Studie zu überprüfen, ist die technische Umsetzbarkeit eines solchen Schonungsansatzes – zusätzlich zu der Hippocampus-Schonung – essentiell. Hier gibt es im Gegensatz zur Schonung des Hippocampus bislang nur wenige Erfahrungen. Die technische Umsetzbarkeit des Schonungsansatzes wurde in der vierten Arbeit untersucht.

Als onkologisches Informationssystem wurde ARIA, Version 15.5 (Varian Medial Systems, Inc., Palo Alto, CA, USA) verwendet, welches das implementierte Planungssystem (*Treatment planning system*, TPS) Eclipse© enthält. Im TPS finden sowohl die Konturierung der Risikoorgane als auch die Bestrahlungsplanung und die Dosisberechnung statt. Die 3D-Dosisberechnung für die optimierten Bestrahlungspläne erfolgte in Eclipse© mit dem Algorithmus *Anisotropic Analytical Algorithm* (AAA).

Es wurden die CT-Datensätze (Siemens Biograph™ 40 m, Schichtdicke: 3 mm) von 20 Patienten verwendet, die von 2007 bis 2019 am Universitätsklinikum Schleswig-Holstein Campus Lübeck mit einer WBRT therapiert worden waren. In diese sind mithilfe von fusionierten T1-gewichteten MRT-Datensätzen die Risikostrukturen (*Ogans at risk*, OAR) und Metastasen konturiert worden. Analog zum Hippocampus [Konturierung nach der RTOG 0933 Leitlinie (Gondi et al., 2010)] wurden der Hypothalamus und die Hypophyse konturiert und durch Hinzufügen eines Sicherheitssaums von 5 mm das jeweilige geplante Risikovolumen (*planning risk volume*, PRV) generiert. CT-Datensätze, bei denen sich Metastasen innerhalb dieses Saums befanden, sind von der Planungsstudie ausgeschlossen worden. Das Zielvolumen (*planning target volume*, PTV), bestehend aus dem Ganzhirn, wurde konturiert und die PRV aus dieser Struktur ausgeschnitten. Diese Hilfsstruktur wurde

mit einem Sicherheitssaum versehen, um einen möglichst starken Gradientenabfall von Risikostrukturen zum PTV zu ermöglichen. Es wurden Bestrahlungspläne für einen Clinac DHX Linearbeschleuniger (Varian Medical Systems, Inc., USA) mit einem Millenium 120 Multilamellen-Kollimator (m*ultileaf-collimator*, MLC) erstellt. Der Normalisierungspunkt lag in allen Fällen bei 100 % der mittleren Dosis des Zielvolumens. Alle Bestrahlungspläne wurden mit dem Ziel erstellt, die applizierte Dosis sowohl im Hippocampus, dem Hypothalamus und der Hypophyse so gering wie möglich zu halten als auch die Linsen, die Augen, das Chiasma, die Sehnerven und den Hirnstamm zu schonen. 11 der 20 Patienten erhielten eine WBRT mit einer Dosis von 18 × 2 Gy = 36 Gy und einem simultan integriertem Boost (*simultaneous integrated boost*, SIB) mit einer Dosis von 18 × 0,5 Gy = 9 Gy (Gesamtdosis der Metastasen: 18 × 2,5 Gy = 45 Gy). Die anderen 9 Patienten erhielten als PCI eine Gesamtdosis von 15 × 2 Gy = 30 Gy. Für jeden einzelnen Patienten wurde ein Bestrahlungsplan mit der volumenmodulierten Rotationsbestrahlungstechnik mit einer Energie von 6 MV berechnet.

Für die WBRT+SIB-Pläne und PCI-Pläne wurden jeweils unterschiedliche Feld-, Gantry- und Kollimatoren-Konfigurationen verwendet, um die bestmögliche Schonung der OAR bei zeitgleich idealer Abdeckung des Zielvolumens zu erreichen. Die therapeutischen Pläne enthielten drei Vollrotationen (179°–181° bzw. 181°–179°) mit den Kollimatorwinkeln 320°, 40° und 90°. Dabei sind die Blenden der letzten Rotation so angepasst worden, dass sie nur die Länge der PRV erfassten, um die homogene Abdeckung zwischen diesen Strukturen zu gewährleisten. Die PCI-Bestrahlungspläne hatten analog die Kollimatorwinkel 280°, 90° und 11° mit den entsprechenden Tischrotationen von 15°, 0° und 345°.

Die Grenzwerte für die Planung wurden folgendermaßen definiert: eine Dosisreduktion in den PRV Hippocampus, Hypothalamus und Hypophyse um 50 % der Gesamtdosis und die Dosis der Augenlinsen auf < 10 Gy. Die Qualität der Bestrahlungspläne wurde mithilfe der folgenden Parameter bewertet: Homogenitätsindex (*homogeneity index*, HI), Konformitätsindex (*conformality index* oder *conformation number*, CN) und Zielvolumenabdeckung (*target coverage*, TC).

Der Homogenitätsindex beschreibt, wie homogen die applizierte Dosis das Zielvolumen abdeckt, und ist folgendermaßen definiert:

$$HI = \frac{D_{2\%} - D_{98\%}}{D_{median}} \tag{3.1}$$

Hierbei ist $D_{x\%}$ die Dosis, die $x\,\%$ des Volumens erhält; D_{median} beschreibt die mediane Dosis. Im Idealfall gilt: HI = 0; je kleiner HI, desto homogener die Bestrahlung des Zielvolumens (ICRU Report 83, 2010).
Als weiteren Parameter wurde der Konformitätsindex ermittelt, um die Menge an gesundem Gewebe in Relation zum Zielvolumen zu quantifizieren. CN wurde nach der Formel von van't Riet et al. in 1997 errechnet (van't Riet et al., 1997):

$$CN = \frac{TV_{RI}}{TV} \times \frac{TV_{RI}}{V_{RI}} \tag{3.2}$$

TV_{RI} beschreibt das Zielvolumengebiet, welches von der Referenzisodose (hier: 95 %) umschlossen ist; TV ist das Zielvolumen und V_{RI} beschreibt das Volumen der Referenzdosis (hier: 95 %). Im Idealfall gilt CN = 1, da bei diesem Wert das komplette Zielvolumen die gewünschte Dosis erhalten würde, während das gesunde Gewebe komplett davon unberührt bliebe und somit eine absolute Konformität zur Folge hätte (van't Riet et al., 1997).
Abschließend wurde das Volumen bestimmt, welches innerhalb des Zielvolumens eine Dosis erhält, die größer oder gleich der verschriebenen Dosis (VT_{pres}) ist und als Zielvolumenabdeckung beschrieben wird (Levra et al., 2016):

$$TC = \frac{VT_{pres}}{TV} \tag{3.3}$$

Im Endergebnis betrug das mediane Ganzhirnvolumen inklusive der Schonungsregion 1832,7 cm³ (Spannweite: 1436.4–2286,7 cm³). Das mediane Volumen des Hippocampus-HT-P-Areals lag bei 43,9 cm³ (Spannweite: 34,3–65,8 cm³). Das SIB-Volumen der entsprechenden Patienten betrug im Median 15,9 cm³ (Spannweite: 5,2–105,0 cm³) und entsprach damit im Median 3,3 % (Spannweite: 1,3–11,6 %) des gesamten Zielvolumens. Die Anzahl der Metastasen bei den Patienten, die eine WBRT erhielten, reichte von 1 bis 9 Metastasen (Median: 2 Metastasen). In den 11 therapeutischen Plänen betrug die im Median applizierte Dosis der Hippocampus-HT-P-Region 14,9 Gy (Spannweite: 3,2–16,2 Gy); bei den 9 PCI-Plänen 14,8 Gy (Spannweite: 12,8–15 Gy) und < 50 % der Gesamtdosis. Die maximale Linsendosis überstieg bei keinem Patienten 10 Gy (Median: 8,3 Gy).

Entsprechend lagen die medianen Dosiswerte für die Augen, den Hirnstamm, das Chiasma und die Sehnerven in den WBRT+SIB-Bestrahlungsplänen bei 25 Gy, 31 Gy, 29 Gy, 31 Gy bzw. bei 30 Gy, 40 Gy, 33 Gy, 39 Gy in den PCI-Plänen. Der mediane Homogenitätsindex der Bestrahlungspläne lag bei der therapeutischen WBRT bei 0,16 (Spannweite: 0,11–0,23) und bei der prophylaktischen WBRT bei 0,10 (Spannweite: 0,08–0,17). Die mediane $D_{95\%}$ der SIB-Pläne betrug 97,8 % (Spannweite: 97,3–98,3 %) und 96,4 % (Spannweite: 95,5–96,7 %) für die PCI-Pläne. Der mediane Konformitätsindex betrug 0,85 für alle Pläne (0,82 für die SIB-Pläne (Spannweite: 0,72–0,86) und 0,86 für die PCI-Pläne (Spannweite: 0,82–0,87). Die Zielvolumenabdeckung lag für WBRT+SIB-Pläne und PCI-Pläne gleichermaßen bei 0,7.

4 Diskussion

Bedingt durch verbesserte Therapiemöglichkeiten von Krebspatienten nimmt die Rate an Langzeitüberlebenden stetig zu (Quaresma et al., 2015). Dies hat zur Folge, dass therapieassoziierte Landzeitnebenwirkungen eine immer wichtigere Rolle spielen. Während Patienten, die im Kindesalter an einem Tumor bestrahlt wurden, bereits eine dezidierte Nachsorge erhalten, um Nebenwirkungen möglichst früh erkennen und behandeln zu können, existieren solche Leitlinien für erwachsene Krebspatienten nicht. Zu den häufigsten Langzeitnebenwirkungen onkologischer Therapien gehören endokrine Veränderungen.

Bereits 2011 hat die Autorengruppe um Appelmann-Dijkstra basierend auf Daten von Patienten, die aufgrund von Nasopharynxkarzinomen oder nicht-hypophysären Hirntumoren bestrahlt wurden, in einer Übersichtsarbeit die hohe Prävalenz endokriner Schädigungen nach einer Hirnbestrahlung beschrieben und eine strukturierte periodische endokrinologische Kontrolle empfohlen (Appelmann-Dijkstra et al., 2011). Seitdem sind zehn weitere Artikel zu diesem Thema mit insgesamt 915 Patienten publiziert worden, weshalb die Durchführung einer erneuten Bestandsaufnahme der bestehenden Literatur zu endokrinen Veränderungen nach kranialer Bestrahlung sinnvoll erschien. In einer systematischen Literaturrecherche wurden 28 Originalpublikationen mit insgesamt 1728 behandelten Patienten eingeschlossen (Arbeit 1 der kumulativen Dissertation). Dabei lag die Inzidenz von Hormonveränderungen nach einer kranialen Bestrahlung bei 20–93 %. Alle Studien bezogen sich ausschließlich auf Patienten mit Nasopharynxkarzinomen und nicht-hypophysären Hirntumoren. Für Patienten, die aufgrund von diagnostizierten Hirnmetastasen mit einer WBRT behandelt worden sind, wurden keine Daten gefunden (Mehta et al., 2019). Da in der Literatur hormonelle Veränderungen nach onkologischer Therapie meist als dosisabhängige Langzeitfolgen beschrieben sind (Vatner et al., 2018; Lamba et al., 2019; Kyriakakis et al., 2019), stellen sich, bezogen auf die Relevanz bei Patienten mit Hirnmetastasen, nach Ganzhirnbestrahlung zwei wesentliche Fragen:

1. Frage: Sind mögliche hormonelle Veränderungen bei Patienten mit reduzierter Lebenserwartung überhaupt relevant?

Während die Ganzhirnbestrahlung noch immer der Therapiestandard bei Patienten mit einer limitierten Anzahl von Metastasen ist, hat sich ein Paradigmenshift von der WBRT hin zur stereotaktischen Hochpräzisionsbestrahlung (*stereotactical radiosurgery*, SRS) ergeben. Die Ergebnisse randomisierter Studien sprechen daher für die Verwendung einer SRS bei 1 bis 3 Läsionen (Andrews et al., 2004; Aoyama et al., 2006; Kocher et al., 2011), aber auch bei bis zu 10 Metastasen (Yamamoto et al., 2014). In der klinischen Routine wird meist bei bis zu 5 Hirnmetastasen eine Präzisionsbestrahlung angeboten. Dennoch gibt es keine klare Grenze und eine WBRT bleibt häufig eine Behandlungsoption, insbesondere für Patienten mit mehreren Hirnmetastasen.

Die Überlebensprognose von Patienten mit Hirnmetastasen ist generell begrenzt (Khuntia et al., 2006). Die rekursive Partitions-Analyse (*recursive partition analysis*, RPA) von prognostischen Faktoren, die in verschiedenen RTOG-Studien für Patienten mit Hirnmetastasen etabliert wurde, beschreibt drei prognostische Gruppen mit Gesamtüberlebensraten von 2,3 Monaten bis 7,1 Monaten (Gaspar et al., 1997). Neuere Publikationen mit aktuelleren Prognose-Scores, die nicht nur auf dem KPS und Alter beruhen, zeigen eine differenziertere Lebenserwartung bei Patienten mit Hirntumoren (Spertudo et al., 2010; Rades et al., 2008; Dziggel et al., 2013). Entsprechend dem Scoring-System der Arbeitsgruppe von Rades et al. wies die Gruppe mit der besten Prognose eine 1-Jahr-Überlebensrate von 49 % auf (Rades et al., 2008). Mit dem primärturmorspezifischen Score (*disease-specific Graded Prognostic Assessment*, ds-GPA) von Spertudo et al. konnten je nach Primärtumor sogar mediane Überlebensraten von bis zu 18,7 Monaten nachgewiesen werden (Sperduto et al., 2010). Allgemein zeigte sich, dass es bei Patienten mit Hirnmetastasen durchaus Subgruppen gab, die in und nach der Therapie wesentlich länger lebten, als im Durchschnitt zu erwarten wäre, und die maßgeblich von einer endokrinologischen Nachsorge profitieren würden.

Neben der therapeutischen Behandlung stellt die PCI, die bei Patienten mit einem kleinzelligen Lungenkarzinom ohne Nachweis von Hirnmetastasen angewandt wird, bei gutem Ansprechen nach einer (Radio-)chemotherapie eine Therapieoption im „limited disease“ Stadium dar (Simone et al., 2020). Dabei sind nach 1 bzw. 2 Jahren nach Behandlungsende Überlebensraten von 60 % bzw. 35 % beschrieben worden (Aupérin et al., 1999). Der mediane Nachsorgezeitraum lag in den meisten analysierten Publikationen aus Arbeit 1 meist deutlich über zwei Jahren; dennoch

zeigten etliche Studien, dass eine Hypophyseninsuffizienz bereits im ersten Jahr nach Abschluss der Behandlung auftreten kann (Lamba et al., 2019; Handisurya et al., 2019; Ipekci et al., 2015; Appelman-Dijkstra et al., 2014; Madaschi et al., 2011; Snyers et al., 2008; Bhandare et al., 2008; Taphoom et al., 1995; Lam et al., 1991; Samaan et al., 1987; Huang et al., 1994). Bei Lamba et al. und Madaschi et al. traten sogar alle endokrinen Veränderungen innerhalb von 11-32 Monaten auf (Lamba et al., 2019; Madaschi et al., 2011). Ihr ihrer Studie beschrieben Handisurya et al. außerdem, dass verminderte Werte der Schilddrüsen- und Sexualhormone zu einem Großteil innerhalb der ersten Monate nach Abschluss der Strahlentherapie nachgewiesen werden konnten (Handisurya et al., 2019). Die Autoren schlussfolgerten, dass eine frühzeitige Schädigung der Hormone eine Reaktion des Körpers ist und daher durchaus der Grund für eine klinisch, manifeste Fatigue-Symptomatik und allgemeine Abgeschlagenheit während oder nach einer zerebralen Bestrahlung sein kann. Zwar wird diese meist als akute Nebenwirkung der Bestrahlung interpretiert, es ist aber nicht ausgeschlossen, dass auch endokrine Veränderungen dazu beitragen können, diese Nebenwirkungen auszulösen (Warner et al., 2010).

2. Frage: Können die bei einer Ganzhirnbestrahlung zur Anwendung kommenden Bestrahlungsdosen potentiell zur Veränderung der Hypothalamus-Hypophyse-Achse und damit zu hormonellen Veränderungen führen?

Für eine Ganzhirnbestrahlung existieren verschiedene standardisierte Bestrahlungskonzepte: 5 × 4 Gy = 20 Gy, 10 × 3 Gy = 30 Gy, 15 × 2,5 Gy = 37,5 Gy und 20 × 2 Gy = 40 Gy (Rades et al., 2008b; Rades et al., 2010; Rades et al., 2012; Kyriakakis et al., 2019). Da bei der WBRT das gesamte Hirngewebe bestrahlt wird, erhält auch die HT-P-Achse bei einer Ganzhirnbestrahlung die vollständig verordnete Dosis. Bezüglich der Entstehung einer Hypophyseninsuffizienz weisen zahlreiche Studien auf einen dosisabhängigen Effekt hin (Vatner et al., 2018; Lamba et al., 2019; Bhandare et al., 2008; Agha et al., 2005; Kyriakakis et al., 2016; Pekic et al., 2018). Bisher ist allerdings kein Dosisschwellenwert beschrieben, ab dem eine hormonelle Schädigung zu erwarten ist. In der Literaturrecherche fanden sich Dosiswerte von 4 Gy bis 97 Gy. In der Hälfte dieser Studien wurde dem HT-P-Areal eine Mindestdosis von unter 40 Gy appliziert. Kyriakakis et al. haben für alle

Patienten, bei denen die HT-P-Region mehr als 30 Gy erhielt, eine strukturierte endokrinologische Nachsorge empfohlen (Kyriakakis et al., 2016). Dieser Dosiswert wird bei nahezu allen gängigen WBRT-Dosiskonzepten erreicht.

Der Großteil der Patienten aus den Studien wurde mit einem konventionell fraktionierten Bestrahlungsschema behandelt (1,8 Gy bzw. 2 Gy pro Fraktion). Bei einer Ganzhirnbestrahlung kommen in den meisten Fällen hypofraktionierte Konzepte mit Dosen pro Fraktion von > 2 Gy zur Anwendung, was bei gleicher Gesamtdosis höheren biologisch effektiven Dosen entspricht. Die Aufteilung der Gesamtdosis in kleinere Dosen pro Fraktion führt in der Regel zu einer besseren Schonung des spät reagierenden Gewebes (Sathyapalan et al., 2012). Die HT-P-Achse reagiert bekanntermaßen wie spät reagierendes Gewebe (Pekic et al., 2018; Ahmad et al., 2013). Älteren Studien zeigten, dass eine Hypophyseninsuffizienz bei höheren Einzeldosen (> 2 Gy pro Fraktion) auftritt – also, dass Dosen pro Fraktion > 2 Gy einen verstärkten Effekt auf spät reagierendes Gewebe haben (Littley et al., 1989). Außer einigen historischen Beschreibungen existieren allerdings bislang keine klinischen Daten, die diese Hypothese stützen. Darüber hinaus beinhalten moderne Krebstherapien, wie Immuntherapien, das Risiko, Veränderungen der Hypophyse, wie z. B. eine Hypophysitis, hervorrufen zu können, und so den Effekt der Strahlentherapie zu verstärken (Crowne et al., 2015). Auch hierzu gibt es bislang keine Beschreibungen in der Literatur. In der Theorie haben aber hypofraktionierte Regime, wie auch Immuntherapien, das Potential, Veränderungen der HT-P-Achse zu verstärken.

Zusammenfassend lässt sich konstatieren, dass bislang keine Daten zu hormonellen Veränderungen nach einer Ganzhirnbestrahlung existieren. Aus der Extrapolation von Bestrahlungen bei Patienten mit Nasophyarynxkarzinomen und nicht-hypophysären Hirntumoren lässt sich aber schlussfolgern, dass endokrine Veränderungen nach einer Ganzhirnbestrahlung mit den gängigen Bestrahlungskonzepten, zumindest bei Patienten mit einer guten Prognose, nicht unwahrscheinlich sind. Demzufolge kann eine frühzeitige endokrinologische Nachsorge, d. h. innerhalb des ersten Jahres nach einer cRT, von Patienten nach einer WBRT oder PCI sinnvoll sein. Um dieser Frage weiter nachzugehen, wurden endokrinologische Untersuchungen an einem Kollektiv von 26 Langzeitüberlebenden nach einer Ganzhirnbestrahlung durchgeführt (Arbeit 2 der kumulativen Dissertation). Diese Patienten wurden über einen medianen Nachbeobachtungszeitraum von mehr

als 20 Monaten beobachtet. Dabei zeigte die Hälfte der Patienten eine endokrine Dysfunktion, zumindest von einer HT-P-Achse; bei 8 % traten Dysfunktionen mehrerer Achsen auf. Allerdings konnte keine Korrelation von endokrinen Dysfunktionen und einer Fatigue-Symptomatik gefunden werden. Limitierende Faktoren dieser Studie sind außerdem das retrospektive Studiendesign mit den bekannten Risiken einer Verzerrung, die vergleichsweise kleine Patientenkohorte, fehlende Referenzwerte bezüglich der Hormone vor Beginn der Strahlentherapie und die singuläre Testung zu unterschiedlichen Zeitpunkten nach Abschluss der Bestrahlung bei den einzelnen Patienten. Des Weiteren wurden in den meisten Fällen die HT-P-Dysfunktionen ohne Stimulationstests ausgewertet, wie es von der Arbeitsgruppe von Fernandez et al. in ihrer Studie vorgeschlagen wird und bereits zum Teil in die aktuellen Richtlinien bei der Nachsorge für kindliche Tumoren übernommen wurde (Hua 2012, Pekic 2018). Dennoch ist dies die erste Studie, die sich mit HT-P-Dysfunktionen nach einer Ganzhirnbestrahlung befasst hat. Sie hat gezeigt, dass diese Veränderungen bei den aktuellen Dosiskonzepten bereits innerhalb von sechs Monaten nach Bestrahlungsende auftreten können und durchaus einen relevanten Effekt auf Patienten und dessen Lebensqualität haben können. Neben einer standardisierten endokrinologischen Nachsorge stellt sich aufgrund dieser Erkenntnis die Frage, ob es generell sinnvoll ist, das HT-P-Areal bei der Bestrahlung zu schonen, und ob dies technisch umsetzbar ist.

Eine Ganzhirnbestrahlung führt nicht selten zu einer Verschlechterung der neurokognitiven Funktion mit Beeinträchtigungen des Gedächtnisses und einer daraus resultierenden verminderten Lebensqualität (Gondi et al., 2010). Die Arbeitsgruppe um Gondi et. al hat die Hypothese aufgestellt, dass die neuronalen Stammzellen innerhalb des Hippocampus die Ursache für diesen Patho-Mechanismus sein können. In der RTOG 0933 Studie zeigten die Autoren, dass die Schonung des Hippocampus während einer Ganzhirnbestrahlung zu einer Verbesserung der Gedächtnisfunktion und der Lebensqualität führt (Gondi et al., 2014). Die Hypothese der verbesserten neurokognitiven Funktion bei gleichzeitiger onkologischer Kontrolle wurde bereits in einer vorläufigen Analyse einer prospektiven Phase-III-Studie bestätigt (Gondi et al., 2020). Die gleiche Arbeitsgruppe hat sich vor Initiierung der RTOG 0933 Studie mit der Befallswahrscheinlichkeit von Metastasen in der Hippocampus-Region beschäftigt und herausgefunden, dass diese bei 8,6 %

liegt. Diese geringe Wahrscheinlichkeit ist Voraussetzung für die Umsetzung einer Schonung des Hippocampus, um die onkologische Sicherheit nicht zu gefährden.
Analog zu den Arbeiten mit dem Ziel einer Hippocampus-Schonung wurde die Prävalenz von Hirnmetastasen im HT-P-Bereich untersucht (Arbeit 3 der kumulativen Dissertation). In einer retrospektiven Analyse sind dabei die Daten von 865 Patienten mit insgesamt 4280 Hirnmetastasen untersucht worden. Mithilfe von T1-gewichteten MRT-Sequenzen wurden die anatomischen Strukturen des HT-P-Areals mit einem Sicherheitssaum von 5 mm in ein CT konturiert (analog zu Fan et al., 2019). Im Bereich des Hypothalamus lag die Prävalenz des Befalls bei 3 % aller Patienten bzw. 1 % aller Metastasen. Das Hypophysen-Areal war in 1 % aller Patienten von einer Metastasierung betroffen; dies entsprach < 1 % aller Metastasen. Damit lag die Prävalenz in der HT-P-Region deutlich unter der von Gondi et al. beschriebenen Befallswahrscheinlichkeit des Hippocampus. Korrelationen mit der primären Tumorentität, dem Alter oder Geschlecht gab es keine. Nur bei mehr als 10 Hirnmetastasen konnte ein höherer Befall der Hypothalamus-Region nachgewiesen werden. Somit wäre insgesamt ein möglicher Schonungsansatz der HT-P-Region bei Patienten mit weniger als 10 Hirnmetastasen durchaus vorstellbar. Als limitierende Faktoren gelten auch hier die möglichen Verzerrungen im Rahmen einer retrospektiven Studie und die nicht vorhandene Datenlage bezüglich endokriner Funktionen vor und nach der Bestrahlung. Dennoch sprechen die geringe Metastasenprävalenz und das Vorwissen, dass Veränderungen der Hormonachse dosisabhängig sind (Follin et al., 2016), es aber keinen konkreten Grenzwert gibt, für eine Schonung der HT-P-Region analog zur Hippocampus-Schonung.
Demzufolge wurde die technische Umsetzbarkeit der Schonung der HT-P-Region in einer Planungsstudie untersucht (Arbeit 4 der kumulativen Dissertation). Es wurden sowohl therapeutische als auch prophylaktische WBRT-Konzepte in die Planungsstudie mit einbezogen. Mithilfe der VMAT-Technik wurden Bestrahlungspläne erstellt, bei denen eine Dosisreduktion im Bereich des Hippocampus und der HT-P-Achse von < 50 % der Gesamtdosis der Ganzhirnbestrahlung erreicht wurde, ohne die Homogenität der Dosisabdeckung des Zielvolumens zu kompromittieren. Gondi et al. haben in der RTOG 0933 Studie einen Mittelwert von 9 Gy und einer maximalen Dosis von 16 Gy für den Hippocampus erreicht (Gondi et al., 2014). Andere Studien lagen abhängig von der Technik und dem Dosiskonzept zwischen 5 Gy und 20 Gy für den Hippocampus (Darzy et al.,

2013). Die Arbeitsgruppe von Fan et al. hatte diesen Ansatz bereits zuvor in einer Planungsstudie mit einer IMRT-Technik verfolgt und dabei geringere Dosen im Hippocampus (Mittelwert 9,6 Gy) und dem Hypothalamus bzw. der Hypophyse (Mittelwerte 11,1 Gy und 10,7 Gy) erreicht (Fan et al., 2019). Diese lagen deutlich unter den von uns in der vierten Arbeit errechneten Mittelwerten (15 Gy für die gesamte Hippocampus-HT-P-Region). Im Vergleich zu dieser Planungsstudie haben Fan et al. allerdings geringere Gesamtdosen simuliert (36 Gy/45 Gy bzw. 30 Gy vs. 25 Gy). Darüber hinaus führte unser VMAT-Ansatz im Vergleich zu dem IMRT-Ansatz von Fan et al. zu einer verbesserten Homogenität, einer besseren Abdeckung des Zielvolumens und einer Schonung der Linsen als Risikoorgan (Zieminski et al., 2015; Wang et al., 2016; Lee et al., 2015; Fan et al., 2019). Ein weiterer Vorteil der VMAT-Technik ist die schnellere Applikationszeit, die laut Wang et al. um 25 % geringer ist, als bei der IMRT-Technik (Pokhrel et al., 2015). Einzig die Ganzhirnbestrahlung mit der helikalen Tomotherapie führte, zumindest beim Ansatz der Hippocampus-Schonung bei einer WBRT, zu einer geringfügig besseren Abdeckung des Zielvolumens und besseren Homogenitätsindizes im Vergleich zu IMRT und VMAT (Rong 2015, Jiang 2019). Allerdings ist die Verfügbarkeit eines Tomotherapiegeräts eingeschränkt und die Planungszeit signifikant länger.

5 Ausblick und Zusammenfassung

Trotz des vermehrten Einsatzes von Hochpräzisionstechniken bei der Bestrahlung einzelner Hirnmetastasen ist die Ganzhirnbestrahlung weiterhin eine häufige Therapieoption bei Patienten mit mehr als drei Metastasen. Neuere Techniken wie die Hippocampus-Schonung, die zu einer Verbesserung der neurokognitiven Funktion geführt haben, sind mittlerweile weltweit etabliert. Darüber hinaus hat sich Memantine, ein N-Methyl-D-Aspartat-Rezeptor-Antagonist, der in der Therapie der vaskulären Demenz angewandt wird, als wirksam bei der Verbesserung kognitiver Funktionen nach einer Ganzhirnbestrahlung erwiesen (Brown et al., 2013). Gemäß einer aktuell publizierten Phase-III-Studie wird die Kombination aus einer Hippocampus-Schonung mit Memantine bei Patienten in guten Allgemeinzustand als Standard bei einer Ganzhirnbestrahlung angesehen (Brown et al., 2020).

Ziel dieser kumulativen Dissertation war es, eine Technik zu entwickeln, die die Hypophysen-Hypothalamus-Achse bei einer Ganzhirnbestrahlung schont, um das Risiko von endokrinen Defiziten und neurokognitiven Veränderungen bei den bestrahlten Patienten zu senken. In der ersten Arbeit wurde dazu eine Literaturrecherche durchgeführt, um die aus einer Ganzhirnbestrahlung resultierenden, möglichen hormonellen Defizite der Hypophysen-Hypothalamus-Achse für erwachsene Krebspatienten zu untersuchen. Dabei konnte gezeigt werden, dass es keine Daten zu endokrinen Veränderungen nach einer WBRT gibt. Zudem konnte kein Dosisschwellenwert festgestellt werden, ab welchem endokrine Veränderungen nach einer kranialen Bestrahlung häufig auftreten. Jedoch konnte nachgewiesen werden, dass nach der Bestrahlung von Nasopharynx-/Schädelbasis-Tumoren und nicht-hypophysären Hirntumoren oftmals endokrine Defizite vorkamen. Vor dem Hintergrund der unzureichenden Datenlage nach WBRT wurden in der zweiten Arbeit die Veränderungen der Hypophysen-Hypothalamus-Achse bei Patienten quantifiziert, die eine Ganzhirnbestrahlung erhalten hatten. Anschließend wurde in der dritten Arbeit erstmalig die Prävalenz von Hirnmetastasen im HT-P-Bereich untersucht. Diese lag in einem großen Patientenkollektiv bei max. 3 %. Diese Information ist relevant, um im Falle einer möglichen Aussparung dieser Strukturen die onkologische Sicherheit nicht zu gefährden. Die geringe Prävalenz und die bekannte Dosisabhängigkeit endokriner Veränderungen rechtfertigen einen Schonungsansatz der HT-P-Achse analog zur Hippocampus-Schonung. Mithilfe einer

neu entwickelten VMAT-Technik wurden daher in der vierten Arbeit abschließend Bestrahlungspläne für prophylaktische und therapeutische Bestrahlungskonzepte erstellt, bei denen im Bereich des Hippocampus und der HT-P-Achse eine Dosisreduktion von < 50 % der Gesamtdosis der Ganzhirnbestrahlung und eine Schonung der Augenlinsen erreicht werden konnte.

Als nächster Schritt ist eine prospektive Studie bei Patienten mit Ganzhirnbestrahlung (ohne HT-P-Schonung) geplant, bei der zu vordefinierten Zeitpunkten endokrinologische Tests erfolgen sollen, um endokrine Veränderungen quantifizieren zu können. Diese sollen die Ergebnisse der retrospektiven Studie (Arbeit 2) in einem prospektiven Rahmen überprüfen. Langfristiges Ziel ist eine randomisierte prospektive Studie mit dem Vergleich einer WBRT mit und ohne HT-P-Schonung.

6 Literaturverzeichnis

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UNIVERSITÄT ZU LÜBECK

Ethik-Kommission

Universität zu Lübeck · Ratzeburger Allee 160 · 23538 Lübeck

Herrn
Prof. Dr. med. Dirk Rades
Klinik für Strahlentherapie

im Hause

Vorsitzender:
Herr Prof. Dr. med. Alexander Katalinic
Stellv. Vorsitzender:
Herr Prof. Dr. med. Frank Gieseler

Ratzeburger Allee 160
23538 Lübeck

Sachbearbeitung: Frau Janine Erdmann
Tel.: +49 451 3101 1008
Fax: +49 451 3101 1024
ethikkommission@uni-luebeck.de

Aktenzeichen: 19-409A
Datum: 10. Dezember 2019

Beurteilung von hormonellen Veränderungen bei PatientenInnen nach einer Ganzhirnbestrahlung
Ihr Schreiben vom 22. Oktober 2019 – hier eingehend am 04. Dezember 2019

Sehr geehrter Herr Prof. Rades,

mit Ihrem o.g. Schreiben informieren Sie die Ethik-Kommission über Ihr geplantes Vorhaben.

Es werden ausschließlich anonymisierte Daten verarbeitet.

Die Ethik-Kommission nimmt das von Ihnen in Ihrem Anschreiben beschriebene Vorhaben zur Kenntnis. Eine Behandlung im normalen Antragsverfahren wird nicht für notwendig erachtet.

Mit freundlichen Grüßen

Prof. Dr. med. Alexander Katalinic
Vorsitzender

UNIVERSITÄT ZU LÜBECK

Universität zu Lübeck · Ratzeburger Allee 160 · 23538 Lübeck

Herrn
Prof. Dr. med. Dirk Rades
Klinik für Strahlentherapie

im Hause

Ethik-Kommission

Vorsitzender:
Herr Prof. Dr. med. Alexander Katalinic
Stellv. Vorsitzender:
Herr Prof. Dr. med. Frank Gieseler

Ratzeburger Allee 160
23538 Lübeck

Sachbearbeitung: Frau Janine Erdmann
Tel.: +49 451 3101 1008
Fax: +49 451 3101 1024
ethikkommission@uni-luebeck.de

Aktenzeichen: 19-075A
Datum: 26. Februar 2019

Quantitative Bestimmung des Befalls der Hypothalamus/Hypophysen-Region bei Patienten/innen mit Hirnmetastasen sowie Durchführbarkeitsanalyse einer Schonung der Hypothalamus/Hypophysen-Region während einer Ganzhirnbestrahlung
Ihr Schreiben vom 07. Februar 2019

Sehr geehrter Herr Prof. Rades,

mit Ihrem o.g. Schreiben informieren Sie die Ethik-Kommission über Ihr geplantes Vorhaben.

Es werden ausschließlich anonymisierte Daten verarbeitet.

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Are hypothalamic- pituitary (HP) axis deficiencies after whole brain radiotherapy (WBRT) of relevance for adult cancer patients? – a systematic review of the literature

P. Mehta[1†], F. B. Fahlbusch[2†], D. Rades[1], S. M. Schmid[3,4], J. Gebauer[3] and S. Janssen[1,5*]

Abstract

Background: Cranial radiotherapy (cRT) can induce hormonal deficiencies as a consequence of significant doses to the hypothalamic-pituitary (HP) axis. In contrast to profound endocrinological follow-up data from survivors of childhood cancer treated with cRT, little knowledge exists for adult cancer patients.

Methods: A systematic search of the literature was conducted using the PubMed database and the Cochrane library offering the basis for our debate of the relevance of HP axis impairment after cRT in adult cancer patients. Against the background of potential relevance for patients receiving whole brain radiotherapy (WBRT), a particular focus was set on the temporal onset of hypopituitarism and the radiation dose to the HP axis.

Results: Twenty-eight original papers with a total of 1728 patients met the inclusion criteria. Radiation doses to the HP area ranged from 4 to 97 Gray (Gy). Hypopituitarism incidences ranged from 20 to 93% for adult patients with nasopharyngeal cancer or non-pituitary brain tumors. No study focused particularly on hypopituitarism after WBRT. The onset of hypopituitarism occurred as early as within the first year following cRT (range: 3 months to 25.6 years). However, since most studies started follow-up evaluation only several years after cRT, early onset of hypopituitarism might have gone unnoticed.

Conclusion: Hypopituitarism occurs frequently after cRT in adult cancer patients. Despite the general conception that it develops only after several years, onset of endocrine sequelae can occur within the first year after cRT without a clear threshold. This finding is worth debating particularly in respect of treatment options for patients with brain metastases and favorable survival prognoses.

Keywords: Whole brain radiotherapy, Endocrine deficiencies, Hypothalamus, Pituitary, Hypopituitarism

Background

Endocrine long-term complications are common in childhood cancer survivors [1–6]. After cranial radiotherapy (cRT), multiple endocrine functions can be affected [7, 8]. In a large retrospective study with a cohort of 748 childhood cancer survivors treated with cRT, the estimated point prevalence for growth hormone (GH) deficiency was 46.5%, 10.8% for thyroid-stimulating (TSH) hormone deficiency and 4% for adrenocorticotropic hormone deficiency (ACTH) [9], respectively. As young age at the time of radiation represents a risk factor for the development of endocrine deficiencies after cRT [10], the prevalence of cRT-induced hypothalamic-pituitary (HP) axis-related sequelae in adult patients may vary.

In contrast to comprehensive data on childhood cancer patients, information on hormonal impairment after cRT in adults is scarce. Reviewing eighteen studies with

* Correspondence: Stefan.janssen@UKSH.de
†P. Mehta and F. B. Fahlbusch contributed equally to this work.
[1]Department of Radiation Oncology, University of Lübeck, Ratzeburger Allee 160, 23538 Lübeck, Germany
[5]Private Practice of Radiation Oncology, Hannover, Germany
Full list of author information is available at the end of the article

a total of 813 adult cancer patients treated with cRT (nasopharyngeal cancer and non-pituitary brain tumors) in 2011, Appelman-Dijkstra et al. were able to show that the prevalence of cRT-induced hypopituitarism was of clinical relevance and argued for a structured periodical endocrine follow-up of these adults [11].

We aimed to update the existing knowledge database on HP axis dysfunction after cRT in adult cancer patients (non-pituitary brain tumors and nasopharyngeal cancer) by including current literature for further debate. We were able to gather more detailed information on the course of HP axis impairment after WBRT in adults, enabling the discussion of the following clinical questions in particular: i) What is the current evidence on HP axis dysfunction after WBRT in literature? ii) Are WBRT doses within the range of potential harm? iii) Can we neglect the impact of cRT-related hormonal deficiency in patients with brain metastases and limited life expectancy as a typically late manifesting side effect?

Methods

On April 25th, 2019 the PubMed database and the Cochrane library were searched for the following terms: "cranial radiotherapy" OR "cranial irradiation" AND "hypopituitarism" OR "pituitary deficiency" OR "hormonal changes" OR "hormonal impairment" OR "hormonal deficiency". Only studies written in English on adult cancer patients (≥18 years, non-pituitary brain tumors, head and neck cancers and brain metastases) with information on endocrine function after cRT were considered. The initial search was supplemented with manual searches of the reference lists and cross-referencing. A PRISMA flow chart [12] summarizes the selection process (Fig. 1).

Results

The initial search returned 889 citations, with 286 remaining after removing duplicates and limiting the results to adult cancer patients (Fig. 1). After screening titles and abstracts, 28 original full papers with a total of 1728 patients were included.

Search results could mainly be assigned to the tumor entities nasopharynx carcinoma/ skull base tumors (15 studies) and non-pituitary brain tumors (13 studies). No study with a focus on endocrine assessment after WBRT in adult cancer patients was found.

The overall prevalence of pituitary dysfunction ranged from 20 to 93% (GH: 19–100%, ACTH: 4–73%, TSH: 4–70%, LH/FSH: 0–55%, PRL: 7–100%). The time interval from cRT to endocrine assessment ranged from 3 months to 25.6 years. In 13 studies, the median start of follow-up exceeded three years. The total radiation dose to the pituitary gland/hypothalamus ranged from 4 to 97 Gy. Eight studies did not supply estimated doses to the HP axis. Table 1 summarizes the search results.

Discussion

The review of 28 original articles showed that hypopituitarism occurs frequently in adult patients after cRT for nasopharyngeal cancer and non-pituitary brain tumors. The fact that not a single article was focused on hypopituitarism after WBRT in particular highlights the general need for our review of HP axis deficiencies after cRT to improve extrapolation of the results for WBRT patients.

In 2011, Appelman-Dijkstra et al. published a review and meta-analysis on pituitary dysfunction in adult patients after cRT including 18 studies with a total of 813 patients [11]. The authors found hypopituitarism prevalent and concluded that all patients treated with cRT should undergo structured periodical assessment of pituitary functions [11]. In the meantime, ten additional articles published including 915 new patients, justifying an update of the pre-existing database regarding the current literature. Our analysis additionally contributes to the debate of whether the onset of pituitary dysfunction and

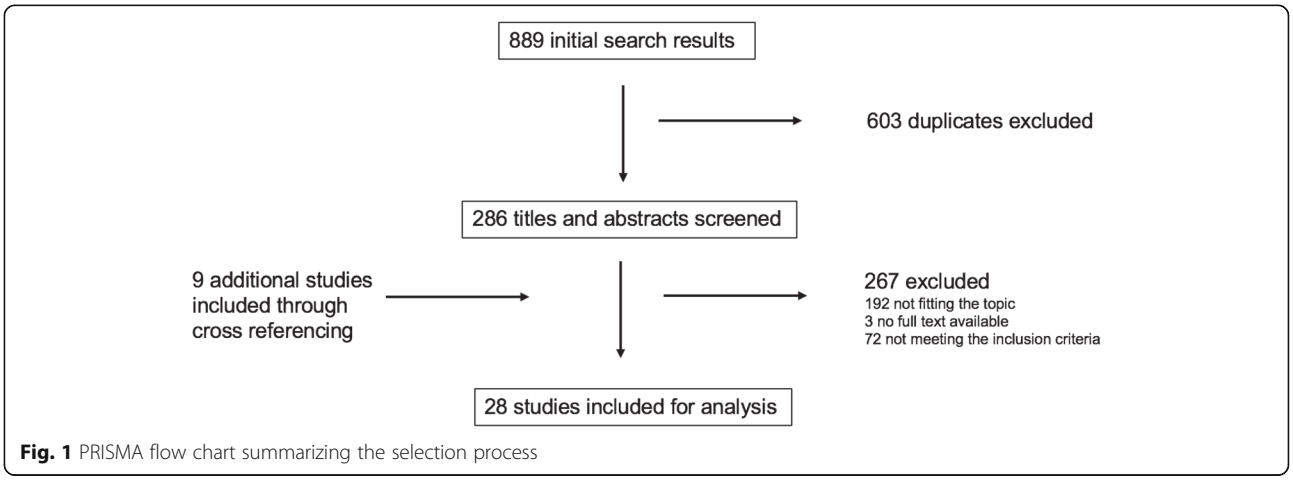

Fig. 1 PRISMA flow chart summarizing the selection process

Table 1 Studies with data on pituitary hormonal impairment after cranial radiotherapy in adult cancer patients

Author	Patients	Age (years)	Tumor entity	RT dose (Gy)	Time since RT	Pituitary hormonal impairment (axis)					
						Any deficiency	GH deficiency	ACTH deficiency	TSH deficiency	LH/FSH deficiency	PRL (hyperprolactinemia)
Lamba 2019 [13]	74	NR	Meningeoma	NR	Follow up: mean: 43 months Mean time to develop hormone deficiency: 11–32 months		19% (14/74)	24% (18/74)	24% (18/74)	10% (7/74)	NR
Handisurya 2018 (prospective) [14]	436	52 (19–83)	Brain	54–60 Gy No statement on dose to the pituitary/hypothalamus	Baseline 3 months after RT 6 months after RT 1 years after RT 2 years after RT 3 years after RT > 3 years after RT		NR	NR	21% 16.8% 11.3% 10.2% 1.4% 5.7% 10.9%	0% / 0%* 7.1% / 0%* 32.7% / 0%* 35.3% / 0%* 41.7% / 0%* 52.2% / 0%* 24% / 0%* LH: always 0%	20% / 11%* 2% / 18.8%* 1.3% / 6.8%* 3.1% / 10.3%* 22.2% / 0%* 55.6% / 4.3%* 26% / 42.1%*
Kyriakakis 2016 [15]	107	40 ± 13.1	Brain	54Gy, estimated dose to the HP axis 35.9 ± 15.5Gy**	8 years 5.3–11 years	88%	86.9%	23.4%	11.2%	34.6%	15%
Ipekci 2014 [16]	30	45.2 ± 9.8	Nasopharyngeal	Mean dose to the pituitary: 46Gy (23–66) Mean dose to the hypothalamus: 10Gy (4–41)	10–133 months	93% (28/30)	77% (23/30)	73% (22/30)	27% (8/30)	NR	43% (13/30)
Ratnasingam 2014 [17]	50	57 ± 12.2	Nasopharyngeal	No statement on dose to the pituitary/hypothalamus	Median: 8 years (3–21)	82% (41/50)	78% (39/50)	40% (20/50)	4% (4/50)	22% (11/50)	30% (15/50)
Seland 2014 [18]	140	42.5 (15–76)	Head and neck	Pituitary: 13Gy (0–68)	16 years (5–29)	73% (102/140)	25% (32/140)	34% (45/140)	34% (45/140)	55%	NR
Appelman-Dijstra 2014 [19]	80	47.5 (18.6–89.7)	Brain	Pituitary: 56.27 (40–70)	2 years after RT 5 years after RT 10 years after RT 15 years after RT	21% (17/80) 47% (23/49) 60% (27/45) 89% (31/35)	33% (27/80)	31% (25/80)	14% (11/80)	25% (20/80)	21% (17/80)
Madischi 2011 [20]	26	38.5 (33–47)	Brain	Mean dose to the pituitary and hypothalamus: 41.8 Gy (30.7–49.8)	< 32 months (median: 27 months)	38% (10/26)	29% (7/26)	22% (6/26)	14% (4/26)	4% (1/26)	NR

Table 1 Studies with data on pituitary hormonal impairment after cranial radiotherapy in adult cancer patients *(Continued)*

Author	Patients	Age (years)	Tumor entity	RT dose (Gy)	Time since RT	Pituitary hormonal impairment (axis)					
						Any deficiency	GH deficiency	ACTH deficiency	TSH deficiency	LH/FSH deficiency	PRL (hyperprolactinemia)
Snyders 2009 [21]	76, 21 with endocrine evaluation	56 (28–74)	Sinunasal	44-66Gy, estimated dose to the pituitary: 51–56, estimated dose to the hypothalamus: 44-52Gy	107 months (11–253)	62% (13/21)	24% (5/21)	19% (4/21)	14% (3/21)	19% (4/21)	10% (2/21)
Bhadare 2008 [22]	312, 112 with endocrine evaluation	NR	Nasopharyngeal	40-70Gy	63 months (6–365)	60% (67/112)	36% (16/44)	32% (14/44)	70% (31/44)	27% (12/44)	15% (10/68)
Schneider 2006 [23]	68, 44 with endocrine evaluation	20–79	Brain	NR	NR	38% (17/44)	28% (12/44)	19% (8/44)	18% (7/44)	29.5% (13/44)	7% (3/44)
Agha 2005 [24]	56	39.3 ± 11.9	Brain	Estimated dose to the pituitary: 54Gy (4–97)	6 years	41% (23/56)	32% (18/56)	21% (12/56)	9% (5/56)	27% (15/56)	32% (18/56)
Johannesen 2003 [25]	33, 25 with endocrine evaluation	38 (14–68)	Brain	54 Gy (45–59)	13.1 years (6–25.6)	64% (16/25)	NR	4% (1/25)	56% (14/25)	16% (4/25)	0% (0/25)
Popovic 2002 [26]	22 6 > 18y	NR	Brain	56 Gy, estimated dose to the pituitary: 25-30Gy	7.6 ± 0.7 years (2–3)	67% (4/6)	67% (4/6)	NR	NR	NR	NR
Pai 2001 [27]	107	41.2 (17–75)	Chordoma/ chondrosarcoma	Estimated dose to pituitary and hypothalamus: < 50-70Gy	5.5 years	87%	NR	19%	30%	29%	72%
Arlt 1997 [28]	31	26–66	Brain	Mean dose pituitary: 51.1Gy (±12.1) mean dose hypothalamus: 57Gy (± 7.8)	1.5–11 years	77% (24/31)				NR	29% (9/31)
Taphoorn 1995 [29]	13	24–66	Brain	45–61 Gy, mean pituitary dose: 36.1 Gy (0–50)	3 years (1–11.5)	77% (10/13)	31% (4/13)	62% (8/13)	0% (0/13)	15% (2/13)	23% (3/13)
Constine 1993 [30]	32	6–65	Brain	39.6–70.2Gy	2–13 years	91% (28/32)	NR	NR	NR	NR	NR
Lam 1991 [31]	20	43.7 ± 8.4 (male) 36.8 ± 9 (female)	Nasopharyngeal	Estimated dose to the pituitary 62Gy, estimated dose to the hypothalamus: 40Gy	60 months	75% (15/20)	55% (11/20)	25% (5/20)	15% (3/20)	35% (7/20)	30% (6/20)
Woo 1988 [32]	11	33–64	Nasopharyngeal	Estimated dose to pituitary 62-67Gy, estimated dose to the hypothalamus: 41-45Gy	72–240 months	82% (9/11)	90% (9/10)	18% (2/11)	45% (5/11)	55% (6/11)	27% (3/11)
Samaan 1987 [33]	166	47 (6–80)	Nasopharyngeal and paranasal sinus	Estimated dose to the pituitary: 57 (4–75), estimated dose to the hypothalamus: 50 (11–75)	12–312 months	75% (124/166)	75% (124/166)	18% (30/166)	20% (33/166)	20% LH (33/166) 35% FSH (58/166)	36% (60/166)
Lam 1987	32	27–50	Nasopharyngeal	46–60	60–204 months	25% (8/	19% (6/	6% (2/32)	13% (4/	16% (5/	19% (6/32)

Table 1 Studies with data on pituitary hormonal impairment after cranial radiotherapy in adult cancer patients *(Continued)*

Author	Patients	Age (years)	Tumor entity	RT dose (Gy)	Time since RT	Pituitary hormonal impairment (axis)					
						Any deficiency	GH deficiency	ACTH deficiency	TSH deficiency	LH/FSH deficiency	PRL (hyperprolactinemia)
[34]						32)	32)		32)	32)	
Mechanik 1986 [35]	15	22–59	Brain	40–50 to whole brain	2–9 years	93% (14/15)	NR	NR	14.3% (1/7)	NR	100% (9/9)
Lam 1986 [36]	8	27–52	Nasopharyngeal	46–61, estimated to the pituitary 55–67	> 60 months	100% (8/8)	100% (8/8)	50% (4/8)	50% (4/8)	25% (2/8)	88% (7/8)
Huang 1979 (prospective) [37]	37	16–65	Nasopharyngeal	estimated dose to pituitary/ hypothalamus: 46–56 Gy	Before RT 6 months after RT 1 years after RT 2 years after RT	NR	8.1% 18.9% 18.9% 21.6% NS	46% 73% 83.8% 83.8% p = < 0.01	0% 21.6% 27% 37.8% p = < 0.01	10.8% / 48.6% 56.8% / 83.8% 51.4% / 83.8% 56.8% / 81.1% (LH/FSH) $p < 0.01$	NR
Harrop 1976 [38]	17 8 < 18y	8 < 18	Brain	40–52	6 years (1–15)	62.5% (5/8)	50% (4/8)	12.5% (1/8)	12.5% (1/8)	37.5% (3/8)	NR
Rosenthal 1976 [39]	6	35–66	Nasopharyngeal	55–65	12–96 months	67% (4/6)	100% (2/2)	50% (1/2)	67% (4/6)	NR	NR
Samaan 1975 [40]	10	26–55	Nasopharyngeal	Estimated dose to pituitary: 50–83	60–240 months	100% (10/10)	60% (6/10)	50% (5/10)	40% (4/10)	30% (3/10)	50% (5/10)

Abbreviations: *GH* growth hormone, *ACTH* adrenocorticotropic hormone, *TSH* thyroid-stimulating hormone, *LH* luteinizing hormone, *FSH* follicle-stimulating hormone, *PRL* prolactin, *Gy* Gray, *RT* radiation therapy, *NR* Not reported; * younger and older than 50 years, ** subgroup analysis of the study group (Kyriakakis et al.)

radiation dose leading to pituitary dysfunction could be of relevance for patients treated with WBRT.

Manifestation of cRT-induced endocrine deficiencies - potential relevance for patients with brain metastases and limited life expectancy?

Brain metastases are the most common brain tumors in adults, occurring in approximately 10–30% of adult cancer patients [41]. While WBRT remains a primary treatment modality for many patients with high intracranial tumor burden, there has been a paradigm shift from WBRT to stereotactic small volume high precision RT (stereotactic surgery (SRS)) in patients with a limited number a brain metastases. However, there is no general consensus defining the cut-off for the number of lesions. Randomized studies support the use of SRS in 1–3 lesions [42–44] or up to 10 metastases [45]. Still, WBRT (preferably with hippocampal sparing technique) remains an option for patients with more than a "limited number" of brain metastases.

In general, life expectancy of patients with brain metastases is limited [41]. Recursive partioning analysis (RPA) of prognostic factors in Radiation Treatment Oncology Group (RTOG) brain metastases trials suggested three prognostic classes with median survival rates from 2.3 months to 7.1 months [46]. More recently published prognostic scores, not only based on performance status and age, showed a more differentiated range of life expectancies in patients with brain metastases [47–49]. According to the scoring system established by Rades et al., the group with the best prognosis showed a 1-year survival rate of 49% [48]. With the disease specific Graded Prognostic Assessment (GPA) score introduced by Spertudo et al., median survival of up to 18.7 months can be reached depending on the primary tumor site [47].

All together, there are subgroups of patients with brain metastases that live significantly longer than the average. Apart from patients presenting with brain metastases, a prophylactic brain irradiation (PCI) was shown to be beneficial in patients with small cell lung cancer (SCLC) without evidence of intracranial disease [50, 51]. In cases of limited disease and complete remission after chemotherapy, survival rates sum up to approximately 60 and 35% after 1-year and 2-years, respectively [50].

While the mean time to follow-up was longer than two years in the majority of analyzed studies, most studies also showed that hypopituitarism can already occur in the first year after treatment [13, 14, 16, 19–22, 29, 31, 33, 37]. In particular, Lamba et al. reported all hormonal deficiencies in their study after a mean time of 11–32 months [13]. All hypothalamic-pituitary insufficiencies occurred within 32 months after cRT in the study of Madaschi et al. [20]. Handisurya et al. showed in their longitudinal study that low levels of thyroid and sexual hormones occur in a significant proportion of patients within the first months after initiation of therapy [14]. The authors assumed that early hormonal impairment might be a coping mechanism of the body that contributes to the increased fatigue and weakness reported by many patients during or after cRT. While this toxicity is mostly interpreted as acute toxicity of cRT and/or side effect of steroid medication (used for symptomatic treatment of vasogenic edema), it is plausible that hormonal deficiencies, especially of anabolic hormones, and the lack of sexual functioning might contribute to an acute illness syndrome in this period [52]. The incidence of hormonal deficiencies within six months after treatment start has not yet been reported and a potential benefit of hormonal replacement therapies has not yet been studied, as most studies started their endocrine follow-up in the second year after cRT or later [14].

Are doses being used for WBRT within the range of potential harm to the HP axis?

Multiple dose regimes are common for WBRT ranging from $5 \times 4 = 20$ Gy, $10 \times 3 = 30$ Gy, $15 \times 2.5 = 37.5$ Gy and $20 \times 2 = 40$ Gy [53–56]. As the irradiated volume encompasses the entire cerebrum, the HP axis is always being treated with the total description dose. Several studies showed a dose-dependent effect on the development of hypopituitarism [10, 13, 22, 24, 56, 57]. So far, however, no threshold dose for hormonal impairment has been established. In the studies reviewed, doses to the pituitary and the hypothalamus ranged between 4 and 97 Gy. In half of the studies, a minimum dose to the HP area of less than 40 Gy was mentioned. Kyriakakis et al. suggested a threshold dose above 30 Gy to the HP area for long term endocrine surveillance [56]. This is thoroughly within the dose range of a WBRT.

The vast majority of patients in the analyzed studies was treated with conventionally fractionated RT (1.8–2.0 Gy per fraction). In case of WBRT, a hypo-fractionated regime is often used (e.g. $10 \times 3 = 30$ Gy). Assuming an $\alpha/ß$ ratio of 3 for normal brain tissue, this biologically equals significantly higher doses. The lower the dose per fraction, the greater the sparing of late-reaction tissue [58]. The HP axis behaves as a late-reacting tissue. A dose per fraction of more than 2 Gy administered over a shorter time period has a more severe effect on late-reacting tissues such as myelinated neurons and blood vessels [7, 59]. More profound cRT-induced hypopituitarism has been demonstrated with a dose per fraction greater than 2 Gy in older series [60]. So far, however, no direct comparative data exists clearly supporting this hypothesis.

Moreover, modern cancer treatment approaches like immunotherapy carry the risk of additional autoimmune hypophysitis [61]. To the best of our knowledge, no data exists on a synergistic risk of HP axis impairment with

cRT and immunotherapy. In expectation of a more frequent use of immunotherapy, this topic might become of importance in the future.

Certain limitations might limit the scope of our analysis: Data on onset of hypopituitarism and estimated dose to the HP area were not completely reported by all included studies. For instance, eight studies did not supply estimated doses to the HP axis at all. The time interval from cRT to assessment of endocrine deficiencies was often documented as a range. In those cases, it is not known, how many patients developed a deficiency within the first two years and how many patients after a longer follow-up period. These ranges were included in our overview (Table 1). Moreover, our analysis revealed a large variability in the prevalence of pituitary dysfunction (range 20–93%) and the total radiation dose to the HP axis (range 4–97 Gy) complicating interpretation. In addition, endocrine function testing varied substantially in the included studies. Also, as described by Merchant et al. in pediatric patients, pre-irradiation endocrinopathies might lead to a potential overestimation of the incidence of radiation-induced endocrinopathy [62].

In lack of sufficient data, our conclusions were drawn from subpopulations, retrospective and heterogenous patient groups. Thus, while our hypotheses fall short of translating into patient care strategies, it clearly demonstrates the current need for future studies regarding dose constraints in order to improve care delivery, such as a sparing approach in WBRT and/or endocrine follow-up. Such trials should especially emphasize on rigorous data acquisition including relevant dose constraints to the HP axis so that ongoing prospective efforts can better address these issues.

Nonetheless, we believe that the extrapolation of published data on hypopituitarism in adult cancer patients with nasopharyngeal cancer and brain tumors should suffice to justify early routine endocrinological follow-up (within the first year after cRT) for patients with brain metastases and a favorable prognosis receiving WBRT or in patients with SCLC in need for a PCI. In order to prevent hypopituitarism after WBRT, a sparing approach of the HP axis might be an option and appears technically feasible (unpublished data of our study group).

Conclusion

Hypopituitarism after cRT in adult cancer patients occurs frequently, is dose dependent and can evolve within the first year after RT. A search of the current literature returned no data on hypopituitarism after WBRT in particular. Especially when treating a subgroup of patients with a favorable prognosis with WBRT one should consider the presented follow-up data from patients receiving cRT of nasopharyngeal cancer and brain tumors, as hypopituitarism has been described to occur within the dose range of WBRT (20–40 Gy) without a dose threshold. On the basis of the current literature, our debate further highlights the need for endocrinological evaluation following cRT and should encourage the initiation of further studies regarding a sparing approach of the HP area during WBRT.

Abbreviations

ACTH: Adrenocorticotropin hormone; cRT: cranial radiotherapy; GH: Growth hormone; GPA: Graded prognostic assessment; Gy: Gray; HP: Hypothalamic-pituitary; LF/FSH: Luteinizing hormone/follicle-stimulating hormone; PCI: Prophylactic cranial irradiation; PRL: Prolactin; RPA: Recursive partioning analysis; RTOG: Radiation Therapy Oncology Group; SCLC: Small cell lung cancer; SRS: Stereotactic radiosurgery; TSH: Thyroid-stimulating hormone; WBRT: Whole brain radiotherapy

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Authors' contributions

All authors read and approved the final version of the manuscript. Idea and conception: SJ, DR, FF, JG. Data collection: SJ, PM, SS; DR. Data interpretation: SJ, DR, PM, FF, JG. Manuscript writing: SJ, PM, SS, DR, FF, JG. Manuscript revision: SJ, FF.

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Competing interests

DR and SJ are editorial board members of BMC Cancer. All authors declare that they have no competing interests.

Author details

[1]Department of Radiation Oncology, University of Lübeck, Ratzeburger Allee 160, 23538 Lübeck, Germany. [2]Department of Pediatrics and Adolescent Medicine, Friedrich-Alexander-University of Erlangen-Nürnberg, Erlangen, Germany. [3]Department of Endocrinology, University of Lübeck, Lübeck, Germany. [4]German Center for Diabetes Research (DZD), Neuherberg, Germany. [5]Private Practice of Radiation Oncology, Hannover, Germany.

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Hypothalamic-Pituitary Axis Dysfunction after Whole Brain Radiotherapy – A Cohort Study

JUDITH GEBAUER[1], PREENA MEHTA[2], FABIAN B. FAHLBUSCH[3], SEBASTIAN M. SCHMID[1], DIRK RADES[2] and STEFAN JANSSEN[2,4]

[1]*Institute for Endocrinology and Diabetes, University of Luebeck, Luebeck, Germany;*
[2]*Department of Radiation Oncology, University Hospital of Schleswig-Holstein, Campus Luebeck, Luebeck, Germany;*
[3]*Department of Pediatrics and Adolescent Medicine, University Hospital of Erlangen, Erlangen, Germany;*
[4]*Private Practice of Radiation Oncology, Hannover, Germany*

Abstract. *Background/Aim: Hypothalamic-pituitary (HT-P) dysfunction is one of the most common endocrine late effects following cranial radiotherapy. However, there are currently no specific data describing this complication in adult-onset cancer patients after whole brain radiotherapy (WBRT). The present cohort study aims to establish the prevalence of HT-P axis dysfunction in this group of patients. Patients and Methods: Twenty-six cancer patients previously treated with WBRT (median follow-up=20.5 months) received standardized endocrine check-up focusing on HT-P function. Results: In 50% of the patients, impaired hypothalamic-pituitary function was detected during follow-up. While functional loss of a single hormonal axis was evident in 34.6% of patients, 7.7% showed an impairment of multiple endocrine axes, and one patient developed adrenocorticotropic hormone deficiency. Hypothalamic-pituitary dysfunction did not directly correlate with the applied WBRT total doses. Conclusion: In our cohort, hypothalamic-pituitary dysfunction appeared to be common after WBRT and was diagnosed as early as 6 months following radiation. This finding highlights the need for routine endocrine follow-up even in patients with limited life expectancy.*

During the last decades, cancer survival rates have increased steadily mainly due to advances in early diagnosis and treatment (1). However, many cancer survivors are affected by therapy-related chronic health conditions. Endocrine sequelae are among the most frequent late effects of cancer therapy and affect up to 50 % of long-term childhood cancer survivors (2). Subsequently, specific long-term follow-up recommendations have been published for pediatric patients to ensure early diagnosis and treatment of endocrine sequelae (3). Only a small number of studies addressed adult-onset cancer survivors and for most cancer entities no long-term follow-up guidelines have been established so far (2).

Whole brain radiotherapy (WBRT) is commonly used in patients with multiple brain metastases or in a prophylactic setting (prophylactic cranial irradiation, PCI) in patients with small cell lung cancer (SCLC) (4). Due to the palliative nature of this therapy, endocrine assessment is mostly not performed. However, it has become obvious that endocrine dysfunction can lead to a reduction in quality of life (QoL), in addition to the potential neurocognitive degeneration induced by radiation (5).

Cranial radiotherapy (CR) represents a major risk factor for the development of hypothalamic-pituitary (HT-P) dysfunction. All hormonal axes of the anterior pituitary gland can be affected, resulting in isolated or combined deficiencies of: i) growth hormone (GH), ii) luteinizing hormone/follicle-stimulating hormone (LH/FSH), iii) thyroid-stimulating hormone (TSH), and iv) adrenocorticotropic hormone (ACTH) (2). Moreover, reduced hypothalamic release of the inhibitory neurotransmitter dopamine may occur and can result in hyperprolactinemia, which contributes to gonadal dysfunction (2). In adult-onset cancer survivors, the overall prevalence of HT-P dysfunction following CR ranges from 20 to 93%, depending on the follow-up time since CR and the applied radiation dose to the HT-P area [reviewed by Mehta *et al.* (6)].

Currently, there are no specific data on HT-P dysfunction following WBRT. However, the extrapolation of data from patients being treated with CR for non-pituitary brain tumors or nasopharynx carcinomas suggests that current WBRT dose levels are within a range of potential harm (6). Especially for long-term survivors with a good performance status prior to

Correspondence to: Stefan Janssen, Department of Radiation Oncology, University of Lübeck, Ratzeburger Allee 160, 23562 Lübeck, Germany. Tel: +49 45150045401, Fax: +49 45150045404, e-mail: st-janssen@gmx.net

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treatment or for small cell lung cancer (SCLC) patients without evidence of disease requiring a prophylactic cranial irradiation (PCI), endocrine dysfunction may be of clinical relevance. As endocrine dysfunction can lead to reduction in QoL, even patients facing limited life expectancy might benefit from a respective follow-up.

To our knowledge, the present cohort study is the first that evaluates the prevalence of HT-P axis dysfunction in adult-onset cancer survivors treated with WBRT. All patients received a standardized endocrine check-up, which, in the absence of specific guidelines for adult-onset cancer survivors, followed recommendations of the current Endocrine Society Clinical Practice guideline for "Hypothalamic-Pituitary and Growth Disorders in Survivors of Childhood Cancer" (3).

Patients and Methods

The local ethical committee of the University of Luebeck (19-409-A) approved the study protocol, which was in accordance with the Declaration of Helsinki. Due to the retrospective and non-interventional nature of the study, requirement of individual informed consent was waived.

All patients were treated with WBRT as part of their cancer treatment at the department of radiation oncology at the University hospital of Luebeck between 2007 and 2018. Inclusion criteria for this retrospective analysis were the following: i) a halted cerebral progress of their disease, ii) a follow-up interval of ≥6 months after completion of WBRT, and iii) a current endocrine check-up including parameters of HT-P function. Exclusion criteria were: i) patients with pituitary metastasis or adenoma and ii) patients receiving dopamine antagonists or agonist. Mainly, WBRT treatment schedules fell into two categories involving either a prophylactic scenario for SCLC patients without evidence of intracranial disease or a therapeutic WBRT with higher doses for patients with brain metastases. Table I summarizes patient- and treatment-related parameters.

Endocrine follow-up was performed in accordance with published guidelines for long-term childhood cancer survivors (3) and was routinely offered to every patient with a stable intracerebral disease surviving ≥6 months following the completion of WBRT. The examination included an early-morning measurement of: i) insulin-like growth factor (IGF1), ii) LH, iii) FSH, iv) testosterone and sex hormone binding globulin (SHBG) (men) or 17 beta-estradiol (women), respectively, v) prolactin, vi) TSH, vii) free thyroxine (fT4), viii) cortisol and ix) ACTH. In cases with indeterminate results, a control examination or a stimulation test (in cases with a suspected ACTH insufficiency) was performed (7). ACTH, cortisol, prolactin, LH, FSH, oestradiol, testosterone, SHBG, TSH and free T4 were measured by electro-chemiluminescence immunoassay (ECLIA); IGF-I was analyzed by chemiluminescence immunoassay (CIA) (both cobas platform, Roche diagnostics, Mannheim, Germany). All assays were performed in the routine clinical biochemistry laboratory at the University Medical Center Schleswig-Holstein, Campus Luebeck, where they have been regularly validated. For the identification of endocrine dysfunction, we applied assay-dependent age and sex-adjusted reference values.

GH deficiency was defined by an IGF-1 level below the reference value. LH/FSH deficiency in males was defined by a low serum testosterone in combination with low to (inappropriately) normal LH/FSH levels. In premenopausal females, LH/FSH deficiency was defined by a low oestradiol level, low or (inappropriately) normal LH/FSH levels and symptoms of oligo-/amenorrhoea, while in postmenopausal women diagnosis was based on the absence of elevated LH/FSH concentration (8). TSH deficiency was defined by low to (inappropriately) normal TSH level in combination with a low serum fT4. The diagnosis of hyperprolactinemia was based on prolactin levels above the upper reference limit (2). ACTH deficiency was suspected in patients with a morning cortisol <140 nmol/l in combination with low to normal ACTH level and confirmed with a standard dose (250 μg) corticotropin stimulation test if peak cortisol levels were below 500 nmol/l (9).

Furthermore, clinical examination and taking the patient's history took place on the day of endocrine assessment. This included an evaluation of the performance status (Karnofsky performance score, KPS), fatigue score (points: 1-10) and National Comprehensive Cancer Network (NCCN) distress thermometer, in which patients were asked to circle the number (range: 0-10) that describes how much distress they experienced during the past week, including the day of assessment (10).

Based on the prevalence of endocrine disorders, we compared age, radiation dose, the interval from WBRT to endocrine assessment and the above-mentioned scores per group using the non-parametric Mann-Whitney *U*-test, with a significance level of 5% in the IBM SPSS Statistics software for Windows, Version 25.0 (IBM Corp., Armonk, NY, USA). Correlations were analyzed by non-parametric Spearman's Rho test.

Table I. *Patient- and treatment-related parameters.*

Gender	
Female	16/26 (61.5%)
Male	10/26 (38.5%)
Age (years)	
At WBRT, median (range)	58 (36-81)
At the time of endocrine follow-up, median (range)	60 (37-90)
Time interval of WBRT to endocrine follow-up (months), median (range)	20.5 (6-151)
RT dose concepts, total dose/single dose (Gy)	
30/2	12
36/2	6
35-37.5/2.5	6
40/2	2
Primary cancer	
NSCLC	6
Breast	3
SCLC (brain metastases)	2
SCLC (PCI)	12
Urothelial	2

RT: Radiotherapy; Gy: Gray; NSCLC: non-small cell lung cancer; SCLC: small cell lung cancer; WBRT: whole brain radiotherapy; PCI: prophylactic cranial irradiation.

Results

A total of 26 patients, 16 females (61.5%), and 10 males (38.5%), were included in this retrospective study. The median age was 58 years (range=36-81) at WBRT and 60

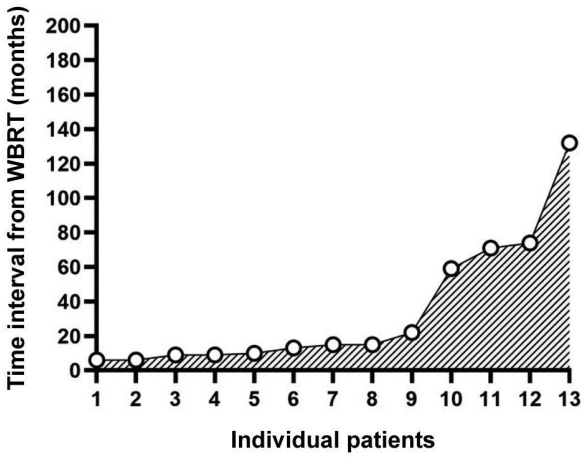

Figure 1. *Hypothalamic-pituitary dysfunction. This was assessed in 13/26 patients treated with whole brain radiotherapy (WBRT) in relation with time interval from WBRT.*

Table II. *Incidence of hypothalamic- pituitary dysfunction for all patients following whole brain radiotherapy.*

GH deficiency	2/25 (8.0%)*
LH/FSH deficiency	9/24 (37.5%)**
TSH deficiency	1/20 (5.0%)°
Hyperprolactinaemia	7/26 (26.9%)
ACTH deficiency	1/21 (4.8%)^
Patients with any HP dysfunction	13/26 (50.0%)
Patients with 1 HP dysfunction	9/26 (34.6%)
Patients with 2 HP dysfunctions	2/26 (7.7%)
Patients with 3 HP dysfunctions	2/26 (7.7%)

*One patient with missing data, **1 patient with hormone replacement therapy, 1 patient with endocrine therapy, °6 patients with ongoing levothyroxine treatment, ^5 patients with ongoing dexamethasone treatment. GH: Growth hormone; LH: luteinizing hormone; TSH: thyroid-stimulating hormone; ACTH: adrenocorticotropic hormone; FSH: follicle-stimulating hormone.

Table III. *Measurement of patients' parameters at the time of endocrine examination.*

KPS, median (range)	80 (50-100)
Fatigue score (1-10), median (range)	6 (0-10)
Distress score (0-10), median (range)	6 (0-10)
BMI (kg/m^2), median (range)	26.4 (20.3-39.8)

KPS: Karnofsky performance score; MMSE: mini-mental state examination; BMI: body mass index.

years (range=37-90) at the time of endocrinological examination (Table I). Twelve patients were treated with PCI, and 14 patients received a WBRT with a therapeutic dose for brain metastases. The median interval from WBRT to endocrine examination was 20.5 months (range=6-151) (Table I). Patients with HT-P dysfunction showed a trend towards shorter interval times, with a median interval of 15 months (range=6-132 months) (Figure 1).

HT-P function was impaired in 50.0% (13/26) of the patients (Table II). Nine of 26 patients (34.6%) presented with one HT-P axis dysfunction, and 2 of 26 patients with two (7.7%) or three (7.7%) dysfunctions, respectively. GH deficiency was present in 8.0% of the patients (2/25 patients) (Table II). LH/FSH deficiency was reported in 37.5% (9/24 patients). Five of 14 female patients (35.7 %, missing data for 2 patients) and 4 of 10 male patients (40.0%), respectively, were affected (Table II). Ten of 14 female patients (71.4%) were already postmenopausal, one had premature ovarian failure, one hysterectomy, and two did not experience any cycle irregularities. Two female patients were excluded from the analysis of LH/FSH deficiency; one patient on hormone replacement and another on endocrine therapy. Erectile dysfunction (ED) was reported by 3 of 7 men (42.9%, 3 with missing data); 2 of 3 (66.6%) of these patients were also diagnosed with LH/FSH deficiency.

Hyperprolactinemia was present in 7 of 26 patients (26.9%), of which 3 of 16 were females (18.8%) and 4 of 10 were males (40.0%) (Table II). TSH deficiency was only diagnosed in one patient (1/20, 5.0%); 6 patients already received levothyroxine treatment for hypothyroidism prior to WBRT and thus had to be excluded from the analysis. However, in 2 of 20 patients (10.0%), subclinical hypothyroidism was still present despite their hormone substitution. Furthermore, 2 of 20 patients (10.0%) presented with subclinical hyperthyroidism, characterized by low TSH levels but with fT3 and fT4 levels within the normal range. In one patient (1 of 21, 4.8%; 5 patients with ongoing dexamethasone treatment were excluded from the analysis), we were able to diagnose ACTH deficiency with significantly reduced morning cortisol levels (12 nmol/l). Hydrocortisone replacement was initiated immediately and the diagnosis was confirmed by two consecutive corticotropin stimulation tests; one performed directly after the diagnosis and the second one 3 months later. The patient was instructed regarding stress-dose and emergency glucocorticoid administration and obtained an emergency card and an emergency kit containing injectable high-dose glucocorticoid (3).

Patient assessment scores are given in Table III. At the time of endocrine follow-up, median KPS was 80 (range=50-100). Median fatigue score was 6 (range=1-9) and median points on the NCCN Distress thermometer were 6 (range=2-10). We did not find a significant difference in any of the above scores between patients with or without endocrine deficiencies. Moreover, no significant association was

detected between the applied total radiation dose, age, fatigue and distress scores, and the follow-up time from WBRT to endocrine assessment.

Discussion

Endocrine complications following CR are among the most frequent late onset effects of cancer treatment and, as a consequence of improved survival rates (11) affect an increasing number of cancer survivors (2). Although risk-adapted long-term follow-up of childhood cancer survivors has been implemented in the corresponding guidelines for several years, specific recommendations for adult-onset cancer survivors are lacking for most cancer entities. Considering that the number of newly diagnosed (mainly adult-onset) cancer patients exceeded 18 million worldwide in 2018 (12), there is still a large and growing group of cancer survivors with the need of risk-adapted follow-up examinations. Studies focusing on endocrine late effects of CR in adult-onset cancer survivors are rare and mostly based on survivors of non-pituitary brain tumors and nasopharyngeal cancer (13, 14). Currently, no specific data on HT-P dysfunction for adult cancer patients following WBRT exist (6).

The prevalence of hypopituitarism after CR for nasopharyngeal cancer and non-pituitary brain tumors is 20.0 to 93.0% but varies considerably between studies, depending on radiation dose to the HT-P area and the follow-up time since CR (6, 13). In this study, we demonstrated that half of the patients treated with WBRT developed at least one HT-P axis dysfunction and approximately 8.0 % were affected by multiple HT-P axis deficiencies initially diagnosed during routine follow-up.

LH/FSH deficiencies and hyperprolactinemia were the most common complications in our cohort, whereas only 8.0% presented with GH deficiency, as defined by low IGF-1. Although the somatotropic axis is considered as the most vulnerable one to radiation damage, GH deficiency in adult-onset cancer survivors seems less common compared to childhood cancer survivors (2). However, in a study by Kyriakakis *et al.*, which assessed pituitary dysfunction following CR in adult-onset non-pituitary brain tumors by performing regular dynamic pituitary testing, partial or severe GH deficiency was present in 86.9% of patients (15). As normal IGF1 levels do not exclude GH deficiency, the percentage of study patients affected by GH deficiency may have been higher than reported by us, as no routine stimulation testing was performed here. It is important to emphasize that, although GH deficiency in adults is associated with an impaired quality of life, GH replacement therapy in adult cancer survivors is controversial in terms of a potentially elevated risk for cancer recurrence and should thus remain a case-by-case decision, depending on the time of relapse-free follow-up and extent of impairment (2, 15).

Testosterone deficiency as a result of hypogonadotropic hypogonadism may present with depression symptoms, decreased muscle mass, increased abdominal fat and decreased energy as well as with typical signs of gonadal dysfunction (16). This may possibly be aggravated by concomitant hyperprolactinemia, which typically affects about one third of patients after CR (13, 17) and 27% of our study participants. ED can be caused by various conditions, but is also a common symptom of testosterone deficiency (18). This was reported in 42.9% of our male participants of which two thirds were also diagnosed with LH/FSH deficiency. This is in line with results from a previous study assessing endocrine late effects in a larger cohort of adults treated for brain tumors, Hodgkin and non-Hodgkin lymphoma, in which ED was reported in 41.1% of male participants (19). In females, premature menopause as a consequence of LH/FSH deficiency is associated with osteoporosis, an increased risk of atherosclerosis and with symptoms of depression (2). Sex hormone substitution is generally recommended in these patients to avoid cardiovascular complications and reduced bone mass (2). Moreover, hypogonadism was already suggested as a possible contributor to increased fatigue and weakness after radiotherapy (16), which was also demonstrated in our study. Consequently, regular assessment of sex hormone levels in patients following WBRT can facilitate early diagnosis and treatment of hypogonadism and contribute to an improved QoL.

Interestingly, we were able to diagnose ACTH deficiency in an asymptomatic patient as part of the endocrine check-up. Clinical signs of adrenal insufficiency, such as weakness/fatigue, susceptibility to infections or abdominal pain/vomiting were absent. The patient was also affected by TSH deficiency and levothyroxine treatment was initiated several weeks after the beginning of hydrocortisone replacement therapy. ACTH deficiency is the most life-threatening HT-P deficiency and an early diagnosis and start of replacement therapy are essential to avoid adrenal crisis (8).

Noteworthy, our study focused on the detection of secondary hypothyreoidism, meanwhile 20.0% of study participants presented with subclinical primary hyper- or hypothyroidism. When adding patients who already received levothyroxine treatment due to previously diagnosed hypothyroidism (23%) plus one patient (4%) with TSH deficiency, almost half of the study population was affected by thyroid dysfunctions, clearly exceeding the prevalence of these disorders in the general population (20).

Our results emphasize the need for a routine endocrine follow-up of patients treated with WBRT within their first post-treatment year. Our cohort showed HT-P axis dysfunctions as early as 6 months after the end of radiation therapy. In contrast to CR studies that demonstrate dose dependency (21-23), no such correlation was found in our cohort following WBRT, further arguing for shorter endocrine follow-up intervals. In line with this finding, the median follow-up time from WBRT to endocrine assessment

of our whole study collective was 20.5 months, while patients with a HT-P dysfunction had a trend towards shorter median follow-up times of 15 months.

Depending on the study, a distress score of more than 3-4 indicates patients with clinically elevated levels of distress (24, 25). Mock *et al*. rated fatigue in a score of 1-10 (26). The distress and fatigue scores of our collective were elevated with a median of 6. The finding that these scores were not significantly different between patients with and without endocrine deficiencies should not discourage from endocrine testing. Quite the contrary, treatment of these deficiencies might improve QoL in affected patients, a prospective effect that was not encompassed by the retrospective design of our study.

Our retrospective cohort study has several limitations. Although all patients treated with WBRT for more than a decade were considered as potential study participants, only 26 patients met the inclusion criteria. In this respect, overrepresentation of hypothyroidism might represent an oversampling bias of our cohort study. Although the radiation dose to the HT-P area has been demonstrated to be a major risk factor for the development of HT-P complications (2), there was no significant difference regarding the radiation dose in patients with or without an HT-P axis dysfunction. Furthermore, diagnosis of HT-P dysfunction was mainly based on single evaluations of hormone levels. In most cases, the HT-P dysfunction has not been validated by stimulation tests. However, this approach has been suggested in a review of Fernandez *et al*. summarizing evidence for basal hormone measurements in the evaluation of HT-P axis dysfunctions and has been (partially) incorporated into the current HT-P guidelines for childhood cancer survivors (3, 7). Moreover, our pretreatment endocrine assessment was only based on retrospective records of clinically evident HT-P dysfunction or intake of respective medication and did not include the determination of hormone levels before the start of radiotherapy.

To our knowledge, this study is the first to assess HT-P function in cancer survivors treated with WBRT. We could demonstrate that HT-P axis dysfunctions develop frequently in these patients and can occur early following WBRT. Thus, patients with limited life expectancy may also be affected. Therefore, routine endocrine follow-up is essential to ensure early diagnosis and treatment of endocrine complications to maintain QoL. Moreover, sparing of the HT-P axis like sparing of the hippocampus (5) could be of value as no threshold radiation dose to develop HT-P dysfunction is established and therefore the dose to this area should be as low as reasonably achievable. Our group already showed feasibility of such a sparing approach using a VMAT technique (27). Against the background of a low prevalence of metastases within the HT-P region (28), we plan a prospective trial to further investigate this approach and overcome the limitations of this retrospective study.

Conflicts of Interest

On behalf of all Authors, the corresponding author states that there are no conflicts of interest related to this study.

Authors' Contributions

JG, SS, DR, and FF participated in the design of the study, SJ, PM, and JG provided data. SJ, FF, SS, JG and PM performed the analyses of the data. SJ and DR drafted the manuscript, which has been reviewed and approved by all Authors.

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Prevalence of metastases within the hypothalamic-pituitary area in patients with brain metastases

Stefan Janssen[1,2,7*†], Preena Mehta[1†], Tobias Bartscht[3], Sebastian M. Schmid[4,5], Fabian B. Fahlbusch[6] and Dirk Rades[1]

Abstract

Aim: To quantify the prevalence of brain metastases involving the hypothalamic-pituitary (HT-P) area.

Introduction: Cognitive impairment and fatigue are common side effects of whole brain irradiation (WBI) comprising the quality of life (QoL) for survivors. While the former is related to radiation-induced hippocampal injury, the latter could be secondary to hormonal disbalance as a consequence of radiation of the HT-P area. Thus, sparing both regions from higher irradiation doses could reduce these sequelae.

Methods: T1 contrast medium enhanced magnetic resonance imaging (MRI) scans of 865 patients with brain metastases (4,280 metastases) were reviewed. HT-P area was individually contoured with a margin of 5 mm in order to evaluate the prevalence of brain metastases in this region.

Results: Involvement of the hypothalamic region was found in 26 patients (involvement rate of 3% for patients and 1% for metastases), involvement of the pituitary gland in 9 patients (1% for patients and < 1% for metastases). Binary logistical regression analysis revealed the presence of > 10 brain metastases as the only factor associated with hypothalamic involvement while no distinct factor was associated with an involvement of the pituitary gland.

Conclusion: The low prevalence of metastases within the HT-P area in patients with brain metastases calls for further studies examining whether sparing of this region might improve patients QoL.

Keywords: Brain metastases, Whole brain radiotherapy, Hormonal impairment, Hypothalamus/pituitary gland sparing, QoL

Introduction

Brain metastases are the most common intracranial tumors and occur in approximately 10 to 30% of adult cancer patients [1]. Even in modern times of high precision radiotherapy, whole brain irradiation (WBI) is an option for patients with multiple brain metastases or as prophylactic cranial irradiation (PCI) in patients with small-cell lung cancer (SCLC). However, cognitive impairment and fatigue are common long-term side effects that relevantly comprise the quality of life (QoL) for survivors [2]. Hippocampal neural stem-cell injury due to irradiation might play a mechanistic role in memory decline [3] while affection of the hypothalamic-pituitary (HT-P) axis further promotes symptoms like fatigue [4]. Impaired HT-P axis activity is common after radiotherapy of brain tumors [5–8] as well as head-and-neck cancer [9–14]. Although the degree of irradiation damage is dose-dependent [7], relevant impairment of the HT-P axis can already occur upon low doses of ~ 18 Gy [15].

Long-term endocrine follow-up data from adult survivors of childhood and adolescent cancer [16, 17] who received WBI (mainly 24 Gy) show that the vast majority of patients developed some kind of HT-P insufficiency. The hormonal deficiency typically follows a predictable course [15] with growth-hormone (GH) secretion being the most sensitive to radiotherapy. In fact, it might be the first or only hormone deficiency apparent [16]. Clinically, radiation-induced GH deficiency in adults mimics signs and symptoms of adult GH deficiency syndrome,

* Correspondence: st-janssen@gmx.ne
†S. Janssen and P. Mehta contributed equally to this work.
[1]Department of Radiation Oncology, University of Lübeck, Lübeck, Germany
[2]Private Practice of Radiation Oncology, Hannover, Germany
Full list of author information is available at the end of the article

in particular increased fatigue and impaired QoL [18]. Thus, radiation-related endocrinopathy affects the patient not only physiologically, but also psychologically [16]. Other WBI-associated HT-P endocrinopathies include gonadotropin (follicle-stimulating hormone and luteinising hormone) deficiency, thyroid-stimulating hormone (TSH) deficiency, adrenocorticotropic hormone (ACTH) deficiency and hyperprolactinaemia [16].

As GH replacement therapy might improve the above symptoms [18] among survivors of childhood acute lymphoblastic leukemia and CNS tumors, provocative endocrine follow-up testing for isolated GH deficiency, e.g. by insulin tolerance test (ITT), is crucial to establish a robust diagnosis for the timely implementation of GH replacement therapy [17]. In this context, a priori avoidance of radiation-induced injury of the HT-P region might pose a feasible alternative for certain patients, especially in the palliative setting of brain metastases where preservation of QoL is the main objective. In accordance to a phase II study showing better memory function QoL when sparing hippocampus area during WBI [19], sparing the HT-P area during WBI may result in better endocrine and functional outcome.

To assess the practicability of HT-P sparing in patients with brain metastases detailed knowledge on the prevalence of metastatic lesions within this potential avoidance region is crucial. As scientific data is scarce to date, the present study aims to systematically assess the prevalence of HT-P metastases in patients with brain metastases.

Methods

Pre-treatment gadolinium-enhanced T1-weighted magnetic resonance image (MRI) datasets of 865 patients with brain metastases from the years 2014–2018 were reviewed at the University of Luebeck, Germany. The HT-P area was contoured on axial planes for each patient as described previously by others [20, 21]. In short, minimal requirements for sufficient contouring and delineation were as following: CT images (axial planes) were fused to images obtained via T1-weighted MRI images (gadolinium contrast enhanced) acquired on 1.5 T resonance scans with a slice thickness of 1.5 mm. The hypothalamus and pituitary gland (including the pituitary stalk) were contoured on T1-weighted axial MRI sequences and a margin of 5 mm was added (see Fig. 1) [20, 21].

We excluded examinations not fulfilling a minimum of standards e.g. providing only one MRI sequence, blurred sequences, slice thickness > 1.5 mm or no contrast medium.

For each patient, data regarding the primary tumor type, age at the diagnosis of brain metastases, gender, maximum size of brain metastases, and the total number of brain metastases was recorded (Table 1). In case of more than 30 brain metastases, the number was rated as ≥30. Patients with leptomeningeal disease and previous brain irradiation were excluded from analysis.

According to previously published analysis on hippocampal involvement, the number of metastases within 5 mm from the pituitary gland as well as from the hypothalamus was correlated with the above-mentioned variables. A binary logistical regression model using a backward step-wise approach was developed, and a two-sided p value of < 0.05 was considered statistically significant [22]. For the logistic regression analysis of the number of brain metastasis, we chose to analyze $n = 1–3$ vs. $n > 10$, as several randomized studies support the use of radiosurgery in 1–3 lesions [23, 24]. Moreover, some authors have shown a survival difference for this threshold [25]. Additionally, the Graded Prognostic Assessment (GPA) from the Radiation Therapy Oncology Group (RTOG) and the diagnosis-specific GPA score (ds-GPA) also differentiates between > 3 and less than three metastases [26, 27].

The protocol of this retrospective study was approved by the local ethics committee of the University of Luebeck (# 19-075A).

Results

A total number of 4,280 brain metastases in 865 patients were identified with a mean of 5 metastases per patient.

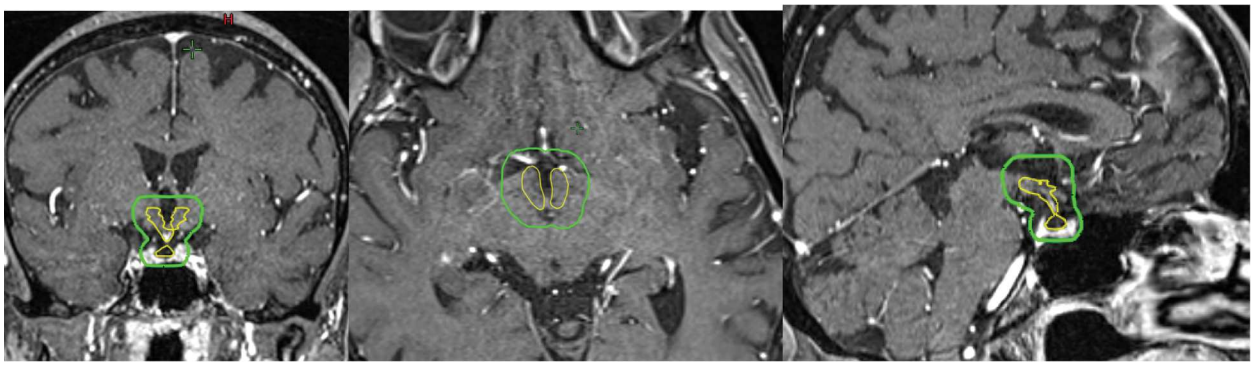

Fig. 1 Contouring example of the HT-P axis (gadolinium enhanced T1 MRI)

Table 1 Patient characteristics (NSCLC: non-small cell lung cancer, SCLC: small cell lung cancer)

Sex	
male	434 (50%)
female	431 (50%)
Age	Mean: 64 years (29–90)
< 64 years	424 (49%)
> 64 years	441 (51%)
Primary tumor entity	*involvement of hypothalamus and pituitary gland*
NSCLC	401 (46%) 13/401
SCLC	121 (14%) 8/121
Breast	106 (12%) 5/106
Melanoma	62 (7%) 1/62
Renal	27 (3%) 0/27
Colorectal	35 (4%) 2/35
Other	113 (13%) 6/113
Number of metastases	Mean: 5, median: 2 (range: 1–30)
Maximum size	Mean: 2 cm, median: 1.8 cm (range: 0.2 cm to 11 cm)

Individual maximum size of metastases ranged from 0.2 to 11 cm (median: 1.8 cm). Patients mean age was 64 years (range: 29–90 years) and the primary tumor entity was non-small cell lung cancer (NSCLC) in 46% of the patients. Patient and disease characteristics are summarized in Table 1. Involvement of the hypothalamus region (hypothalamus + 5 mm) was found in 26 patients translating to HT involvement of ~ 3% of patients and ~ 1% of all metastases. Involvement of the pituitary region (pituitary gland + 5 mm) was observed in 9 patients, i.e. 1% of all patients and < 1% of all metastases, respectively. Binary logistical regression models revealed a high number of metastases, i.e. > 10 vs. < 3 metastases as the only factor significantly associated with hypothalamic involvement ($p = 0.0002$; Table 2). In contrast, examined factors were not related to the involvement of the pituitary gland region (Table 3).

Discussion

This retrospective analysis of 865 patients with a cumulative total of 4,280 brain metastases reveals that only ~ 4% of all metastases were located within the HT-P area. This study clearly extends our knowledge on the low prevalence of hypothalamic and pituitary region metastases.

Until now, most of current data were based on smaller studies, case reports, and reviews [28–34]. Marsh et al. reported on 155 retrospectively analyzed patients with a total of 935 brain metastases and only one case (< 1%) of pituitary involvement [29].

Metastases within the HT-P area are relatively rare and can arise from various tumors like thyroid carcinoma [28, 30, 31], melanoma [32], breast cancer [33] and prostate cancer [34]. Smaller case series could not identify a specific tumor predisposing for hypothalamic/pituitary metastases. These observations are in line with the structured analysis of our large cohort. There is no specific tumor entity correlated with HT-P involvement.

Brain metastases are common for many cancers and can be treated with surgery, high precision radiotherapy or, in case of multiple metastases, WBI. Furthermore, PCI can be applied in patients with SCLC, respectively. Although beneficial for oncological treatment, WBI is accompanied with various side effects such as neurocognitive impairment, fatigue, and endocrine disorders, all resulting in reduced QoL.

The HT-P area is highly sensible for irradiation and impairment of the endocrine hypothalamus-pituitary axes is common after radiotherapy. The somatotropic axis is most vulnerable to irradiation damage and can occur after doses as low as 18 Gy [15] or even 10 Gy in children or young adults [35]. However, endocrine disturbance can further include all other hormonal axis, i.e. the corticotropic, thyreotropic, and gonadotropic axis on the level of the hypothalamus and/or pituitary, respectively. Long term survivors of cancer with radiotherapy for head-and-neck tumors developed a dysfunction of at least one hormonal axis (46%), 24% had impairment of two axes, and 3% had a dysfunction in three axes [10].

Table 2 Logistic regression analysis for incidence of metastases within 5 mm of the hypothalamus

Variable	Point estimate	95% Wald confidence limits	*p*-value
Age (age > 64 years vs. <=64 years)	2.019	0.845–4.824	0.1140
Sex (female vs. male)	0.820	0.335–2.009	0.6644
Tumor type (NSCLC as reference)			0.7543
SCLC	1.916	0.638–5.749	
Breast	1.427	0.327–6.219	
Melanoma/renal/colorectal	1.348	0.341–5.337	
Maximal diameter (> = 1.9 cm vs. <=1.8 cm)	2.146	0.899–5.125	0.0854
Number of brain metastases (> 10 vs. 1–3)	6.668	2.643–16.827	0.0002

Table 3 Logistic regression analysis for incidence of metastases within 5 mm of the pituitary gland

Variable	Point estimate	95% Wald confidence limits	*p*-value
Age (age > 64 years vs. <=64 years)	0.858	0.224–3.280	0.8238
Sex (female vs male)	1.722	0.380–7.794	0.4805
Tumor type (NSCLC as reference)			0.8121
SCLC	0.585	0.066–5.184	
Breast	1.118	0.189–6.614	
Melanoma/renal/colorectal	0.389	0.044–3.417	
Maximal diameter (> = 1.9 cm vs. <=1.8 cm)	2.108	0.518–8.576	0.2976
Number of brain metastases (> 10 vs 1–3)	2.410	0.427–13.601	0.4892

Other studies report on hypopituitarism of at least one axis in up to 93% of patients treated with radiotherapy for nasopharynx cancer [12] and Madaschi et al. revealed clinically relevant hormone deficiency for the somatotropic (29%), corticotropic (22%), thyreotripic (14%) and gonadotropic (4%) axis in patients irradiated for extraselar brain tumors [36]. Together, the overall prevalence of any degree of hypopituitarism is considered 25–100% in patients treated for nasopharynx cancer and 37–77% in patients with intracerebral tumors [14]. Of note, irradiation induced impairment of HP-axes appears to be a late onset sequela accompanied by a progression in severity over time but can also appear within the first year after radiotherapy [14].

All mentioned side effects after radiotherapy are dose-dependent [9, 10, 15, 37–40] with a clearly increased incidence of HT-P axes impairments at doses above 30 Gy. However, there are no data defining a clinically significant threshold [39]. Accordingly, established dose-fractionation concepts in WBI (10×3 Gy, 15×2.5 Gy or 20×2 Gy) are within the dose range of potential impairment.

It is tempting to speculate that avoiding irradiation of the HT-P area by HT-P sparing WBI technique might lower endocrine and neurocognitive burden of classical WBI and preserve patients QoL. Recently, the groups of Fan and Marsh, respectively, showed that sparing of the hippocampus and the HT-P axis during WBI is technically feasible [20, 41]. However, the question remains whether the oncological prognosis is acceptable when sparing HT-P area during WBI. The reported low prevalence below 4% of HT-P involvement in our large cohort of patients with brain metastases argues for further studies to justify the concept of HT-P area sparing WBI in analogy to the hippocampus sparing technique recently introduced by Gondi and colleagues [19]. On the background of a low risk of 8.6% for hippocampal metastases in 371 patients with brain metastases [22], hippocampus sparing WBI has been established in many radiation oncology centers worldwide.

Further supporting oncological safety of a HT-P area sparing WBI concept, the only predictor for involvement of the hypothalamus region was a total number of more than 10 brain metastases. Interestingly, Gondi et al. excluded patients with more than 10 brain metastases inherently from their analysis [22]. Considering the exclusion criteria of Gondi et al. and the results of our present study, we would recommend a HT-P sparing approach only in patients with less than 10 brain metastases. Although stereotactic radiosurgery (SRS) or fractionated stereotactic radiotherapy (FSRT) are increasingly applied concepts in patients with a limited number of brain metastases, there are still clinical indications for therapeutic and prophylactic WBI. Reducing potential side effects by a HT-P sparing WBI approach could improve patient's endocrine outcome and QoL.

To our knowledge, our study involved the largest cohort regarding the assessment of the prevalence of HT-P area metastases by now. Our findings are somewhat limited by the fact that data were analyzed retrospectively and we cannot report on endocrine function in our patients. Moreover, our study did not cover radio-surgical approaches or their combination with WBI. Also, we did not examine the total volume of metastasis (as opposed to the diameter of the largest lesion) as proxy for intracranial tumor burden, which might additionally pose a potential risk factor for HT-P region involvement and decision making in HT-P sparing radiotherapy.

However, we are confident that the low prevalence of HT-P metastases seems worthy of further clinical evaluation of a sparing approach in selected patients. Although potential benefits of HT-P sparing WBI appear likely, a prospective intervention study is needed.

Conclusion

Only 4% of brain metastases in this large study cohort of 865 patients with 4,280 metastases were located within the HT-P area. HT-P radiation-sparing might pose a treatment option for patients with a limited number of brain metastases and those without involvement of the HT-P

region analogue to current hippocampus sparing approaches. As palliative therapy, WBI treatment courses should aim to improve or at least stabilize QoL. A prospective study evaluating potential endocrine and functional benefit of such a sparing approach during WBI is planned.

Abbreviations

ACTH: Adrenocorticotropic hormone; FSRT: Fractionated stereotactic radiotherapy; GH: Growth hormone; GPA: Graded Prognostic Assessment; HT-P: Hypothalamic-pituitary; ITT: Insulin tolerance test; MRI: Magnetic resonance imaging; NSCLC: Non-small cell lung cancer; PCI: Prophylactic cranial irradiation; QoL: Quality of life; RTOG: Radiation Therapy Oncology Group; SCLC: Small cell lung cancer; SRS: Stereotactic radiosurgery; TSH: Thyroid-stimulating hormone; WBI: Whole brain irradiation

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Authors' contributions

All authors read and approved the final version of the manuscript. Idea and conception: SJ, DR. Data collection: SJ, PM, TB, SS; DR. Data interpretation: SJ, DR, PM, FF. Manuscript writing: SJ, PM, TB, SS, DR, FF.

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Ethics approval and consent to participate

The protocol of this retrospective study was approved by the local ethics committee of the University of Luebeck (# 19-075A).

Consent for publication

Not applicable

Competing interests

The authors declare that they have no competing interests

Author details

[1]Department of Radiation Oncology, University of Lübeck, Lübeck, Germany. [2]Private Practice of Radiation Oncology, Hannover, Germany. [3]Department of Haematology and Oncology, University of Lübeck, Lübeck, Germany. [4]Department of Endocrinology, University of Lübeck, Lübeck, Germany. [5]German Center for Diabetes Research (DZD), Neuherberg, Germany. [6]Department of Pediatrics and Adolescent Medicine, Friedrich-Alexander-University of Erlangen-Nürnberg, Erlangen, Germany. [7]Klinik für Strahlentherapie, Universität zu Lübeck, Ratzeburger Allee 160, Haus 40, 23562 Lübeck, Germany.

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RESEARCH ARTICLE Open Access

Sparing the hippocampus and the hypothalamic- pituitary region during whole brain radiotherapy: a volumetric modulated arc therapy planning study

P. Mehta[1†], S. Janssen[1,2*†], F. B. Fahlbusch[3], S. M. Schmid[4,5], J. Gebauer[4], F. Cremers[1], C. Ziemann[1], M. Tartz[2] and D. Rades[1]

Abstract

Background: Feasibility testing of a simultaneous sparing approach of hippocampus, hypothalamus and pituitary gland in patients undergoing whole-brain radiotherapy (WBRT) with and without a concomitant boost to metastatic sites.

Introduction: Cognitive impairment and hormonal dysfunction are common side effects of cranial radiotherapy. A reduced dose application to the patho-physiologically involved functional brain areas, i.e. hippocampus, hypothalamus and pituitary gland, could reduce these common side effects. While hippocampal sparing is already a common practice to improve cognitive outcome, technical experience of additional combined sparing of the hypothalamus/pituitary gland (HT-P) is insufficient.

Methods: Twenty patients were included in the planning study. In 11 patients, a total dose of 36 Gy of WBRT (2 Gy per fraction) plus a simultaneous integrated boost (SIB) of 9 Gy (0.5 Gy per fraction, total dose: 45 Gy) to the brain metastases was applied. In 9 patients, prophylactic cranial irradiation (PCI) was simulated with a total dose of 30 Gy (2 Gy per fraction). In both patient cohorts, a sparing approach of the hippocampus and the HT-P area was simulated during WBRT. For all treatment plans, volumetric modulated arc therapy (VMAT) was used. Quality assurance included assessment of homogeneity, conformality and target coverage.

Results: The mean dose to the hippocampus and HT-P region was limited to less than 50% of the prescribed dose to the planning target volume (PTV) in all treatment plans. Dose homogeneity (HI) of the target volume was satisfying (median HI = 0.16 for WBRT+SIB and 0.1 for PCI) and target coverage (conformation number, CN) was not compromised (median CN = 0.82 for SIB and 0.86 for PCI).

(Continued on next page)

* Correspondence: Stefan.janssen@UKSH.de
†P. Mehta and S. Janssen contributed equally to this work.
[1]Department of Radiation Oncology, University of Lübeck, Lübeck, Germany
[2]Private Practice of Radiation Oncology, Hannover, Germany
Full list of author information is available at the end of the article

(Continued from previous page)
Conclusion: Simultaneous dose reduction to the hippocampus and the HT-P area did not compromise the PTV coverage in patients undergoing WBRT+SIB or PCI using VMAT. While the feasibility of the presented approach is promising, prospective neurologic, endocrine outcome and safety studies are required.

Keywords: Whole brain radiotherapy (WBRT), Brain metastases, Hippocampus sparing, Hypothalamus, Pituitary gland, Volumetric modulated arc therapy (VMAT)

Background

Up to 30% of cancer patients develop brain metastases during their disease [1]. Despite the increasing use of high precision radiation techniques for small volumes [2–4], whole brain radiotherapy (WBRT) remains the treatment of choice for patients with multiple brain metastases [5] as well as for prophylactic cranial irradiation (PCI) in patients with small cell lung cancer (SCLC) [6, 7]. However, cognitive and neuroendocrine impairment following cranial radiotherapy remains a concern. Mechanistically, damage to the stem cells within the hippocampus might play a major role in the observed memory decline [8]. In line with this finding, Gondi et al. were able to show that conformal avoidance of the hippocampus during WBRT was associated with preservation of memory function and quality of life (QoL), as compared to a non-sparing historical series [9]. Apart from neurocognitive decline, another common sequela of cranial radiation therapy is functional endocrine impairment due to critical doses to the hypothalamus and the pituitary gland. A significant percentage of patients with brain tumors [10–12] and head and neck cancer [13–15] develop hormonal deficiencies after radiotherapy. At the time of our research period, endocrine follow-up data after WBRT was scarce. Nevertheless, it has been shown that hormonal changes can occur after applied doses as low as 18 Gy in patients with radiotherapy to head and neck cancers and brain tumors [13]. This dichotomy led us to investigate a combined sparing approach involving both the hippocampal and the hypothalamus/pituitary gland (HT-P) area during WBRT. In our planning study we examined the feasibility of such an approach using volumetric modulated arc therapy (VMAT).

Methods

The computed tomography (CT)-data sets of 20 patients who previously received WBRT in our institution from 2017 to 2019 were included. The CT-scans were performed with a Siemens Biograph 40 m with a slice thickness of 3 mm. To facilitate contouring of the brain structures and metastases T1-weighted contrast-enhanced magnetic resonance images (MRI) were fused to the planning CT. In addition to the contoured hippocampus (according the RTOG 0933 study [9]), the hypothalamus and pituitary gland (including the pituitary stalk) were contoured and planning risk volumes (PRV) were created using a 5-mm margin [16, 17]. CT data sets with metastases within 5 mm around the avoidance structures were excluded from this planning study. Further, the whole brain planning target volume (PTV) was contoured and cropped by the hippocampus and HT-P as a planning risk volume (PRV). An auxiliary PTV structure consisting of the part of the optimization PTV surrounding the HT-P and hippocampus helped to control the dose drop in the immediate vicinity of the hippocampus and the HT-P (Fig. 1).

Treatment plans were then created using Eclipse 15.5 (Varian Medical Systems, Inc., Palo Alto, CA, USA) for a Clinac DHX linear accelerator equipped with a Millennium 120 MLC. The Photon Optimizer (PO) and Anisotropic Analytical Algorithm (AAA), both in versions 15.5.11, were utilized [18]. The normalization point was set to 100% of the mean dose of the target volume. All treatment plans were created on the basis of sparing both the hippocampal and the HT-P area, concomitantly avoiding dose peaks to lenses, eyes, chiasm, optical nerves and brainstem. 11 of 20 patients were planned with a dose of 18×2 Gy = 36 Gy as a WBRT with a SIB (18×0.5 Gy = 9 Gy, total dose: 45 Gy) to the metastases resulting in a total dose of 18×2.5 Gy in the area of the SIB, whereas the other 9 patients were planned as a PCI with a dose of 15×2 Gy = 30 Gy. A VMAT treatment plan was generated individually for each patient by a medical physicist (P.M.). Table 1 summarizes patient and treatment parameters.

Two different planning approaches were used for therapeutic WBRT with SIB to metastases and for PCI. Both were planned with three 6 Megavolt (MV) photon beam full arcs using the VMAT technique. For the treatment plans including SIB two of the arcs had a rotation collimator of 320° and 40°, while in the third arc the collimator was rotated by 90° and the jaws were adjusted to the length of the organs of risk (OAR), i.e. the hypothalamus, hippocampus and pituitary gland to guarantee homogenous dose coverage between the OAR. For the PCI plans the collimator angles were 280°, 90° and 11° respectively. Couch rotations of 15°, 0°, and 345° were used. These different techniques provided the optimal combined sparing approaches of both hippocampal/HT-P structures and ocular lenses, while concomitantly ensuring the best PTV-dose coverage.

The treatment plans were generated with the goal to achieve a dose of lower than 50% of the prescription dose

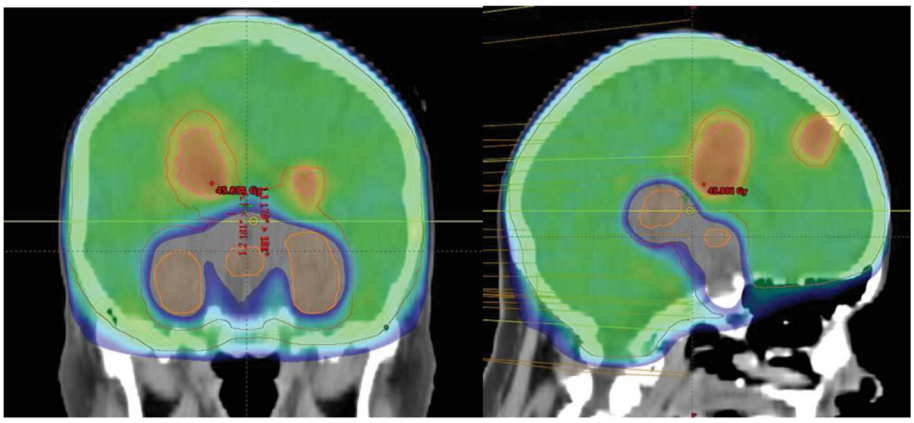

Fig. 1 a and b Representative example of a VMAT plan with avoidance of the hippocampus and HT-P area and SIB (color-wash, coronar (**a**) and sagittal (**b**) view, dose levels: blue: 25–32 Gy, cyan: 32–37 Gy, green: 37–42 Gy, yellow: 42–44 Gy, orange: 44–46 Gy, red: > 46 Gy)

of the PTV in the sparing regions without compromising conformal dose coverage. Additionally, mean maximum doses to the ocular lenses were kept below 10 Gy. Homogeneity index (HI) was calculated as follows [19]:

$$HI = \frac{D_{2\%}\text{-}D_{98\%}}{D_{median}}$$

Where $D_{x\%}$ is the dose which is at least delivered to x% of the volume and D_{median} is the median dose. Smaller values of HI correspond to a more homogeneous irradiation of the target volume, and a value of 0 corresponds to a completely homogeneous dose distribution within the target [16].

Conformality index or conformation number (CN) was calculated according the formula introduced by van't Riet et al. in 1997 [20]:

Table 1 Patient and treatment related parameters, HI = homogeneity index, HT-P = hypothalamus-pituitary area, CN = conformation number, SIB: simultaneous integrated boost, n.a. =not applicable; m = male, f = female

	PTV volume [cm^3]	Hippocampal volume [cm^3]	Hippocampal HT-P- + 5 mm volumes V_{PRV} [cm^3]	Number of metastases	Metastases volumes [cm^3]	% SIB of PTV	D95 (%)	Hippocampal HT-P- + 5 mm mean dose D_{PRV} [Gy]	HI	CN
1	1748.1	12.6	58.9	n.a.	n.a.		96.4	12.8	0.09	0.85
2	2048.5	12.6	58.0	n.a.	n.a.		95.9	14.1	0.17	0.86
3	2140.7	6.1	43.9	n.a.	n.a.		95.5	14.6	0.12	0.86
4	2083.5	10.7	65.6	n.a.	n.a.		96.4	14.2	0.09	0.86
5	1974.4	4.5	43.2	n.a.	n.a.		95.3	14.9	0.12	0.86
6	1797.2	4.7	59.6	n.a.	n.a.		95.3	14.9	0.11	0.84
7	1805.3	8.1	51.4	n.a.	n.a.		96.7	15	0.08	0.86
8	1521.4	10.4	58.8	n.a.	n.a.		96.4	14.9	0.09	0.82
9	1991.4	6.7	45.9	n.a.	n.a.		96.4	15	0.09	0.87
10	1593.9	7.4	47.9	2	5.2	0.33	98.1	15.1	0.11	0.84
11	1924.7	22.4	51.2	1	9.4	0.49	98.1	15	0.13	0.85
12	1761.8	2.7	38.9	2	7.1	0.40	98.0	14.1	0.14	0.84
13	1436.4	4.0	39.6	1	15.9	1.11	97.8	14.9	0.19	0.81
14	1860.0	4.7	44.1	1	4.1	0.22	98.0	13.2	0.16	0.86
15	1802.7	6.0	42.2	9	31.7	1.76	97.6	14	0.214	0.79
16	2286.7	10.1	65.8	3	73.0	3.19	97.3	14.2	0.16	0.79
17	1641.1	8.8	53.6	1	6.5	0.40	98.3	13.6	0.17	0.85
18	2029.0	9.6	59.4	1	105.0	5.17	97.5	15.4	0.15	0.72
19	1941.3	2.5	34.3	4	20.6	1.06	97.6	14.8	0.23	0.82
20	1781.4	5.8	41.5	2	19.8	1.11	97.6	15	0.13	0.82

$$CN = \frac{TV_{RI}}{TV} \times \frac{TV_{RI}}{V_{RI}}$$

Where TV_{RI} is target volume covered by the reference isodose (95% isodose), TV is the target volume and V_{RI} is the volume of the reference isodose (95% isodose). The conformation number reaches a value between 0 and 1. A value of 1 represents a reference isodose covering the exact target volume without irradiation of healthy tissue and indicates optimal conformation. On the other hand, a value of 0 equals no conformation at all [20].

The target coverage (TC) was measured as the volume within the target receiving a dose greater or equal to the prescription dose (VTpres) divided by the target volume (TV) [21].

$$TC = \frac{V_{Tpres}}{TV}$$

No patients consent was obtained as all patients' data were irreversibly anonymized before analysis. The in silico analysis included CT database data only. In this form, the study was approved by the local ethics committee of the University of Lübeck, Germany (reference number: 19-075A).

Results

The median total brain volume including the avoidance region was 1832.7 cm^3 (range: 1436.4 cm^3–2286.7 cm^3). The median volume of the hippocampus/HT-P area (including a margin of 5 mm) was 43.9 cm^3 (range: 34.3–65.8 cm^3). For patients receiving a SIB to brain metastases, the median value of the SIB volume was 15.9 cm^3 (range: 5.2–105.0 cm^3). Number of metastases treated with a SIB ranged from 1 to 9 (median: 2). The median percentage of the SIB volumes of the entire planning treatment volume (PTV) was 3.3% (range: 1.3–11.6%). In the 11 WBRT plans including SIB to brain metastases the median delivered dose to the hippocampus/HT-P area was 14.9 Gy (range: 13.2–16.2 Gy). In the 9 PCI plans the delivered dose to the hippocampus/HT-P could be held below 15Gy (median: 14.8 Gy, range: 12.8–15.0 Gy). Maximum dose to the ocular lenses was limited to 10 Gy for each patient. Median maximum dose for all plans within in lenses was 8.3 Gy. The corresponding values for the eyes, the brainstem, chiasma and optic nerves were 25/30 Gy, 31/40 Gy, 29/33 Gy and 31/39 Gy for prophylactic and therapeutic plans, respectively. The median homogeneity index was 0.16 (range: 0.11–0.23) for the SIB plans and 0.10 (range: 0.08–0.17) for the PCI plans. The median $D_{95\%}$ for the WBRT plans including SIB 97.8% (range: 97.3–98.3%) and 96.4% (range: 95.5–96.7%) for PCI plans. The median conformity index was 0.85 for all plans, 0.82 for the therapeutic plans including SIB (range: 0.72–0.86) and 0.86 for the PCI plans (range: 0.82–0.87). The target coverage was 0.7 (range: 6.3–8.7) for prophylactic and therapeutic plans, respectively. Figure 2a and b show the dose volume histograms (DVH) for SIB plans and PCI plans.

Discussion

WBRT for brain metastases can impair neuro-cognitive functions in terms of memory loss and reduced QoL [8]. Neural stem cells within the hippocampus may play an important role in this patho-mechanism. In RTOG 0933, avoidance of the hippocampus during WBRT was associated with preservation of memory and QoL as compared with a non-sparing historical series [9]. Preliminary analysis of a randomized phase III trial confirms the hypothesis of preserved neurocognitive function while achieving similar intracranial control and survival [22].

Functional endocrine deficiencies after brain radiotherapy are common [23]. Long term follow-up studies indicate that radiation induced HT-P dysfunction may occur in up to 80% of patients and is often associated with an adverse impact on growth, body image, skeletal health, fertility, sexual function and physical and psychological health [24]. Several studies showed the hormonal impairment to be dose-dependent with an increased incidence at doses above 30 Gy [17]. Until now, most data of radiation induced endocrine sequelae in adults originate from patients being treated for head and neck cancer and non-pituitary brain tumors. Endocrine follow-up data on hormonal changes after WBRT are scarce [23]. As the hormonal impairment is described to be dose-dependent, limiting the dose to the HT-P area could be beneficial. During WBRT, this could be realized with a sparing approach analogue to the hippocampus sparing technique introduced by Gondi et al. [9], as previously discussed by us [23]. Arguments against a theoretical benefit of such a sparing approach are the limited life expectancy of patients with brain metastases and lower doses to the HT-P region compared to RT in head and neck cancers and brain tumors. Still, in a current review of literature we could reveal a potential effect of RT for doses of less than 30 Gy being within the dose range of WBRT [23]. Moreover, the potential negative endocrine effect might already occur as early as within the first year after RT [23]. This is of relevance especially for patients with a more favorable prognosis, e.g. for patients with good performance status and a limited tumor burden or in the prophylactic setting in SCLC patients. For this reason, we carried out a planning approach for both, therapeutic and prophylactic scenarios encompassing a combined sparing of the hippocampus and the HT-P area.

According to the present VMAT planning study, simultaneous sparing the hippocampus and the HT-P axis

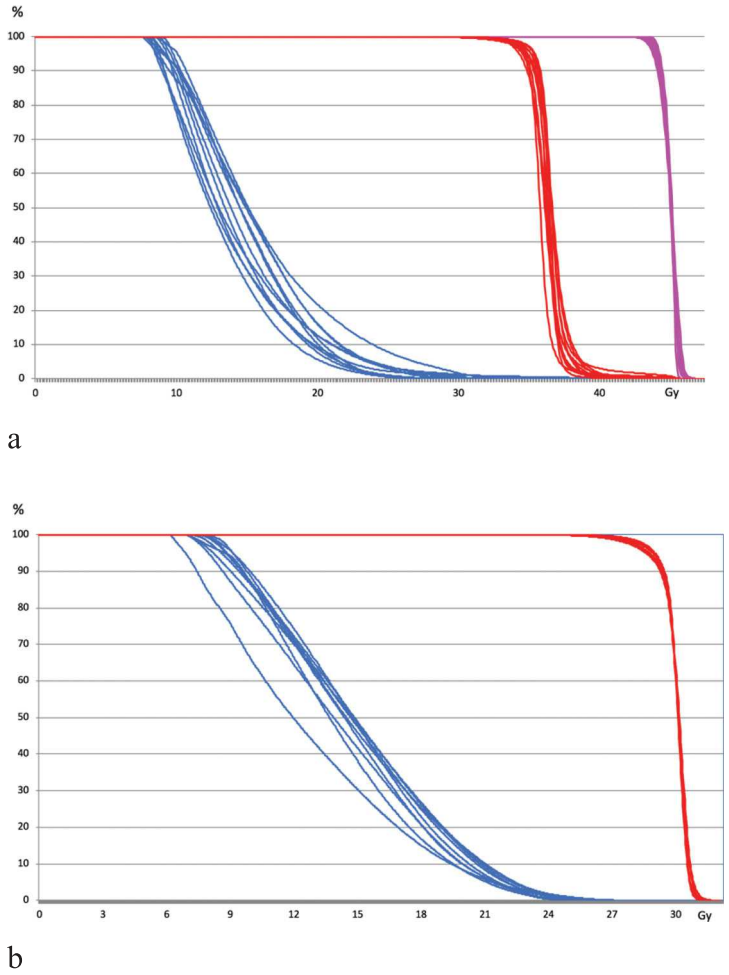

Fig. 2 a and b Representative cumulative dose volume histograms (DVH) for SIB plans (**a**) and PCI plans (**b**). Blue: sparing region, red: PTV whole brain, pink: SIB

was feasible. The dose to the avoidance regions could be limited to less than 50% of the prescribed doses to the PTV. For the hippocampus, several dose constraints were suggested in previous studies. In the RTOG 0933 protocol, the dose to 100% of hippocampus did not exceed 9 Gy ($D_{100\%} < 9$ Gy), and the maximal hippocampal dose did not exceed 16 Gy [9]. Other studies involving hippocampal sparing approaches in patients treated with WBRT delivered mean doses to the hippocampi ranging from 5 Gy to 20 Gy, depending on radiation techniques and total doses [24]. Until now, no threshold dose for the HT-P area has been established. Kyriakakis et al. assessed the effects of cranial RT on pituitary function in adults with gliomas distant to the HT-P axis. The dose exposure of the HT-P axis was correlated with individual axis dysfunction to establish dose thresholds. The authors argued for the implementation of long-term endocrine surveillance in RT cases exceeding 30 Gy to the HT-P axis [25].

In a study by Fan et al., in which the hippocampus and the HT-P area were spared simultaneously using intensity modulated radiotherapy (IMRT), the hippocampus received a mean dose of 9.6 Gy, and the hypothalamus and the pituitary gland mean doses of 11.06 and 10.66 Gy, respectively [16]. In the present study, the mean doses to the hippocampus and the HT-P area were 15 Gy i.e. comparably higher. This finding might result from higher doses to the total brain volume in our study when compared to previous studies (36 Gy and 30 Gy versus 30 Gy and 25 Gy) [9, 16]. In the present study, the metastases even received 45 Gy. Moreover, we also attempted to spare the ocular lenses during WBRT and to achieve conformal dose coverage. However, our boost doses to a maximum 45Gy (normo-fractionated) are a rather cautious approach and are currently under discussion.

In contrast to Fan et al., who were the first group describing a combined sparing approach of the

hippocampus and the HT-P area using IMRT, we chose a VMAT approach. For hippocampal sparing during WBRT (without the HT-P area), the use of VMAT was shown to significantly improve dose distribution in terms of target coverage and homogeneity [26–28]. In the study of Sood et al., the use of a VMAT-technique also reduced mean and maximum doses to other organs at risk (OAR) such as cochleae and parotid glands [29]. These promising results inspired us to use VMAT in our approach to spare the hippocampus and the HT-P. In addition, when comparing our VMAT data to the IMRT approach used by Fan et al., we were able to achieve less heterogeneity with respect to the dose coverage of the PTV (homogeneity index: 0.23 vs. 0.10 and 0.16 in our study). Further, we kept the maximum dose to the ocular lenses below 10 Gy; no information concerning the doses to the lenses was provided by Fan et al. [16]. Another advantage of VMAT is its faster treatment delivery. For hippocampal sparing in WBRT, Wang et al. demonstrated a significant shorter treatment time of approximately 25% using VMAT in comparison to IMRT [30]. Moreover, Rong et al. found faster treatment delivery of VMAT when compared to IMRT [31].

For hippocampal sparing in WBRT, slightly superior homogeneity indices and target coverage were found for tomotherapy when compared to IMRT and VMAT [31, 32]. However, the availability of tomotherapy is limited, and the treatment planning time is significantly longer. Another possibility to improve the quality of the treatment planning could be an inclined head position [33, 34]. In a recently published study, Zheng et al. showed feasibility using VMAT and tomotherapy for HT-P and hippocampal axis sparing for cranio-spinal irradiation. They also found that VMAT was able to achieve good conformality [35].

In line with data from hippocampal sparing WBRT, simultaneous sparing of the hippocampus and HT-P via VMAT delivered highly conformal and fast-to-apply treatment plans, resulting in a direct advantage for patients in their daily treatment sessions.

A sparing approach of certain brain regions bears the risk of jeopardizing oncologic outcomes in terms of intracranial control and consecutive overall survival. Therefore, the estimated risk of metastases within spared structures and their proximity have to be taken into careful consideration. Gondi et al. deemed hippocampus sparing WBRT safe with an estimated risk of peri-hippocampal metastases of 8.6% [36]. Our group has recently analyzed 865 patients with 4280 metastases and showed an incidence of involvement of the HT-P area of approximately 4% [37]. Against that background, an approach of sparing the HT-P area in addition to the hippocampus during WBRT appears reasonable. Thus, in order to reveal a clinical meaningful effect of HT-P region sparing within WBRT, a prospective study is planned evaluating a sparing approach with simultaneous avoidance of the hippocampus and the HT-P area including endocrine follow-up. The current planning study, which is a prerequisite for the planned prospective trial, showed technical feasibility of such an approach using VMAT even for dose escalation with a SIB. In the absence of safety data, the presented approach remains experimental and should not be applied outside a clinical study.

Conclusion

Simultaneous dose reduction to the hippocampus and the HT-P area did not compromise the PTV coverage in patients undergoing WBRT+SIB or PCI when using VMAT. While the feasibility of the presented approach is promising, prospective neurologic and endocrine outcome studies are required to properly evaluate the usefulness of such an approach.

Abbreviations

CN: Conformation number; DVH: Dose volume histograms; IMRT: Intensity modulated radiotherapy; HI: Homogeneity index; HT-P: Hypothalamus/pituitary gland; PCI: Prophylactic cranial irradiation; PTV: Planning target volume; SCLC: Small cell lung cancer; SIB: Simultaneous integrated boost; TC: Target coverage; OAR: Organs at risk; VMAT: Volumetric modulated arc therapy; WBRT: Whole brain radiotherapy

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Authors' contributions

All authors have read and approved the final version of the manuscript. Idea and conception: SJ, DR, FF, PM, FC, MT, SS. Planning; PM, MT, FC, CZ. Interpretation: SJ, DR, FF, FC, MT, CZ SS, JG. Manuscript writing: SJ, FF, JG, SS, DR.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

Administrative permission was acquired to access data used in the research. The analysis was not an intervention study. Only fully anonymized CT dataset were used. The study was approved by the ethics committee of the University of Lübeck with administrative permission to access the raw data (reference number: 19-075A). The study was conducted in accordance with the principles laid out in the Declaration of Helsinki and in accordance with the principles of Good Clinical Practice.

Consent for publication

Not applicable.

Competing interests

DR and SJ are editorial board members of BMC Cancer, all authors declare that they have no competing interests.

Author details

[1]Department of Radiation Oncology, University of Lübeck, Lübeck, Germany. [2]Private Practice of Radiation Oncology, Hannover, Germany. [3]Department of Pediatrics and Adolescent Medicine, Friedrich-Alexander-University of Erlangen-Nürnberg, Erlangen, Germany. [4]Institute for Endocrinology and Diabetes, University of Lübeck, Lübeck, Germany. [5]German Center for Diabetes Research (DZD), Neuherberg, Germany.

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