Sundhedsstyrelsen
Danish Health and Medicines Authority

NKR Nationale Kliniske Retningslinjer

Marts 2014

Høringssvar til National Klinisk Retningslinje for behandling af hjernemetastaser

1. Kræftens Bekæmpelse
2. Dansk Neuroonkologisk Gruppe (DNOG)
3. Dansk Onkologisk Lungecancer Gruppe (DOLG)
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7. Peer Review Bruce Mickey
8. Peer Review Christer Lindquist
9. Peer Review Ernest Doodoos

Kræftens Bekæmpelse

13. marts 2014

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UNDER PROTEKTION AF
HENDES MAJESTÆT DRONNINGEN

Høringssvar til national klinisk retningslinje for behandling af hjernemetastaser

Helt overordnet finder Kræftens Bekæmpelse det meget positivt, at der er taget initiativ til udarbejdelse af retningslinjer for behandling af hjernemetastaser. En stor del af kræftpatienter udvikler i deres sygdomsforløb metastaser i hjernen. Kræftens Bekæmpelse håber, at retningslinjerne vil bidrage til at sikre den store patientgruppe bedre, ensartet behandling på tværs af landet, som bygger på den tilgængelige evidens på området. Kræftens Bekæmpelse har været repræsenteret i referencegruppen og finder som helhed, at retningslinjen er godt gennemarbejdet med relevante fokuserede spørgsmål inden for et felt, hvor det er vanskeligt at opnå høj evidens.

Det fremgår af kommissoriet, at arbejdet med den nationale kliniske retningslinje for hjernemetastaser – foruden kortlægning af evidens for behandling af hjernemetastaser – også skal omfatte patientinformation, overvejelser omkring implementering af de kliniske retningslinjer og beskrivelse af behov for kvalitetsudvikling og monitorering.

Kræftens Bekæmpelse savner en nærmere beskrivelse af ovenstående områder. Det gælder især en nærmere beskrivelse af implementeringen, herunder hvilken betydning retningslinjerne får for patientforløbet. Kræftens Bekæmpelse vil desuden med interesse følge, hvilke indikatorer som udvælges til at overvåge kvaliteten af behandlingen og implementeringen af retningslinjerne.

Kræftens Bekæmpelse forventer, at arbejdet med de kliniske retningslinjer følges op af tilstrækkelig og uddybende patientinformation. Det er vigtigt, at patienter har mulighed for at finde relevant information om deres behandlingsmuligheder, og de kliniske retningslinjer kan ikke læses af patienter. Kræftens Bekæmpelse stiller sig gerne til rådighed til at deltage i dette arbejde, såfremt det måtte ønskes.

Kræftens Bekæmpelse ser endvidere gerne, at patientperspektivet, dvs. hvordan patienternes livskvalitet under og efter behandlingerne er eller udvikler sig, får en fremtrædende plads i evalueringen af behandlingen.

Kræftens Bekæmpelse har i forhold til indholdet af de nationale kliniske retningslinjer særligt hæftet sig ved:

- at med de fokuserede spørgsmål (resume: bilag 5) kommer retningslinjen gennem den væsentligste del af de kliniske situationer, der opstår hos patienter med hjernemetastaser.

- at retningslinjen kun helt perifert berører hjernemetastaser fra tumorer, som er særlig kemofølsomme (småceller lungecancer, germinative tumorer og lymfomer). Retningslinjer for disse særlig følsomme tumorer skal søges i vejledninger for de respektive sygdomme.

- at evidenskvaliteten som helhed er bedømt lav til meget lav, hvilket skal tages i betragtning ved implementering af retningslinjerne i forhold til de allerede eksisterende procedurer og retningslinjer i regionerne. Dette er også nævnt i implementeringsdelen, således at de kliniske erfaringer, man har på de enkelte centre, stadig kan komme patienterne til gode.

- at der er i de fleste situationer er lav evidens ved monitorering af livskvalitet og PROM (Patient Recorded Outcome Measures) ved behandling for hjernemetastaser Det må således være op til den behandlende afdeling at monitorere dette hos den enkelte patient i forhold til prognose. Desuden vil Kræftens Bekæmpelse anbefale, at der nationalt følges op med en systematisk monitorering.

- at der behandlingsmæssigt ikke skelnes mellem metastasernes histopatologiske oprindelse (kræftformen) bortset fra hjernemetastaser ved særlig kemofølsomme tumorer. Stråledosis tænkes således formentligt som en standard eller afgøres i det enkelte tilfælde.

Kræftens Bekæmpelse stiller sig gerne til rådighed, såfremt ovenstående ønskes uddybet eller præciseret.

Med venlig hilsen

Leif Vestergaard Pedersen
Adm. direktør

Høringsvar nr. 2 – Dansk Neuroonkologisk Gruppe (DNOG)

Mange tak for muligheden for at kommentere på de fremsendte retningslinjer for behandling af hjernemetastaser.
Vi, i Dansk Neuroonkologisk Gruppe, har med interesse læst udkastet igennem og må sige at vi er imponeret over den systematik der brugt ved gennemgangen af de enkelte fokusspørgsmål og at man har besvaret nogen af de spørgsmål man står med, når patienter med hjernemetastaser melder sig i klinikken og skal behandles.

Imidlertid savner vi nogle anbefalinger/retningslinjer når man taler om ”nationale retningslinjer” og det første fokusspørgsmål som melder sig hos alle sundhedsmedarbejdere, når de står med en patient med en/flere hjernemetastaser er: Hvad gør jeg nu? Hvem kontakter jeg? Mange af medlemmerne i DNOG har ofte oplevet uhensigtsmæssige forløb hos patienter med hjernemetastaser – specielt hvor patienten uden kendt primær/ekstrakraniel cancer gennemgår lange (og ofte unødvendige) udredningsforløb i medicinske afdelinger/diagnostiske centre, etc. inden de bliver henvist til neurokirurgisk vurdering.

Kirurgerne i DNOG mangler at få besvaret om man undlader at operere når der er > 1 hjernemetastase? Det er svært at afdække/belyse en problemstilling, når man begrænser antallet af fokusspørgsmål, men spørgsmålet om hvordan man forholder sig ved > 1 metastase er et hyppigt stillet spørgsmål i den daglige klinik og bør belyses med samme grundighed som de øvrige fokusspørgsmål. Når dette spørgsmål er besvaret ville det være muligt at lave et overskuelig flowdiagram som guider klinikeren igennem problemstilling ”Hvad gør jeg med en patient som har en hjernemetastase”.

Vi håber at arbejdsgruppen under SST vil tage disse mangler til efterretning og få dem implementeret i den endelige version af de nationale retningslinjer til behandling af hjernemetastaser.

På vegne af DNOG
René

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Kommentar vedrørende:

National Klinisk retningslinje for behandling af hjernemetastaser.

Retningslinien har ikke været fremsendt til høring i Dansk Onkologisk Lungecancer Gruppe (DOLG). Da vi imidlertid har fået kendskab til udkastet til Retningslinjen via omtale i Dagens medicin har vi i DOLG drøftet indholdet.

Vi synes i DOLG at det kunne have været hensigtsmæssigt at sende Retningslinjen i høring hos de grupper som behandler mange af disse patienter, idet vi har ganske mange lungecancer patienter med denne problemstilling.

Overordnet finder vi Retningslinjen afbalanceret og generelt indenfor almindelig klinisk praksis. Et diskussionspunkt er den mest hensigtsmæssige behandling af multiple hjernemetastaser og hvor skæringspunktet skal være mellem stereotaktisk stråleterapi eller helhjernebestråling. Men formuleringen i Retningslinjen vurderes at være tilstrækkelig rummelig og med vægt på individualisering således at vi i DOLG vurderer at det er indenfor daglig klinisk praksis.

På vegne af Dansk Onkologisk Lungecancer Gruppe,

Jens Benn Sørensen, overlæge, dr.med.
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17.3.2014

Høringssvar nr. 4 vedr. NKR behandling af hjernemetastaser – Ministeret for Sundhed og Forebyggelse

Ved e-mail af 24. februar 2014 har Sundhedsstyrelsen anmodet Ministeriet for Sundhed og Forebyggelse om bemærkninger til ovennævnte retningslinjer.

Ministeriet for Sundhed og Forebyggelse har ingen bemærkninger.

Med venlig hilsen

Frederik Rechenback Enelund

Fuldmægtig

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MINISTERIET
FOR SUNDHED
OG FOREBYGGELSE

Til sundhedsstyrelsen

DANSKE REGIONER

Svar på høring vedr. kliniske retningslinjer for hjernemetastaser

18-03-2014
Sag nr. 14/1370
Dokumentnr. 16177/14
Josefina Hindenburg Krausing

Hermed fremsendes kommentarer fra regionerne på høring vedr. national klinisk retningslinje vedr. " behandling af hjernemetastaser" i høring.

Generelt roser regionerne retningslinjerne, og peger bl.a. på, at det er et flot og grundigt arbejde, og af høj faglig kvalitet. Imidlertid peges på, at retningslinjerne er hæmmet af den relativt svage evidens på området.

Det bemærkes, at retningslinjen sætter høj faglig standart for behandling af patienter med hjernemetastaser, som ligger tæt op af den behandling, der allerede tilbydes.

Konkrete bemærkninger:

Side 7: Foreslås afsnittet omformuleret til følgende ordlyd: "Det er god praksis kun efter nøje overvejelse af tilbyde fornyet strålebehandling eller resektion lokalt, da der kun foreligger lav evidens for den gavnlige effekt efter tidligere helhjernebestråling".

Side 17 (linje 3 afsnit 3.2) står der "Derimod bør centralt beliggende metastaser og metastaser beliggende i elokvente funktionelle områder af hjernen behandles med stereotaktisk strålebehandling" dette foreslås omformuleret til "Ved centralt beliggende metastaser og metastaser beliggende i elokvente funktionelle områder af hjernen bør stereotaktisk strålebehandling overvejes som behandling".
Begrundelsen for denne forslagsændring er, at den nuværende formulering indikerer, at det vil være forkert at behandle patienter med disse lokaliseringer af metastaser kirurgisk. Dette er ikke tilfældet, ligesom der ikke er god evidens for denne antagelse. Eksempelvis kan der være tale om patienter med et betydeligt ødem omkring en metastase i et elokvent område uden signifikant effekt af steorid behandling, eller patienter som tidligere har modtaget stereotaktisk strålebehandling af samme metastase og siden har udviklet vækst / strålefølger / strålenekrose.

Side 23 (afsnit 3 i andre overvejelser): Samme kommentar som overfor, reformulering anbefales.

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Side 37 (afsnit 3 i andre overvejelser, sidste sætning): Her anvendes en ”blød” formulering om at behandling med Unikalk bør overvejes ved steroid behandling for at undgå osteoporose. Formuleringen ”bør overvejes” anvendes i den kliniske vejledning om forhold for hvilke arbejdsgruppen finder der er ”svag/betinget anbefaling for”. Der anbefales en reformulering så det fremgår, at kalk behandling anbefales ved steroid behandling, evt. med henvisning til SST’s anbefaling vedrørende dette”.

Der er indsneget sig en fejl under Implementering, side 46, linje 3: ”speciallæger i psykiatri” bør erstattes med ”speciallæger i onkologi” eller blot ”speciallæger”.

Øvrige bemærkninger:
Det skal afslutningsvis noteres som meget positivt, at der i retningslinjen lægges op til - som det opfattes - et randomiseret dansk multicenter studie der skal sammenligne kirurgisk behandling og stereotaktiske radiokirurgisk behandling i tilfælde hvor disse behandlinger må anses få ligeværdige.

Med venlig hilsen

Josefina Hindenburg Krausing

Høring:

National Klinisk Retningslinje for Behandling af Hjernemetastaser

Til: Sundhedsstyrelsen

Vi har med stor interesse læst den nationale kliniske retningslinje for behandling af Hjernemetastaser. Dansk Selskab for Fysioterapi tillader sig på eget initiativ at indgive høringssvar. Såfremt der er opklarende spørgsmål eller yderligere behov, er vi naturligvis behjælpelige.

Dette høringssvar er udarbejdet med input fra et fagligt selskab under Dansk selskab for fysioterapi:

- Dansk Selskab for neurologisk fysioterapi

Dansk Selskab for Onkologisk og Palliativ Fysioterapi tilslutter sig kommentarerne fra dette samlede høringssvar, men kommer ikke på nuværende tidspunkt med særskilt høringsbidrag.

Vi håber, Sundhedsstyrelsen og arbejdsgruppen finder kommentarerne i høringssvaret anvendeligt at arbejde videre med i kvalificeringen af den Nationale kliniske Retningslinje for behandling af hjernemetastaser.

Overordnede Kommentarer

Dansk Selskab for fysioterapi anerkender afgrænsningen af denne NKR til kun at indbefatte medicinsk og operativ behandling af hjernemetastaser.

Vi noterer os at Dansk Selskab for Neurologisk Fysioterapi (DSNF), fremhæver at intensiv træning kan reducere bivirkningerne ved kemoterapibehandling.

Videre har DSNF erfaringer med samt opfattelsen af at genoptræning og palliation kan bidrage til øget mobilitet, velvære og livskvalitet hos den enkelte patient, men at det altid skal afvejes af, hvad der tjener den enkelte patient bedst.

Dansk Selskab for Neurologisk fysioterapi er et speciale indenfor fysioterapi, hvor der via specialiseret fysioterapi udøves genoptræning, vedligeholdende træning og palliativ terapi til målgruppen med hjernemetastaser. Denne terapiform er en velanvendt del-modalitet i den samlede efterbehandlings-/ livsforlængende indsats af personer med hjernemetastaser.

Det ville derfor tjene NKR-hjernemetastaser, om Sundhedsstyrelsen i afgrænsnings afsnittet anerkendte, at behandlingen af hjernemetastaser også kan omhandler fysioterapeutisk genoptræning samt andre palliations former end de nævnte i denne NKR. Dette kunne eksempelvis skrives som:

"Fysioterapeutisk genoptræning, og anden palliativ behandling indgår ikke i denne nationale retningslinje for behandling af hjernemetastaser, men det skal understreges, at forudsætningen for et helhedsorienteret behandlingsforløb er, at patienterne for så vidt sygdomsforløbet tillader også tilbydes genoptræning samt fysisk og psykisk palliation.

Vi håber, at Sundhedsstyrelsen hilser budskabet om fokus på genoptræning og anden palliativ behandling velkomment, og finder det relevant kort at nævne væsentlige non-farmakologiske og non-operative behandlingsindgreb ved hjernemetastaser.

Med venlig hilsen

Martin B. Josefsen
Formand for Dansk Selskab for Fysioterapi

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Høringssvar på NKR om hjernemetastaser, af Dansk Selskab for Neurologisk Fysioterapi

Retningslinjen henvender sig til neurokirurgen og retter sig mod operation versus bestråling af hjernen enten som stereotaktisk bestråling eller helhjernebestråling eller en kombination af alle indgreb. Der er desuden et spørgsmål om steroid behandling bør gives i høje eller moderate doser og om bestråling skal kombineres med kemoterapi.

I spørgsmål 6 hvor spørgsmålet drejer sig om man bør supplere hjernebestrålingen med kemoterapi, er kemoterapiens bivirkninger nævnt som en betydelig faktor, som kan være med til at man fravælger denne. Her kunne det måske være på sin plads at nævne, at pt ved fysisk aktivitet og intensiv træning kan nedsætte bivirkninger af kemo såsom kvalme, madlede og træthed, hvilket jeg mener der er god evidens for.
I forhold til Steroid i høje doser kan fysisk træning måske også nedsætte bivirkninger, men jeg ved ikke om der er evidens for det - jeg tror det faktisk ikke, selv om steroid fx nedsætter kalkindholdet i knoglerne og på sigt har mange uheldige bivirkninger fx osteoporose. Mange af patienterne når jo ikke at leve så længe at steroidens uheldige bivirkninger viser sig!

Der er altså alene tale om, at fysioterapi kan være en hjælp imod bivirkninger af behandlingen, og jeg tror ikke der er udarbejdet studier der viser noget om at fysisk aktivitet har nogen som helst virkning på de bivirkninger der fremkommer ved bestråling af hjernen. Mange pt har ingen fysiske gener af bestråling ud over træthed. Det er på sigt (måneder til år) de får epileptiske anfald, kognitive forstyrrelser og symptomer som ved demens og det kommer som følge af stråleskader, som vi ikke kan gøre noget ved.

At man i forordet nævner at det handler om mobilitet, socialt liv og livskvalitet kommer slet ikke frem i den ret tekniske forholden sig til behandlingen, ud over at det hele tiden skal afvejes hvad der tjener pt. bedst. Fysioterapi i nogen form hører ikke hjemme i nogen af anbefalingerne, men det kunne måske nævnes i en slags efterskrift at fysisk træning og palliativ behandling vil kunne øge pt's mobilitet, velvære og livskvalitet.

NATIONAL KLINISK RETNINGSLINJE FOR BEHANDLING AF HJERNEMETASTASER

The National Clinical Guidelines for the Management of Brain Metastases

The authors of the National Clinical Guidelines for the Management of Brain Metastases should be commended for a job well done. The nine focused questions are highly relevant to clinical decision making for patients with brain metastases, and are worthy of the considerable effort they have put forth. The literature pertinent to these questions has been thoroughly reviewed, as recorded in Appendix 8, and the quality of the evidence provided by this literature has been rigorously graded, as illustrated in the tables that follow each question. The authors have demonstrated that most of the evidence available to address these focused questions is of low quality, and for that reason they have been forced to make weak or conditional recommendations, but they have supplemented these recommendations with insightful advice based on their personal experience. I believe that their comments, located within the section labeled "Afgrænsning af patientgruppe" in the Introduction and in the sections labeled "Arbejdsgruppens overvejelser" are as important as the Guidelines themselves, and should be emphasized.

Focused Question 1: Bør man foretage operativ resektion og helhjernebestråling eller operativ resektion alene eller helhjernebestråling alene hos patienter med en solitær hjernemetastase tilgængelig for kirurgi og med gennemsnitlig prognose?

(Should we perform surgical resection and whole brain radiation or surgical resection alone or whole brain radiation alone in patients with a solitary brain metastasis who have an average prognosis and are candidates for surgery?)

↑ Overvej at kombinere operativ resektion og helhjernebestråling ved behandling af en solitær hjernemetastase hos patienter med gennemsnitlig prognose frem for operativ resektion alene eller helhjernebestråling alene (⊕⊕◯◯).

(Consider combining surgical resection and WBRT for the treatment of a solitary brain metastasis in patients with an average prognosis rather than surgical resection alone or WBRT alone)

Despite the conditional nature of this recommendation, and the acknowledgement that the quality of the evidence on which it is based is "low," I am concerned that it has the potential to cause harm if applied to all patients with what has been defined as an "average prognosis." As the authors have indicated, it seems clear that whole brain radiation after the surgical resection of a single metastasis decreases the risk of recurrence, both locally and elsewhere within the brain. What must also be considered is the toxicity of whole brain radiation . Because this toxicity is delayed, it may not be of practical significance for patients with a limited life expectancy, but it may be disabling for those who survive a year or more. The National Clinical Guidelines have defined "average prognosis" by combining Recursive Partitioning Analysis Class I and II, thus creating a group which will include a significant number of patients who are likely to survive a year of more. For example, a meta-analysis of analysis of 2350 patients from 7 RTOG studies revealed that 20% of them lived longer than one year and that nearly 10% lived longer than two years (Barnholtz-Sloan, Yu et al. (2012)).

The literature on the ongoing effort to develop prognostic models capable of identifying subgroups of patients likely to enjoy a longer survival has been recently reviewed by Stelzer (Stelzer (2013)). In the initial description of Recursive Partitioning Analysis for brain metastases, the median survival was 7.1 months for RPA Class I, 4.2 months for RPA Class II, and 2.3 months for RPA Class III (Gaspar, Scott et al. (1997)). Thus the RPA classification system seems well suited to identifying a group of patients with a poor prognosis, as the National Clinical Guidelines have done by defining that group as RPA Class III. The RPA classification system cannot, nor can the Guidelines in their present form, identify a group with a "good prognosis," for whom adjuvant whole brain radiation might be harmful.

The authors acknowledge that whole brain radiation has the potential to impair cognitive function in a delayed fashion, but conclude that this risk is outweighed by the risk of cognitive dysfunction produced by uncontrolled metastatic disease if whole brain radiation is withheld. Their conclusion is not supported by a recent phase III trial of adjuvant whole brain radiation versus observation conducted by the EORTC (Soffietti, Kocher et al. (2013)), which revealed "statistically significant and clinically relevant" differences in cognitive function between the whole brain radiation group and the observation group.

. The authors of the Guidelines predict that some patients and clinicians will choose to forego or delay whole brain radiation following the surgical removal of a single metastasis, and appropriately advise that this group be followed with serial MR scans. In the United States, anecdotal reports of disabling dementia in the long term survivors of whole brain radiation, reports of good local control for supratentorial metastases following surgical resection alone, and the improved conformality and efficiency of the newer radiosurgical devices have led many clinicians to adopt the practice of treating brain metastases focally, observing patients afterward with serial MR scans, and delaying the use of whole brain radiation until later in the patient's course. The lack of high quality evidence to support or refute this practice at the present time has been nicely documented by the extensive literature review performed for focused question 1, and clearly identifies the need for prospective data collection to inform decision making in the future.

Focused Question 2: Bør man foretage operativ resektion eller stereotaktisk strålebehandling hos patienter med en solitær hjernemetastase, tilgængelig for operativ resektion og stereotaktisk strålebehandling, og med gennemsnitlig prognose?

(Should we perform surgical resection or stereotactic radiosurgery in patients with a solitary brain metastasis, accessible to surgical resection and stereotactic radiosurgery, and with an average prognosis?)

↑ Overvej enten operativ resektion eller stereotaktisk strålebehandling til personer med én hjernemetastase, tilgængelig for operativ resektion og stereotaktisk strålebehandling og med en gennemsnitlig prognose, da behandlingerne er ligeværdige (⊕ □ □ □).

(↑ consider either surgical resection or stereotactic radiosurgery for patients with an average prognosis and one brain metastasis, amenable to surgical resection or stereotactic radiosurgery, as the treatments are equal)

I agree that the available evidence, which the authors have assessed as low in quality, suggests that surgical resection and stereotactic radiosurgery provide equivalent local control of a single brain metastasis. As the large MD Anderson series has shown, experienced neurosurgeons can provide lasting local control of a single brain metastasis with surgical resection alone (Patel, Suki et al. (2010)). I believe that the explanations of the relative indications for surgical resection and radiosurgery given in sections 3.2 Baggrund for valg af spørgsmål and 1.2 Kirurgisk resektion eller stereotaktisk strålebehandling are valid, and make it clear that decision making in this setting must include the input of a neurosurgeon experienced in the surgical removal of brain metastases.

I agree that a randomized prospective trial comparing surgical resection alone to stereotactic radiosurgery alone has the potential to provide data that might be used to inform future guidelines. The authors have already pointed out many of the variables that would need to be controlled to allow a meaningful comparison: tumor size, tumor location, presence and extent of surrounding edema. Other variables, equally important, include radiosurgical dose and the experience of the surgical team.

Note that the terms solitary brain metastasis and single brain metastasis refer to different clinical scenarios in the English language literature. The term “solitær hjernemetastase” used in the focused question, if translated as “solitary brain metastasis,” would refer to a brain metastasis which is the only evidence of metastatic disease. The term “én hjernemetastase” used in the anbefaling, if translated as a “single brain metastasis,” implies that there may be extracranial metastatic disease as well. Most of the references cited in the Guidelines describe single brain metastases.

Focused Question 3: Bør man foretage stereotaktisk strålebehandling eller helhjernebestråling ved behandling af 2-4 hjernemetastaser, der er tilgængelige for stereotaktisk strålebehandling, hos patienter med gennemsnitlig prognose?

(Should we perform stereotactic radiosurgery or WBRT for the treatment of 2-4 brain metastases that are available for stereotactic radiotherapy in patients with an average prognosis?)

↑ Overvej at behandle patienter med 2-4 hjernemetastaser på hver 3 cm eller mindre og gennemsnitlig prognose, med stereotaktisk strålebehandling frem for helhjernebestråling (⊕□□□).

(↑ Consider treating patients with 2-4 brain metastases, each 3 cm or less and an average prognosis, with stereotactic radiosurgery rather than WBRT)

As the authors have explained, although only observational evidence is available to support this practice, it is believed by most clinicians to provide good local control with a lower risk of cognitive dysfunction than whole brain radiation.

Focused question 4: Bør man foretage helhjernebestråling og stereotaktisk strålebehandling eller helhjernebestråling alene ved 5 eller flere hjernemetastaser, på hver 3 cm eller mindre, hos patienter med gennemsnitlig prognose?

(Should we use both WBRT and stereotactic radiosurgery or WBRT alone for 5 or more brain metastases, each 3 cm or less, in patients with an average prognosis?)

√ Det er god praksis at anvende helhjernebestråling fremfor stereotaktisk strålebehandling i kombination med helhjernebestråling til patienter med 5 eller flere hjernemetastaser, på hver 3 cm eller mindre, og med gennemsnitlig prognose.

(√ It is good practice to use WBRT rather than stereotactic radiosurgery in combination with WBRT in the treatment of patients with 5 or more brain metastases, each 3 cm or less in diameter, and an average prognosis.)

Although I agree with this statement of good practice, the issues of the conformality and efficiency of the radiosurgical device used, and the size of the metastases, may be more important than the number of metastases for determining whether whole brain radiation or stereotactic radiosurgery is more effective or safer for a given patient.

The treatment of more than 4 metastases with single fraction radiosurgery using an older linear accelerator based system is a labor and time intensive affair. On the other hand, the Gamma Knife Perfexion, which was specifically engineered to optimize the treatment of multiple brain metastases can easily treat 5 or more metastases in a single setting, and has altered decision making in centers which have access to this technology.

Focused question 5: Bør man foretage helhjernebestråling af én eller multiple hjernemetastaser, hos patienter med dårlig prognose?

(Should we use whole brain radiation therapy for one or multiple brain metastases in patients with poor prognosis?)

↓ Anvend kun helhjernebestråling efter nøje overvejelse til patienter med én eller flere hjernemetastaser og med dårlig prognose, da der ikke er dokumenteret en gavnlig effekt, og der er bivirkninger forbundet ved behandlingen (⊕ ⊖ ⊖ ⊖) .

(↓ Use WBRT only after careful consideration for patients with one or more brain metastases and a poor prognosis, as there is no documented beneficial effect and there are side effects associated with the treatment)

In a world in which popular culture celebrates those who never give up, the decision to withhold therapy from a cancer patient is often difficult for families and primary care physicians in addition to oncologists. For that reason, I believe that this guideline is of great potential benefit at many levels. The RPA classification system is not, in my opinion, useful for identifying a subgroup of patients with a good prognosis, but it can identify those with a poor prognosis. In the initial series of patients on which this classification system was based, those in the RPA class III, the group designated as “poor prognosis” for these guidelines, had a median survival of only 2.3 months (Gaspar, Scott et al. (1997)). This short survival time, which is in agreement with those reported in the references reviewed for this guideline, weakens the statistical analysis of those references, but strongly supports the authors’ observation that whole brain radiation is unlikely to be of benefit to these patients.

The language used to express a recommendation plays a subtle but important role in its ability to guide behavior. I believe that the down arrow applied to this guideline, translated as “weakly against,” may lessen its impact on decision making at multiple levels. I believe that it would be better worded as god praksis: “it is good practice not to use whole brain radiation for patients with one or more brain metastases and a poor prognosis, as there is no documented beneficial effect and there are side effects associated with the treatment.”

In the future, improved access to MR imaging will increase the number of end-stage cancer patients found to have brain metastases. Clearly, those patients with a short survival would not benefit from a therapy that consumes their time and energy, and provides little, if any benefit.

Focused Question 6: Bør man supplere helhjernebestråling med kemoterapi ved hjernemetastaser som eneste eller dominerende manifestation fra kendt cancer (undtagen særlig kemofølsomme kræfttyper som småcellet lungecancer, germinative tumorer, lymfomer), hos patienter med gennemsnitlig prognose?

(Should we complement whole brain radiation with chemotherapy for brain metastases as the sole or dominant manifestation of known cancer (excluding special chemo - sensitive cancers like NSCLC , germ cell tumors, lymphomas), in patients with an average prognosis?)

↓ Anvend kun kemoterapi efter nøje overvejelse til patienter med hjernemetastaser som eneste eller dominerende manifestation fra kendt primær cancer (undtagen ved særlig kemofølsomme kræftformer), idet den gavnlige effekt er usikker, og der er bivirkninger forbundet ved behandlingen(⊕ □ □ □).

(↓ Use chemotherapy only after careful consideration in patients with brain metastases as the sole or dominant manifestation of known primary cancer (except for special chemo -sensitive cancers). The beneficial effect is uncertain, and there are side effects associated with the treatment)

The data review for this guideline was thorough, and shows little benefit of cytotoxic chemotherapy for most brain metastases. This observation is an important one, but I believe that care should be taken in its use for decision making. Like the issue of the relative roles of surgery, stereotactic radiosurgery, and whole brain radiation, the issue of the utility of chemotherapy for the treatment of brain metastases does not lend itself to a simple guideline, and patient care decisions should involve input from an experienced medical oncologist.

Chemotherapy is more disease specific than radiation therapy, hence the need to exclude non small cell lung cancer and extra cranial germ cell malignancies from this guideline. It is hoped that other exceptions will become evident as disease specific research progresses.

For reasons similar to those expressed in my response to focused question 5, I would prefer that this recommendation be labeled “good practice.” “It is good practice to use chemotherapy only for brain metastases that have been proven to be chemosensitive (those from non small cell lung cancer and extracranial germ cell malignancies), or as part of a clinical trial.”

Focused question 7: Bør man give steroid til patienter med hjernemetastaser uden symptomer på forhøjet intrakranielt tryk eller neurologiske udfald?

(Should we use steroids in patients with brain metastases without symptoms of increased intracranial pressure or neurological deficits?)

(√) Det er god praksis at undlade steroid til patienter med hjernemetastaser uden neurologiske udfald eller intrakranielle tryksymptomer.

(√ It is good practice to avoid steroids in patients with brain metastases without neurologic deficits or intracranial pressure symptoms.)

I agree with the authors that this is a significant issue and should be addressed. Neurosurgeons and other physicians experienced in the management of brain metastases do not routinely use corticosteroids in the absence of increased intracranial pressure or mass effect but they frequently encounter the practice in patients referred from the community. When less experienced clinicians prescribe corticosteroids in this setting, the patient is exposed to the risks of iatrogenic hypercortisolism (weight gain, diabetes, hypertension) for no benefit. This guideline can serve an important educational role for primary care physicians involved in the care of cancer patients.

Focused question 8: Bør man starte steroidbehandling i høj dosis (f.eks. Prednisolon 50-100 mg3) eller i moderat dosis (f.eks. Prednisolon 25 mg4) i kombination til øvrig behandling til patienter med hjernemestastaser og symptomer på forhøjet intrakranielt tryk eller neurologiske udfald?

(Should we use steroids in high doses (such as Prednisolone 50-100 mg) or moderate doses (eg . Prednisolone 25 mg) in combination with the treatment of patients with brain metastases and symptoms of increased intracranial pressure or neurological deficits?)

(√) Det er god praksis at give moderat dosis (Prednisolon 25 mg eller ekvivalent) steroid behandling til patienter med hjernemetastaser og neurologiske udfald.

√ It is good practice to give moderate dose (Prednisolone 25 mg or its equivalent) steroid treatment for patients with brain metastases and neurological deficits.

(√) Det er god praksis rutinemæssigt at give høj dosis (Prednisolon 50-100 mg eller ekvivalent) steroid behandling til patienter med hjernemetastaser og intrakranielle tryksymptomer.

√ It is good practice to routinely give high dose (50-100 mg Prednisolone or its equivalent) steroid treatment for patients with brain metastases and intracranial pressure symptoms.

Like focused question 7, this guideline will serve an important educational role for clinicians inexperienced in the management of patients with brain metastases, and should serve to reduce the incidence of side effects attributed to hypercortisolism.

The issue of corticosteroid use in patients undergoing whole brain radiation is also an important one. In the early days of whole brain radiation, in the era before CT and MR scanning, cerebral herniation syndromes were often provoked at the initiation of therapy before the practice of pretreating patients with corticosteroids became routine. As the authors have indicated, it is now clear that some patients undergoing whole brain radiation for brain metastases may be managed with lower doses of corticosteroids.

Focused question 9: Bør man hos patienter som tidligere er behandlet med helhjernebestråling og med gennemsnitlig prognose udføre lokal behandling (operativ resektion eller stereotaktisk strålebehandling) af recidiverende hjernemetastaser?

(Should average prognosis patients with recurrent brain metastases after whole brain radiation be offered focal therapy (surgical resection or stereotactic radiosurgery)?)

Det er god praksis, kun efter nøje overvejelse at give lokalbehandling ved recidiv af hjernemetastaser, tidligere behandlet med helhjernebestråling, da der kun foreligger lav kvalitet af evidensen for den gavnlige effekt.

(√ It is good practice to provide local treatment of recurrence of brain metastases previously treated with WBRT only after careful consideration. The quality of the evidence for a beneficial effect is low.)

As discussed in regard to focused questions 1 through 4, the issue of the relative roles of whole brain radiation and focal therapy in the management of brain metastases is a complex one. I believe that the evidence reviewed for focused question 9 nicely supports the wording of this guideline, and appropriately preserves the ability of the neurosurgeon or radiation oncologist to recommend focal therapy for selected patients with recurrent disease after having received whole brain radiation.

The National Clinical Guidelines clearly acknowledge the need for input from experienced physicians and multidisciplinary teams in decision making for individual patients. Such input will always be important, but in the future, I predict that clinical guidelines for the management of brain metastases will be disease specific, mirroring the management of cancer in general, and will be based on the stratification of patients into several prognostic groups. With a geographically stable patient population and scientifically sophisticated physicians, Denmark will make a significant contribution to the creation of the guidelines of the future.

I would like to thank the working group for the opportunity to review these guidelines and to congratulate them again for their success.

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Comments
On the Draft Document

"National Klinisk Retningslinje for Behandling af Hjernemetastaser"

by

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Introduction

A number of important developments have taken place in the diagnosis and treatment of cerebral metastases over the past two decades. At the same time treatment of cancer in general has improved and resulted in longer life expectancy for a large number of patients. Whereas the life expectancy with a good quality of life was previously counted in months, it is now counted in years for many patients (Kondziolka, Martin et al. 2005, Karlsson, Hanssens et al. 2009). A neurologic death is now less common than a death of systemic disease even among patients with brain metastases, if the secondary tumors are properly treated. Paramount for achieving prolonged survival with minimal risk of neurological deficits is high-resolution imaging for diagnosis, treatment and follow-up surveillance. It is commonplace that a high resolution

MRI used at the time of treatment reveals more metastases than the generally used sequences of MRI used for diagnosis (Nagai, Shibamoto et al. 2010). One consequence of this is that patients with single tumors are less commonly found (e.g. the average number of metastases found at the time of treatment in patients with breast cancer has been 6 at the Cromwell Hospital). Another consequence is that there has been a shift in treatment paradigms. Improvements in imaging may also explain discrepancies between reported outcomes of similar treatment schedules.

Comments to the proposed National Guidelines

2 Addresses the management of single cerebral metastasis.

The specific question is: Should surgical resection alone or in combination with whole brain radiotherapy (WBRT) or WBRT alone be the proper treatment for a single brain metastasis?

Background

The combined treatment was reported to be the best option already in 1986 (Patchell, Cirrincione et al. 1986). More recently a number of studies have failed to corroborate these findings. Randomized controlled trials were recently evaluated and published in the "Cochrane Database Syst. Rev." (Soon, Tham et al. 2014). The authors conclude: "There is low quality evidence that adding upfront WBRT to surgery or SRS decreases any intracranial disease progression at one year."

The ill effects of WBRT have come under increased scrutiny in recent years. Cognitive decline when WBRT was added to the management has been demonstrated in many patients (Chang, Wefel et al. 2009). It has also been shown that those patients, who survive WBRT for a year or more, often develop leukoencephalopathy (Monaco, Faraji et al. 2013).

Comments

Reviews of the literature in the current report found 9 references addressing the question of whether WBRT should be used after surgical removal of a single metastasis or not. Only 2 of these studies were published in the 21st century. The others were published from 1990 to 1998. The reviewers considered that only 1 randomized study provided strong evidence for decreased risk of local recurrence after surgery when WBRT was used. It was calculated that 324 patients of 1000 would benefit from the WBRT. From a different perspective this means that 676 out of 1000 patients were unnecessarily exposed to the toxic effects of WBRT, which affords a very low benefit/risk ratio. (See page 12, Table 2A). The publications reviewed did not provide convincing evidence that WBRT affects the incidence of new metastases in the brain or survival in patients operated on for a single metastasis. Nevertheless, the work force for the National Guidelines gives the recommendation that WBRT should be considered after surgical resection of a solitary metastasis. However, the available data clearly shows that many more patients are at risk for developing serious cognitive disturbances from WBRT than patients protected from recurrence of tumor in the surgical bed. Several reports show that SRS to the surgical bed significantly lowers the risk of local recurrence without the toxicity of WBRT(Mathieu, Kondziolka et al. 2008, Soltys, Adler et al. 2008, Do, Pezner et al. 2009, Jagannathan, Yen et al. 2009). At this time is seems clear that *WBRT should not be recommended* as complimentary treatment after microsurgical resection of a single brain metastasis. As suggested, it is reasonable to offer patients frequent post-operative surveillance by MR-scanning.

3 **Addresses the management of single cerebral metastasis**.

The specific question is: Should microsurgery (MS) or stereotactic radiosurgery (SRS) be used?

Background

In discussing the management of single brain metastasis it is worthwhile remembering that single metastasis are relatively rare. In a landmark paper on surgical resection of cerebral metastases from 1990 the assessment was that only 1/4 - 1/3 of brain metastases were single (Patchell, Tibbs et al. 1990). Over the 15 years since this paper was written great strides forward have been made in MRI technology. It is very likely that the resolution of today’s MRI equipment will detect more than 1 metastasis in the majority of patients.

Comments

This section is difficult to comprehend and the task force, on page 18, gives the reason for this. Simply, there are no high quality randomized studies comparing the outcome of MS and SRS.

Indirect evidence has to suffice. The indirect evidence is extracted from reports also involving the use of WBRT, which confounds the issue and makes the power of evidence low. In the end the task force therefore arrives at the conclusion that there is no difference between the outcomes of MS vs. SRS in the management of single metastasis in the brain. A prospective randomized trial comparing the outcome of the two treatment alternatives is called for. However, an increasing number radiation oncologists and neurosurgeons involved in radiosurgery are accepting a very limited role for MS in the management of cerebral metastases. This contention is supported by number of observational studies, but there is a relative lack of reports on outcome of MS (Kondziolka, Kano et al. 2011, Matsunaga, Shuto et al. 2011, Park, Chang et al. 2011, Skeie, Skeie et al. 2011, Yoo, Park et al. 2011, Padovani, Muracciole et al. 2012, Burke, Mascott et al. 2013, Kim, Huh et al. 2013, Lippitz, Lindquist et al. 2013, Lwu, Goetz et al. 2013, Yaeger and Nair 2013). The increasing approval of SRS as the primary treatment modality for the majority of patients with brain metastases is making it very unlikely that a randomized study comparing MS with SRS for the treatment of single metastasis will ever be launched. It should also be pointed out that surgery for metastases surrounded by an edematous brain is more difficult and carries a higher morbidity. On the other hand SRS of large tumors more often than not decrease the brain edema around the tumor (Yang, Kano et al. 2011). Recent evidence suggests that surgical resection should be followed by radiation focused on the surgical bed (Iwai, Yamanaka et al. 2008, Do, Pezner et al. 2009, Jagannathan, Yen et al. 2009, Limbrick, Lusis et al. 2009, Hwang, Abozed et al. 2010, Roberge and Souhami 2010) rather than the more toxic WBRT. Like myself, some neurosurgeons argue you that SRS should precede MS to avoid mechanical spread of viable tumor cells. The risk of leptomeningeal spread after surgery in the posterior fossa has been reported to be as high as 50% whereas it was only 6.5% after SRS (Siomin, Vogelbaum et al. 2004).

On balance, although the immediate result of microsurgery (MS) for small to moderate size metastases (< 10cc) is a better outcome on MRI, the risks of clinical deterioration, local relapse, or leptomeningeal spread are much higher than after SRS. Thus, *even for small (<10cc) superficial tumors MS should be used with great discretion*. MS should be reserved for larger tumors inappropriate to treat by SRS or SRT and located in regions of the brain from where a deficit is an acceptable price to pay.

4 **Addresses the role of SRS in the management of patients with 2-4 cerebral metastases.**

The specific question is: should SRS or WBRT be used in patients with 2-4 tumors amenable to SRS?

Background

It is a truism that the higher the quality of your imaging technique the better is the chance of detecting even the smallest metastases. It is therefore not correct to set an arbitrary limit on the number of metastases, which should be treated by one technique or the other. Setting the upper limit of 4 metastases as reasonable for treatment with SRS was mainly set for technical and practical reasons and not for clinical reasons. It was championed by the group at the Karolinska Hospital in Stockholm working with older models of the Gamma Knife and by the Ayoama group working with a Linac. Intuitively it was thought that more metastases in the brain mean a poorer prognosis. Recent data suggests that there is a much better correlation between the total volume of metastases and prognosis rather than the number of metastases and prognosis (Baschnagel, Meyer et al. 2013, Salvetti, Nagaraja et al. 2013, Ojerholm, Lee et al. 2014).

Comments

The task force argues that WBRT has an advantage over SRS in being able to stop the development of undiscovered metastases in the brain. This is certainly a possibility, but we also know that in many cases WBRT has no or little effect on visualized tumors. It is therefore not a given that WBRT always has an effect on non-visualized tumors. Furthermore, many papers have now reported that new metastases do not appear much more frequently after SRS than after WBRT. New remote brain metastases are reported in 33-42% of patients after WBRT and in 39-52% after SRT. While WBRT can generally only be used once, radiosurgery can be applied repeatedly for remote recurrences (Lippitz, Lindquist et al. 2013). A rough approximation of these figures suggests that only some 10% of the patients benefited from the effect of WBRT on non-visualized tumors. There is reason to believe that the number of new remote metastases can be brought even lower if the stereotactic MR-imaging technique is optimized (e.g. by using thinner slices, double or triple dose of Gadolinium with T1W images, and a 3T or 7T magnet). Whether WBRT or SRS is used there will, of course, always be the risk that hematogenous spread of new cancer cells occurs at any time after the termination of the treatment. Vigilante surveillance is therefore called for after treatment regardless of the technique used. Should a follow up MRI detect new remote tumors after SRS they can easily and safely be treated by SRS (Maranzano, Trippa et al. 2011, Mariya, Sekizawa et al. 2011, Rush, Elliott et al. 2011, Lippitz, Lindquist et al. 2013). We have calculated that one SRS treatment even to >10 tumors gives a 3Gy (a common fractional dose when WBRT is used) exposure to a minor volume of the normal brain. In comparison to SRS, WBRT has the following *disadvantages* compared to SRS: 1/ with some variation, less effective on cerebral metastases from most types of primary tumors (lung, breast, colo-rectal) 2/ ineffective on tumors from some neoplasms (melanoma with some exceptions, renal cell carcinoma with some exceptions). 3/ cannot be repeated if optimal treatment given. 4/ increased risk for SRS as salvage therapy. 5/ disrupt or delays chemotherapy. 6/ high risk for severe cognitive disturbances (including memory deficits) in patients surviving more than 1 year. These disadvantages of WBRT have prompted many radiation oncologists to abandon or strictly limit the use of WBRT. It is recommended for patients with leptomeningial disease, miliary spread of tumors and especially radiosensitive tumors (as mentioned in the National Guidelines).

5 **Addresses the management of 5 or more cerebral metastases**.

The specific question is: Should WBRT and SRS, or WBRT only, be performed on patients with tumors amenable to SRS?

Background

As previously stated: the better the imaging quality, the higher is the chance of detecting more secondary tumors in the brain of cancer patients. The conclusions drawn from studies of management of brain metastases, which are only a few years old, may therefore already be obsolete. It is probable, that the widely held opinion: multiple brain metastases equal a very poor prognosis is subject to conclusions based on obsolete information. Today, we know that there is a better correlation of the total volume of tumor to prognosis as compared to the correlation between number of tumors and prognosis (Baschnagel, Meyer et al. 2013, Salvetti, Nagaraja et al. 2013, Ojerholm, Lee et al. 2014).

Comments

It is unfortunately still true, that in daily practice, most radiation oncologists are inclined to treat patients with more than 4 metastases with WBRT rather than SRS. However, there is strong shift of opinion towards increased use of SRS according to recent surveys at multidisciplinary meetings (Knisely, Yamamoto et al. 2010). In my institution we have treated multiple (>5) metastases by SRS alone for at least 10 years. We follow the patients every 3 months with MRI. The preferred parameters for MRI are a 3D gradient echo T1W sequence after injection of a triple dose of Gadolinium and contiguous 1.5 mm slices. Any new metastases found are treated with another session of SRS. The radiation burden to the normal brain is checked for each dose plan and, if the cumulative exposure is found to be excessive, the patient may be a candidate for salvage WBRT. WBRT is also recommended as the only or adjunctive treatment if leptomeningeal spread is found. Another indication for WBRT may be diffuse borders of the metastases making SRS planning uncertain. In tumors appearing larger at follow-up after SRS the differential diagnosis between radiation induced swelling vs. tumor growth is made with fdg-PET. Only patients with fdg uptake are considered local recurrences and are retreated. So far we have retreated several patients 2 or 3 times and some even 4-5 times. The unpublished data suggest a significant impact on survival and quality of life. It is our impression that the results of repeated SRS will considerably reduce the need for WBRT in the future. At least one recent study from New York University supports this contention (Rush, Elliott et al. 2011). Three studies published in the last 2 years support SRS for treatment also of more than 4 metastatic brain tumors. One is from the Cleveland Clinic (Mohammadi, Recinos et al. 2012) another one from the University of Virginia (Salvetti, Nagaraja et al. 2013). The most important study is a multicenter cooperative study from Japan recently published in Lancet Oncology (Yamamoto, Serizawa et al. 2014). It is a well-designed prospective observational study to show that the result of SRS for treatment of 5-10 metastases is not inferior to treatment of 2-4 metastases. This study will have a pivotal role in the management of cerebral metastases. Overall survival did not differ between the patients with two to four tumors from those with five to ten. SRS induced adverse events occurred in 101 (8%) patients; nine (2%) patients with one tumors had one or more grade 3-4 event compared to 13 (2%) patients with two to four tumors and six (3%) patients with five to ten tumors. The proportion of patients who had one or more treatment-related adverse event of any grade did not differ significantly between the two groups of patients with multiple tumors (50 [9%] patients with two to four tumors vs. 18 [9%] with five to ten; p=0.89). The large Japanese study published very recently was not available to the task force. The outcome of the study should encourage the task force to recommend SRS as the treatment of choice also for multiple brain metastases.

6 Addresses the issue of the benefit of WBRT in patients with a poor prognosis

The specific question is: should WBRT be administered to patients with one or several brain metastases and a poor prognosis?

The recommendation of the task force is: No provided there is no obvious beneficial effect to anticipate.

Comment

I concur with the view of the task force. However, I can see some situations where SRS could be of obvious benefit even if the predicted survival of the patient is only 3 months. Such situations could be the presence of a small metastasis in a functionally very important area causing the patient significant suffering from a neurological deficit. Such tumors could be located in the speech areas, motor cortex, and/or the brain stem. A desired clinical effect of SRS often appears as early as a month after treatment.

7 Addresses the issue of the benefit of chemotherapy in the treatment of patients with cerebral metastases

The specific question is: should adjunctive chemotherapy be given to patients having brain metastases as the only or dominating manifestation of a known primary cancer?

The task force does not recommend chemotherapy with WBRT except for patients with special types of primary cancers.

Comments

The specific question is unclear to me. Is the question if chemotherapy should be given to enhance the effect of WBRT on the brain metastases? Then I concur with the task force view that it additional benefit is questionable and that the risks of complications are increased with the combined therapy WBRT+chemotherapy. On the other hand if SRS is used there is no documentation showing increased risks of the combined therapy. However, neither is there any strong evidence that any drug therapy will enhance the effect of SRS. Any chemotherapy directed at the systemic disease can be continued with impunity if the patient were to receive SRS.

8 Addresses the issue of the benefit of steroids to patients with brain metastases without neurological symptoms

The specific question is: should steroids be administered to patients with brain metastases but without focal neurological symptoms and without symptoms or signs of increased intracranial pressure?

The task force gives a good argument for answering this question with: No

9 Addresses the issue of the benefit of steroids to patients with brain metastases and neurological symptoms

The specific question is: should patients with cerebral metastases be administered a high dose of steroids or moderate dose, if they have neurological deficits or clinical signs of high intracranial pressure

The task force recommends a moderate dose for patients without neurological deficits and a high dose for patients with clinical symptoms or signs of high intracranial pressure.

Comments

In general I concur we the views of the task force. If there is significant edema around the tumor(s), the patients' neurological symptoms or signs usually subside within 48-72 hours. Continued administration of steroids is then questionable. In my practice we do not routinely use before or after SRS. Steroids should be used for as short a time as possible. It is not good clinical practice to delay treatment because the clinical response is excellent.

10 Addresses the issue of how to manage metastases recurring after previous WBRT

The specific question is: Should patients with metastasis(es) recurring after WBRT be offered additional local treatment such as MS or SRS?

The recommendation of the task force is that good medical practice is to recommend treatment of local recurrences by appropriate means but only after careful consideration

Comments

In the infancy of SRS almost all patients treated had been previously subjected to WBRT. The results were encouraging and the next step in the evolution of SRS was to offer the combination of treatments. More recently, as mentioned above, results of SRS based on the best available imaging are better than WBRT in terms of local control and not inferior to WBRT in terms recurrences in remote sites. We now are seeing a surge in the use of repeat SRS for treatment of new remote tumors as well as local recurrences.

Suggested Guidelines

Summary

Patient Selection Criteria
All patients with cerebral metastases and a Karnofsky Performance Status (KPS) of ≥ 70 should be treated. Patients with a lower KPS score should be *considered* for treatment if one or several treatable cerebral metastases are the main contributor to the low score.

Treatment Modalities
Stereotactic Radiosurgery (SRS)
Stereotactic Radiotherapy (SRT)
Whole Brain Radiotherapy (WBRT)
Craniotomy and Microsurgical Removal (MS)
Drug therapy (chemotherapy, immunological therapy and other)
(Other treatments are considered experimental and not considered).

Selection of Primary Treatment Modality

SRS
Indication: Should be considered for all patients, and used in most cases, as the primary treatment modality. Should be used as a secondary treatment in patients with recurrence or remaining tumor(s) after MS, SRS or WBRT. Should be considered for treatment of the surgical bed after microsurgical removal.
Contraindication: Leptomeningeal disease (solid tumors in patients with leptomeningeal disease can be considered for treatment). Large tumors with volumes >10 cc (larger tumors in non-eloquent areas may be safely treated).

SRT
Indication: could be considered for large tumors when MS carries a high risk.

WBRT
Indication: Leptomeningeal disease. Multiple tumors when RS would deliver a more toxic dose to the normal brain than WBRT

(*total* tumor volume in the supratentorial space of > 20cc and in the infratentorial space > 10cc).
Contraindication: Previous WBRT

MS
Indication: Craniotomy and microsurgical removal is indicated for tumors causing a considerable mass effect posing a threat to life or serious neurological deficits if left untreated for 2 months.
Contraindication: Eloquent tumor location.

Drug Therapy
Indications: In selected cases as an adjunct to other treatment modality.

Selection of Secondary Treatment Modality
Patients, who have recurrence of previously treated tumor(s) or new metastases appearing elsewhere in the brain, should be considered for more treatment(s) if their general condition allows (KPS ≥ 70).

SRS
Preferred choice. Calculate average dose of radiation previously delivered to the brain.
Indication: as for primary treatment.
Contraindication: as for primary treatment.

SRT
Indication: as for primary treatment.
WBRT
Indication: as for primary treatment.
Contraindication: if “full dose” of WBRT has been previously given.

MS
Indication: as for primary treatment.
Contraindication: as for primary treatment.
Drug Therapy
Indication: as for primary treatment.

"<Metastates IRSA Guideline2008.pdf>."

Baschnagel, A. M., et al. (2013). "Tumor volume as a predictor of survival and local control in patients with brain metastases treated with gamma knife surgery." J Neurosurg **119**(5): 1139-1144.

OBJECT: The aim of this study was to examine tumor volume as a prognostic factor for patients with brain metastases treated with Gamma Knife surgery (GKS). METHODS: Two hundred fifty patients with 1-14 brain metastases who had initially undergone GKS alone at a single institution were retrospectively reviewed. Patients who received upfront whole brain radiation therapy were excluded. Survival times were estimated using the Kaplan-Meier method. Univariate and multivariate analyses using Cox proportional hazard regression models were used to determine if various prognostic factors could predict overall survival, distant brain failure, and local control. RESULTS: Median overall survival was 7.1 months and the 1-year local control rate was 91.5%. Median time to distant brain failure was 8.0 months. On univariate analysis an increasing total tumor volume was significantly associated with worse survival (p = 0.031) whereas the number of brain metastases, analyzed as a continuous variable, was not (p = 0.082). After adjusting for age, Karnofsky Performance Scale score, and extracranial disease on multivariate analysis, total tumor volume was found to be a better predictor of overall survival (p = 0.046) than number of brain metastases analyzed as a continuous variable (p = 0.098). A total tumor volume cutoff value of >/= 2 cm(3) (p = 0.008) was a stronger predictor of overall survival than the number of brain metastases (p = 0.098). Larger tumor volume and extracranial disease, but not the number of brain metastases, were predictive of distant brain failure on multivariate analysis. Local tumor control at 1 year was 97% for lesions < 2 cm(3) compared with 75% for lesions >/= 2 cm(3) (p < 0.001). CONCLUSIONS: After adjusting for other factors, a total brain metastasis volume was a strong and independent predictor for overall survival, distant brain failure, and local control, even when considering the number of metastases.

Burke, D., et al. (2013). "Stereotactic radiosurgery for the treatment of brain metastases; results from a single institution experience." Irish journal of medical science **182**(3): 481-485.

BACKGROUND: Stereotactic radiosurgery is frequently used for the treatment of brain metastases. This study provides a retrospective evaluation of patients with secondary lesions of the brain treated with stereotactic radiosurgery (SRS) at our institution. AIMS: To provide outcome data from a single institutional experience with SRS and identify any significant prognostic factors in the cohort. METHODS: Sixty-seven patients received first time SRS to 86 intracranial metastases between 2007 and 2010. Sixteen patients were excluded from this study due to the absence of post-treatment neuroimaging, resulting in 51 patients with 64 treated lesions. Of these patients, 37 (72.5 %) received SRS electively, while 14 (27.5 %) received salvage SRS after brain metastasis progression following whole brain radiotherapy. RESULTS: Median survival for the entire group was 15 months from the date of radiosurgery. Patients without active extracranial disease had statistically significant survival time than those with active extracranial disease (P = 0.03). 45 (70.3 %) lesions achieved local tumour control in 34 patients (66.7 %) with a mean follow-up period of 10.7 months (range 1.7-33.6 months, 95 % confidence interval 6.6-9.8 months). CONCLUSIONS: The results reported in this study equate to those reported in other series consolidating SRS as an effective treatment option with few serious complications. Developments in systemic disease control will see further improvements in overall survival.

Chang, E. L., et al. (2009). "Neurocognition in patients with brain metastases treated with radiosurgery or radiosurgery plus whole-brain irradiation: a randomised controlled trial." The lancet oncology **10**(11): 1037-1044.

BACKGROUND: It is unclear whether the benefit of adding whole-brain radiation therapy (WBRT) to stereotactic radiosurgery (SRS) for the control of brain-tumours outweighs the potential neurocognitive risks. We proposed that the learning and memory functions of patients who undergo SRS plus WBRT are worse than those of patients who undergo SRS alone. We did a randomised controlled trial to test our prediction. METHODS: Patients with one to three newly diagnosed brain metastases were randomly assigned using a standard permutated block algorithm with random block sizes to SRS plus WBRT or SRS alone from Jan 2, 2001, to Sept 14, 2007. Patients were stratified by recursive partitioning analysis class, number of brain metastases, and radioresistant histology. The randomisation sequence was masked until assignation, at which point both clinicians and patients were made aware of the treatment allocation. The primary endpoint was neurocognitive function: objectively measured as a significant deterioration (5-point drop compared with baseline) in Hopkins Verbal Learning Test-Revised (HVLT-R) total recall at 4 months. An independent data monitoring committee monitored the trial using Bayesian statistical methods. Analysis was by intention-to-treat. This trial is registered at http://www.ClinicalTrials.gov, number NCT00548756. FINDINGS: After 58 patients were recruited (n=30 in the SRS alone group, n=28 in the SRS plus WBRT group), the trial was stopped by the data monitoring committee according to early stopping rules on the basis that there was a high probability (96%) that patients randomly assigned to receive SRS plus WBRT were significantly more likely to show a decline in learning and memory function (mean posterior probability of decline 52%) at 4 months than patients assigned to receive SRS alone (mean posterior probability of decline 24%). At 4 months there were four deaths (13%) in the group that received SRS alone, and eight deaths (29%) in the group that received SRS plus WBRT. 73% of patients in the SRS plus WBRT group were free from CNS recurrence at 1 year, compared with 27% of patients who received SRS alone (p=0.0003). In the SRS plus WBRT group, one case of grade 3 toxicity (seizures, motor neuropathy, depressed level of consciousness) was attributed to radiation treatment. In the group that received SRS, one case of grade 3 toxicity (aphasia) was attributed to radiation treatment. Two cases of grade 4 toxicity in the group that received SRS alone were diagnosed as radiation necrosis. INTERPRETATION: Patients treated with SRS plus WBRT were at a greater risk of a significant decline in learning and memory function by 4 months compared with the group that received SRS alone. Initial treatment with a combination of SRS and close clinical monitoring is recommended as the preferred treatment strategy to better preserve learning and memory in patients with newly diagnosed brain metastases.

Do, L., et al. (2009). "Resection followed by stereotactic radiosurgery to resection cavity for intracranial metastases." International journal of radiation oncology, biology, physics **73**(2): 486-491.

PURPOSE: In patients who undergo resection of central nervous system metastases, whole brain radiotherapy (WBRT) is added to reduce the rates of recurrence and neurologic death. However, the risk of late neurotoxicity has led many patients to decline WBRT. We offered adjuvant stereotactic radiosurgery (SRS) or stereotactic radiotherapy (SRT) as an alternative to select patients with resected brain metastases. METHODS AND MATERIALS: We performed a retrospective review of patients who underwent brain metastasis resection followed by SRS/SRT. WBRT was administered only as salvage treatment. Patients had one to four brain metastases. The dose was 15-18 Gy for SRS and 22-27.5 Gy in four to six fractions for SRT. Target margins were typically expanded by 1 mm for rigid immobilization and 3 mm for mask immobilization. SRS/SRT involved the use of linear accelerator radiosurgery using the IMRT 21EX or Helical Tomotherapy unit. RESULTS: Between December 1999 and January 2007, 30 patients diagnosed with intracranial metastases were treated with resection followed by SRS or SRT to the resection cavity. Of the 30 patients, 4 (13.3%) developed recurrence in the resection cavity, and 19 (63%) developed recurrences in new intracranial sites. The actuarial 12-month survival rate was 82% for local recurrence-free survival, 31% for freedom from new brain metastases, 67% for neurologic deficit-free survival, and 51% for overall survival. Salvage WBRT was performed in 14 (47%) of the 30 patients. CONCLUSION: Our results suggest that for patients with newly diagnosed brain metastases treated with surgical resection, postoperative SRS/SRT to the resection cavity is a feasible option. WBRT can be reserved as salvage treatment with acceptable neurologic deficit-free survival.

Hwang, S. W., et al. (2010). "Adjuvant Gamma Knife radiosurgery following surgical resection of brain metastases: a 9-year retrospective cohort study." Journal of neuro-oncology **98**(1): 77-82.

Given the potential morbidity of whole brain radiation therapy (WBRT), there has been an increasing trend to defer WBRT and deliver Gamma Knife stereotactic radiosurgery (GKS) to cerebral metastatic lesions. We analyzed our experience delivering GKS to the tumor cavity following surgical resection of brain metastases and compared our results to patients receiving WBRT after surgical resection of a metastatic lesion. We performed a retrospective review of patients undergoing surgical resection of at least one brain metastasis between December 1999 and December 2008. Both univariate and multivariate Cox proportional hazards regression were utilized to analyze the influence of various prognostic factors on survival. Twenty-five patients had a metastatic lesion resected followed by adjuvant GKS to the resection cavity while another 18 had surgical resection followed by WBRT. Aside from a disparity in gender distribution (72% of GKS patients were female while women only constituted 28% of the WBRT group), no significant differences existed between groups. The median survival for patients receiving GKS was 15.00 months as compared to 6.81 months among those receiving WBRT (P = 0.08). Univariate Cox regression analysis identified the number of metastases (HR 1.65, 95% CI 1.07-2.54, P = 0.02) and regional recurrence (RR 5.23, 95% CI 1.78-15.38, P = 0.003) as poor prognostic factors. Multivariate regression analysis showed that regional recurrence (HR 5.17, 95% CI 1.69-15.78, P = 0.004) was again strongly associated with worse survival. Although limited by the retrospective nature of our study and lack of some clinical measures, patients undergoing GKS to the resection cavity had a trend towards longer median survival.

Iwai, Y., et al. (2008). "Boost radiosurgery for treatment of brain metastases after surgical resections." Surgical neurology **69**(2): 181-186; discussion 186.

BACKGROUND: We evaluated results of resection surgery followed by boost radiosurgery for the treatment of brain metastases. METHODS: We treated 21 patients (13 male, 8 female) with surgical resection (subtotal or total) followed by boost radiosurgery. The mean patient age was 61 years (range, 41-80 years); supratentorial lesions were treated in 12 patients, and posterior fossa lesions were treated in 9 patients. The most common primary cancers were lung (24%) and colon (24%). Fifty-three percent of patients had brain metastases only, whereas 47% had extracranial metastases. The radiosurgery dose plan was designed to radiate the operative cavity; the mean treatment volume (50% isodose) was 10.7 mL (range, 3.4-23.3 mL), and the mean marginal dose was 17 Gy (range, 13-20 Gy). RESULTS: Local control was achieved in 16 (76%) patients. However, new intracranial lesions developed in 10 patients, and meningeal carcinomatosis occurred in 5 patients. Local tumor recurrence occurred more often for patients treated with lower radiotherapy doses (<18 vs > or =18 Gy, P = .03), and meningeal carcinomatosis occurred more often in patients with posterior fossa lesions (P = 0.05). Gamma knife radiosurgery was performed in 13 patients, and whole-brain radiation was performed in 2 patients. No patients experienced symptomatic radiation injury, and the median survival time was 20

months. CONCLUSIONS: Although boost radiosurgery is less invasive and reduces morbidity, the radiosurgical dose must be higher than 18 Gy for the treatment to be most effective. Treatment of lesions of the posterior fossa must be considered carefully because of the higher frequency of meningeal carcinomatosis. Also, we recommend that the surgeons who operate on the metastatic tumors must try to decrease the resected cavity volume and to prevent cerebrospinal fluid dissemination at the operation for posterior fossa lesions.

Jagannathan, J., et al. (2009). "Gamma Knife radiosurgery to the surgical cavity following resection of brain metastases." Journal of Neurosurgery **111**(3): 431-438.

OBJECT: This study evaluated the efficacy of postoperative Gamma Knife surgery (GKS) to the tumor cavity following gross-total resection of a brain metastasis. METHODS: A retrospective review was conducted of 700 patients who were treated for brain metastases using GKS. Forty-seven patients with pathologically confirmed metastatic disease underwent GKS to the postoperative resection cavity following gross-total resection of the tumor. Patients who underwent subtotal resection or who had visible tumor in the resection cavity on the postresection neuroimaging study (either CT or MR imaging with and without contrast administration) were excluded. Radiographic and clinical follow-up was assessed using clinic visits and MR imaging. The radiographic end point was defined as tumor growth control (no tumor growth regarding the resection cavity, and stable or decreasing tumor size for the other metastatic targets). Clinical end points were defined as functional status (assessed prospectively using the Karnofsky Performance Scale) and survival. Primary tumor pathology was consistent with lung cancer in 19 cases (40%), melanoma in 10 cases (21%), renal cell carcinoma in 7 cases (15%), breast cancer in 7 cases (15%), and gastrointestinal malignancies in 4 cases (9%). The mean duration between resection and radiosurgery was 15 days (range 2-115 days). The mean volume of the treated cavity was 10.5 cm3 (range 1.75-35.45 cm3), and the mean dose to the cavity margin was 19 Gy. In addition to the resection cavity, 34 patients (72%) underwent GKS for 116 synchronous metastases observed at the time of the initial radiosurgery. RESULTS: The mean radiographic follow-up duration was 14 months (median 10 months, range 4-37 months). Local tumor control at the site of the surgical cavity was achieved in 44 patients (94%), and tumor recurrence at the surgical site was statistically related to the volume of the surgical cavity (p=0.04). During follow-up, 34 patients (72%) underwent additional radiosurgery for 140 new (metachronous) metastases. At the most recent follow-up evaluation, 11 patients (23%) were alive, whereas 36 patients had died (mean duration until death 12 months, median 10 months). Patients who showed good systemic control of their primary tumor tended to have longer survival durations than those who did not (p=0.004). At the last clinical follow-up evaluation, the mean Karnofsky Performance Scale score for the overall group was 78 (median 80, range 40-100). CONCLUSION: Radiosurgery appears to be effective in terms of providing local tumor control at the

resection cavity following resection of a brain metastasis, and in the treatment of synchronous and metachronous tumors. These data suggest that radiosurgery can be used to prevent recurrence following gross-total resection of a brain metastasis.

Karlsson, B., et al. (2009). "Thirty years' experience with Gamma Knife surgery for metastases to the brain." Journal of Neurosurgery **111**(3): 449-457.

OBJECT: The aim of this study was to analyze factors influencing survival time and patterns of distant recurrences after Gamma Knife surgery (GKS) for metastases to the brain. METHODS: Information was available for 1855 of 1921 patients who underwent GKS for single or multiple cerebral metastases at 4 different institutions during different time periods between 1975 and 2007. The total number of Gamma Knife treatments administered was 2448, an average of 1.32 treatments per patient. The median survival time was analyzed, related to patient and treatment parameters, and compared with published data following conventional fractionated whole-brain irradiation. RESULTS: Twenty-five patients survived for longer than 10 years after GKS, and 23 are still alive. Age and primary tumor control were strongly related to survival time. Patients with single metastases had a longer survival than those with multiple metastases, but there was no difference in survival between patients with single and multiple metastases who had controlled primary disease. There were no significant differences in median survival time between patients with 2, 3-4, 5-8, or >8 metastases. The 5-year survival rate was 6% for the whole patient population, and 9% for patients with controlled primary disease. New hematogenous spread was a more significant problem than micrometastases in patients with longer survival. CONCLUSIONS: Patient age and primary tumor control are more important factors in predicting median survival time than number of metastases to the brain. Long-term survivors are more common than previously assumed.

Kim, H. J., et al. (2013). "Clinical outcome with gamma-knife surgery or surgery for brain metastases from colorectal cancer." Journal of clinical neuroscience : official journal of the Neurosurgical Society of Australasia **20**(10): 1417-1421.

The aim of this study was to investigate the clinical outcomes after gamma knife surgery (GKS) or surgery as the first treatment for brain metastases in colorectal cancer (CRC). Of the 4350 patients diagnosed with CRC at our institution identified from 1987 to 2009, 27 patients who underwent GKS (GKS group) and 11 who underwent surgery (surgery group) were included. The oncologic outcomes were compared between the two groups. Local control was significantly better in the surgery group than in the GKS group (90% versus [vs.] 71.4%, respectively; $p=0.006$). The rate of symptom relief after 3 months was significantly higher in the surgery group than in the GKS group (72.7 vs.18.5%, respectively; $p=0.005$). The median survival after GKS was 5.6 months and surgery was 16.2 months. In multivariate analysis, controlled primary tumor ($p=0.038$) and solitary metastasis ($p=0.028$) were correlated with prolonged overall survival, whereas surgery ($p=0.034$) was associated

with longer local control. Surgery for brain metastasis from CRC is more advantageous in local control and neurologic symptom palliation than GSK. In multivariate analysis, overall survival was associated with controlled primary tumor and solitary metastasis.

Knisely, J. P., et al. (2010). "Radiosurgery alone for 5 or more brain metastases: expert opinion survey." Journal of Neurosurgery **113 Suppl**: 84-89.

OBJECT: Oligometastatic brain metastases may be treated with stereotactic radiosurgery (SRS) alone, but no consensus exists as to when SRS alone would be appropriate. A survey was conducted at 2 radiosurgery meetings to determine which factors SRS practitioners emphasize in recommending SRS alone, and what physician characteristics are associated with recommending SRS alone for >/= 5 metastases. METHODS: All physicians attending the 8th Biennial Congress and Exhibition of the International Stereotactic Radiosurgery Society in June 2007 and the 18th Annual Meeting of the Japanese Society of Stereotactic Radiosurgery in July 2009 were asked to complete a questionnaire ranking 14 clinical factors on a 5-point Likert-type scale (ranging from 1 = not important to 5 = very important) to determine how much each factor might influence a decision to recommend SRS alone for brain metastases. Results were condensed into a single dichotomous outcome variable of "influential" (4-5) versus "not influential" (1-3). Respondents were also asked to complete the statement: "In general, a reasonable number of brain metastases treatable by SRS alone would be, at most, ___." The characteristics of physicians willing to recommend SRS alone for >/= 5 metastases were assessed. Chi-square was used for univariate analysis, and logistic regression for multivariate analysis. RESULTS: The final study sample included 95 Gamma Knife and LINAC-using respondents (54% Gamma Knife users) in San Francisco and 54 in Sendai (48% Gamma Knife users). More than 70% at each meeting had >/= 5 years experience with SRS. Sixty-five percent in San Francisco and 83% in Sendai treated >/= 30 cases annually with SRS. The highest number of metastases considered reasonable to treat with SRS alone in both surveys was 50. In San Francisco, the mean and median numbers of metastases considered reasonable to treat with SRS alone were 6.7 and 5, while in Sendai they were 11 and 10. In the San Francisco sample, the clinical factors identified to be most influential in decision making were Karnofsky Performance Scale score (78%), presence/absence of mass effect (76%), and systemic disease control (63%). In Sendai, the most influential factors were the size of the metastases (78%), the Karnofsky Performance Scale score (70%), and metastasis location (68%). In San Francisco, 55% of respondents considered treating >/= 5 metastases and 22% considered treating >/= 10 metastases "reasonable." In Sendai, 83% of respondents considered treating >/= 5 metastases and 57% considered treating >/= 10 metastases "reasonable." In both groups, private practitioners, neurosurgeons, and Gamma Knife users were statistically significantly more likely to treat >/= 5 metastases with SRS alone. CONCLUSIONS: Although there is no clear consensus for how many metastases are reasonable to treat with SRS alone, more than half of the radiosurgeons at 2 international meetings were willing to extend the use of SRS as an initial treatment for >/= 5 brain metastases. Given the substantial variation in clinicians' approaches to SRS use, further research is required to identify patient characteristics associated with optimal SRS outcomes.

Kondziolka, D., et al. (2011). "Stereotactic radiosurgery as primary and salvage treatment for brain metastases from breast cancer. Clinical article." Journal of Neurosurgery **114**(3): 792-800.

OBJECT: To evaluate the role of stereotactic radiosurgery (SRS) in the management of brain metastases from breast cancer, the authors assessed clinical outcomes and prognostic factors for survival. METHODS: The records from 350 consecutive female patients who underwent SRS for 1535 brain metastases from breast cancer were reviewed. The median patient age was 54 years (range 19-84 years), and the median number of tumors per patient was 2 (range 1-18 lesions). One hundred seventeen patients (33%) had a single metastasis to the brain, and 233 patients (67%) had multiple brain metastases. The median tumor volume was 0.7 cm(3) (range 0.01-48.9 cm(3)), and the median total tumor volume for each patient was 4.9 cm(3) (range 0.09-74.1 cm(3)). RESULTS: Overall survival after SRS was 69%, 49%, and 26% at 6, 12, and 24 months, respectively, with a median survival of 11.2 months. Factors associated with a longer survival included controlled extracranial disease, a lower recursive partitioning analysis (RPA) class, a higher Karnofsky Performance Scale score, a smaller number of brain metastases, a smaller total tumor volume per patient, the presence of deep cerebral or brainstem metastases, and HER2/neu overexpression. Sustained local tumor control was achieved in 90% of the patients. Factors associated with longer progression-free survival included a better RPA class, fewer brain metastases, a smaller total tumor volume per patient, and a higher tumor margin dose. Symptomatic adverse radiation effects occurred in 6% of patients. Overall, the condition of 82% of patients improved or remained neurologically stable. CONCLUSIONS: Stereotactic radiosurgery was safe and effective in patients with brain metastases from breast cancer and should be considered for initial treatment.

Kondziolka, D., et al. (2005). "Long-term survivors after gamma knife radiosurgery for brain metastases." Cancer **104**(12): 2784-2791.

BACKGROUND: Stereotactic radiosurgery, with or without whole-brain radiation therapy, has become a valued management choice for patients with brain metastases, although their median survival remains limited. In patients who receive successful extracranial cancer care, patients who have controlled intracranial disease are living longer. The authors evaluated all brain metastasis in patients who lived for > or = 4 years after radiosurgery to determine clinical and treatment patterns potentially responsible for their outcome. METHODS: Six hundred seventy-seven patients with brain metastases underwent 781 radiosurgery procedures between 1988 and 2000. Data from the entire series were reviewed; and, if patients had > or = 4 years of survival, then they were evaluated for

information on brain and extracranial treatment, symptoms, imaging responses, need for further care, and management morbidity. These long-term survivors were compared with a cohort who lived for < 3 months after radiosurgery (n = 100 patients). RESULTS: Forty-four patients (6.5%) survived for > 4 years after radiosurgery (mean, 69 mos with 16 patients still alive). The mean age at radiosurgery was 53 years (maximum age, 72 yrs), and the median Karnofsky performance score (KPS) was 90. The lung (n = 15 patients), breast (n = 9 patients), kidney (n = 7 patients), and skin (melanoma; n = 6 patients) were the most frequent primary sites. Two or more organ sites outside the brain were involved in 18 patients (41%), the primary tumor plus lymph nodes were involved in 10 patients (23%), only the primary tumor was involved in 9 patients (20%), and only brain disease was involved in 7 patients (16%), indicating that extended survival was possible even in patients with multiorgan disease. Serial imaging of 133 tumors showed that 99 tumors were smaller (74%), 22 tumors were unchanged (17%), and 12 tumors were larger (9%). Four patients had a permanent neurologic deficit after brain tumor management, and six patients underwent a resection after radiosurgery. Compared with the patients who had limited survival (< 3 mos), long-term survivors had a higher initial KPS (P = 0.01), fewer brain metastases (P = 0.04), and less extracranial disease (P < 0.00005). CONCLUSIONS: Although the expected survival of patients with brain metastases may be limited, selected patients with effective intracranial and extracranial care for malignant disease can have prolonged, good-quality survival. The extent of extracranial disease at the time of radiosurgery was predictive of outcome, but this does not necessarily mean that patients cannot live for years if treatment is effective.

Limbrick, D. D., Jr., et al. (2009). "Combined surgical resection and stereotactic radiosurgery for treatment of cerebral metastases." Surgical neurology **71**(3): 280-288, disucssion 288-289.

BACKGROUND: Patients with limited intracranial metastatic disease traditionally have been treated with surgery followed by WBRT. However, there is growing concern for the debilitating cognitive effects after WBRT in long-term survivors. We present a series of patients treated with surgery followed by SRS, while reserving WBRT as a salvage therapy for disease progression. METHODS: Medical records from 15 patients with 1 to 2 cerebral metastases who underwent both resection and SRS were reviewed. Outcome measures included overall survival, survival by RPA class, EOR, local tumor control, progression of intracranial disease, need for WBRT salvage therapy, and COD. RESULTS: Fifteen patients with cerebral metastases were treated with the combined surgery-SRS paradigm. Eight of the 15 patients (53.3%) were designated RPA class 1, with 6 of 15 (40.0%) in class 2 and 1 of 15 (6.7%) in class 3. Gross total resection was achieved in 12 cases (80.0%). Overall median survival was 20.0 months, with values of 22.0 and 13.0 months for RPA classes 1 and 2, respectively. Local recurrence occurred in 16.7% of those patients with GTR. Six patients (40.0%) went on to receive WBRT at a median of 8.0 months from initial presentation. Twelve patients (80.0%) had died at the completion of the study, and the COD was CNS progression in 33.3%. CONCLUSIONS: Surgical resection combined with SRS is an effective treatment for selected patients with limited cerebral metastatic disease. Survival using this combined treatment was equivalent to or greater than that reported by other studies using surgery + WBRT or SRS + WBRT.

Lippitz, B., et al. (2013). "Stereotactic radiosurgery in the treatment of brain metastases: The current evidence." Cancer treatment reviews.

Chemotherapy has made substantial progress in the therapy of systemic cancer, but the phar-macological efficacy is insufficient in the treatment of brain metastases. Fractionated whole brain radiotherapy (WBRT) has been a standard treatment of brain metastases, but provides limited local tumor control and often unsatisfactory clinical results. Stereotactic radiosurgery using Gamma Knife, Linac or Cyberknife has overcome several of these limitations, which has influenced recent treatment recommendations. This present review summarizes the current literature of single session radiosurgery concerning survival and quality of life, specific responses, tumor volumes and numbers, about potential treatment combinations and radioresistant metastases. Gamma Knife and Linac based radiosurgery provide consistent results with a reproducible local tumor control in both single and multiple brain metastases. Ideally minimum doses of >/=18Gy are applied. Reported local control rates were 90-94% for breast cancer metastases and 81-98% for brain metastases of lung cancer. Local tumor control rates after radiosurgery of otherwise radioresistant brain metastases were 73-90% for melanoma and 83-96% for renal cell cancer. Currently, there is a tendency to treat a larger number of brain metastases in a single radiosurgical session, since numerous studies document high local tumor control after radiosurgical treatment of >3 brain metastases. New remote brain metastases are reported in 33-42% after WBRT and in 39-52% after radiosurgery, but while WBRT is generally applied only once, radiosurgery can be used repeatedly for remote recurrences or new metastases after WBRT. Larger metastases (>8-10cc) should be removed surgically, but for smaller metastases Gamma Knife radiosurgery appears to be equally effective as surgical tumor resection (level I evidence). Radiosurgery avoids the impairments in cognition and quality of life that can be a consequence of WBRT (level I evidence). High local efficacy, preservation of cerebral functions, short hospitalization and the option to continue a systemic chemotherapy are factors in favor of a minimally invasive approach with stereotactic radiosurgery.

Lwu, S., et al. (2013). "Stereotactic radiosurgery for the treatment of melanoma and renal cell carcinoma brain metastases." Oncology reports **29**(2): 407-412.

Renal cell carcinoma (RCC) and melanoma brain metastases have traditionally been considered radioresistant lesions when treated with conventional radiotherapeutic modalities. Radiosurgery provides high-dose radiation to a defined target volume with steep fall off in dose at lesion margins. Recent evidence suggests that stereotactic radiosurgery (SRS) is effective in improving local control and overall survival for a

number of tumor subtypes including RCC and melanoma brain metastases. The purpose of this study was to compare the response rate to SRS between RCC and melanoma patients and to identify predictors of response to SRS for these 2 specific subtypes of brain metastases. We retrospectively reviewed a prospectively maintained database of all brain metastases treated with Gamma Knife SRS at the University Health Network (Toronto, Ontario) between October 2007 and June 2010, studying RCC and melanoma patients. Demographics, treatment history and dosimetry data were collected; and MRIs were reviewed for treatment response. Log rank, Cox proportional hazard ratio and Kaplan-Meier survival analysis using SPSS were performed. A total of 103 brain metastases patients (41 RCC; 62 melanoma) were included in the study. The median age, Karnofsky performance status score and Eastern Cooperative Oncology Group performance score was 52 years (range 27-81), 90 (range 70-100) and 1 (range 0-2), respectively. Thirty-four lesions received adjuvant chemotherapy and 56 received pre-SRS whole brain radiation therapy. The median follow-up, prescription dose, Radiation Therapy Oncology Group conformity index, target volume and number of shots was 6 months (range 1-41 months), 21 Gy (range 15-25 Gy), 1.93 (range 1.04-9.76), 0.4 cm3 (range 0.005-13.36 cm3) and 2 (range 1-22), respectively. Smaller tumor volume (P=0.007) and RCC pathology (P=0.04) were found to be positive predictors of response. Actuarial local control rate for RCC and melanoma combined was 89% at 6 months, 84% at 12 months, 76% at 18 months and 61% at 24 months. Local control at 12 months was 91 and 75% for RCC and melanoma, respectively. SRS is a valuable treatment option for local control of RCC and melanoma brain metastases. Smaller tumor volume and RCC pathology, predictors of response, suggest distinct differences in tumor biology and the extent of radioresponse between RCC and melanoma.

Maranzano, E., et al. (2011). "Reirradiation of brain metastases with radiosurgery." Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology.

PURPOSE: To assess the outcome of reirradiation with stereotactic radiosurgery (SRS) of brain metastases (BM) recurring after whole brain radiotherapy (WBRT). METHODS AND MATERIALS: Between September 2001 and October 2008, 69 patients who recurred after WBRT were re-irradiated with SRS using a linear accelerator. The dose prescription was generally chosen according to maximum diameter of the tumor as suggested by Radiation Therapy Oncology Group (RTOG) 90-05 protocol. Patients were stratified by Karnofsky Performance Status (KPS), Neurologic Functional Score (NFS), RTOG Recursive Partitioning Analysis (RPA), Score Index for Radiosurgery (SIR), primary disease, dimension and number of BM, and time to first brain recurrence after WBRT. Response, survival, and toxicity were analyzed. RESULTS: At time of this retrospective analysis all patients had died. The 69 patients reirradiated with SRS had 150 metastases. Median interval between prior WBRT and SRS was 11months and median SRS prescribed dose was 20Gy. Response was obtained in 91% of lesions with 1-year local control rate of 74+/-4%.

Significantly longer duration of response was associated with higher doses (23Gy) and response achieved after SRS (complete and partial response better than stable disease). Cause of death was brain failure only in 36 (52%) patients. Median overall survival after reirradiation was 10months. Variables which significantly conditioned survival were KPS and NFS. Four (6%) patients had asymptomatic radionecrosis that developed prevalently when lesion diameters were larger and cumulative doses exceeded the values recommended by RTOG 90-05 protocol. About three-fourth of the patients had a good KPS and NFS after reirradiation. CONCLUSIONS: Reirradiation of BM with SRS resulted feasible and effective. A correct patient selection and an accurate evaluation of the cumulative irradiation dose were suggested.

Mariya, Y., et al. (2011). "Repeat stereotactic radiosurgery in the management of brain metastases from non-small cell lung cancer." The Tohoku journal of experimental medicine **223**(2): 125-131.

Non-small cell lung cancer (NSCLC) is characterized by brain metastases that occur in about 30 to 50% of patients. To control tumor growth potential with maintaining neurocognitive function is important in the recent radiotherapy against brain metastases. From this viewpoint, we investigated the utility of repeat stereotactic radiosurgery (SRS) with a linear accelerator in the management of brain metastases from NSCLC. Between October 1998 and May 2010, 28 patients harboring brain metastases received repeat SRS (20 men and 8 women, with the age ranged from 51 to 79). The total number of SRS sessions ranged from 2 to 5, and the total number of lesions in one patient ranged from 1 to 8. Neurological decline due to uncontrolled brain lesions was identified in 9 of 28 patients after the repeat SRS, while the remaining 19 patients showed no neurological decline. Out of the 28 patients, 18 patients died by July 1, 2010; 12 patients died of active extracranial disease and 6 patients died from progressive brain lesions, considered neurological death. The 2-year and 4-year overall survival rates were 51% and 23%, respectively, and the median survival time was 26 months. In conclusion, repeat SRS is a preferred option to manage brain metastases from NSCLC, leading to a long survival with a decreased neurological decline. Repeat SRS is promising to preserve neurocognition, because the convergent dose distribution decreases the unfavorable influences from radiation on germinal niches, thereby preserving neural stem cells that are responsible for the nervous system repair.

Mathieu, D., et al. (2008). "Tumor bed radiosurgery after resection of cerebral metastases." Neurosurgery **62**(4): 817-823; discussion 823-814.

OBJECTIVE: Adjuvant irradiation after resection of brain metastases reduces the risk of local recurrence. Whole-brain radiation therapy can be associated with significant neurotoxicity in long-term survivors of brain metastases. This retrospective study evaluates the role of tumor bed stereotactic radiosurgery as an alternative method of irradiation after initial resection of brain metastases to prevent local recurrence. METHODS: Forty patients underwent tumor bed radiosurgery after resection of brain metastases at two separate academic medical centers. The median age was 59.5 years. Twenty patients (67.5%) had single metastases. Resection was complete in 80% and partial in 20% of the patients. At the time of radiosurgery, systemic disease was active in 57.5%, inactive in 32.5%, and in remission in 10% of the patients. The median Karnofsky Performance Scale score was 80% (range, 60-100%). Radiosurgery was performed a median of 4 weeks after tumor resection. The median cavity radiosurgery volume was 9.1 ml (range, 0.6-39.9 ml). The median margin and maximum radiation dose were 16 and 32 Gy, respectively. RESULTS: Local control at the resection site was achieved in 73% of patients at a median follow-up period of 13 months. No variable significantly affected local control. New remote brain metastases occurred in 54% of the patients. Symptomatic radiation effect was seen in 5.4% of the patients. The median survival was 13 months after radiosurgery (range, 2-56 mo). CONCLUSION: Tumor bed radiosurgery provides effective local control of the tumor after resection in most patients. These preliminary data support radiosurgery after resection rather than traditional radiation therapy.

Matsunaga, S., et al. (2011). "Gamma Knife surgery for brain metastases from colorectal cancer. Clinical article." Journal of Neurosurgery **114**(3): 782-789.

OBJECT: The outcomes after Gamma Knife surgery (GKS) were retrospectively analyzed in patients with brain metastases from radioresistant primary colorectal cancer to evaluate the efficacy of GKS and the prognostic factors for local tumor control and overall survival. METHODS: The authors reviewed the medical records of 152 patients with 616 tumors. The group included 102 men and 50 women aged 35-85 years (mean age 64.4 years), who underwent GKS for metastatic brain tumors from colorectal cancer between April 1992 and September 2008 at Yokohama Rosai Hospital. RESULTS: The mean prescription dose to the tumor margin was 18.5 Gy (range 8-30 Gy). The mean tumor volume at GKS was 2.0 cm(3) (range 0.004-10.0 cm(3)). The primary tumors were located in the colon in 88 patients and the rectum in 64. The median interval between the diagnosis of primary lesions and the diagnosis of brain metastases was 27 months (range 0-180 months). The median neuroradiological follow-up period after GKS was 3 months (mean 6.4 months, range 1-93 months). The local tumor growth control rate, based on MR imaging, was 91.2%. The significant factors for unfavorable local tumor growth control, based on multivariate analysis, were larger tumor volume (p = 0.001) and lower margin dose (p = 0.016). The median overall survival time was 6 months. Lower Karnofsky Performance Scale (KPS) score (p = 0.026) and the presence of extracranial metastases (p = 0.004) at first GKS were significantly correlated with poor overall survival period in multivariate analysis. The cause of death was systemic disease in 112 patients and neurological disease in 13 patients. Leptomeningeal carcinomatosis was significantly correlated with a shorter duration of neurological survival in multivariate analysis (p < 0.0001). CONCLUSIONS: Gamma Knife surgery is effective for suppression of local tumor growth in patients with brain metastases from radioresistant colorectal primary cancer. Therefore, clinical and radiological screening of intracranial metastases for patients with lower KPS scores and/or the presence of extracranial metastases as well as follow-up examinations after GKS for brain metastases should be performed periodically in patients with colorectal cancer, because the neurological prognosis is improved by initial and repeat GKS for newly diagnosed or recurrent tumors leading to a prolonged high-quality survival period.

Mohammadi, A. M., et al. (2012). "Role of Gamma Knife surgery in patients with 5 or more brain metastases." J Neurosurg **117 Suppl**: 5-12.
OBJECT: The authors evaluated overall survival and factors predicting outcome in patients with >/= 5 brain metastases who were treated with Gamma Knife surgery (GKS). METHODS: Medical records from patients with >/= 5 brain metastases treated with GKS between 1997 and 2010 at the Cleveland Clinic Gamma Knife Center were retrospectively reviewed. Patient demographics, tumor characteristics, treatment-related factors, and outcome data were evaluated. RESULTS: One hundred seventy patients were identified, with a median age of 58 years. The female/male ratio was 1.2:1. Gamma Knife surgery was used as an upfront treatment in 35% of patients and as salvage treatment in 65% of patients with multiple brain metastases. The median overall survival after GKS was 6.7 months (95% CI 5.5-8.1). At the time of GKS, 128 patients (75%) had concurrent extracranial metastases, and in 69 patients (41%) multiple extracranial sites were involved. Ninety-two patients (54%) had a history of whole-brain radiation therapy, and 158 patients (93%) had a Karnofsky Performance Scale (KPS) score >/= 70. The median total intracranial disease volume was 3.2 cm(3) (range 0.2-37.2 cm(3)). A total intracranial tumor volume >/= 10 cm(3) was observed in 32 patients (19%). Lower KPS score at the time of treatment (p < 0.0001), patient age > 60 years (p = 0.004), multiple extracranial metastases (p = 0.0001), and greater intracranial burden of disease (p = 0.03) were prognostic factors for poor outcome in the univariate and multivariate analyses. CONCLUSIONS: In this study, GKS was safe and effective for upfront and salvage treatment in patients with >/= 5 brain metastases. Gamma Knife surgery should be considered as an additional treatment modality for these patients, especially in the subset of patients with favorable prognostic factors.

Monaco, E. A., 3rd, et al. (2013). "Leukoencephalopathy after whole-brain radiation therapy plus radiosurgery versus radiosurgery alone for metastatic lung cancer." Cancer **119**(1): 226-232.
BACKGROUND: As systemic therapies improve and patients live longer, concerns mount about the toxicity of whole-brain radiation therapy (WBRT) for treatment of brain metastases. Development of delayed white matter abnormalities indicative of leukoencephalopathy have been correlated with cognitive dysfunction. This study assesses the risk of imaging-defined leukoencephalopathy in patients whose management included WBRT in addition to stereotactic radiosurgery (SRS). This risk is compared to patients who only underwent SRS. METHODS: We

retrospectively compared 37 patients with non-small cell lung cancer who underwent WBRT plus SRS to 31 patients who underwent only SRS. All patients survived at least 1 year after treatment. We graded the development of delayed white matter changes on magnetic resonance imaging using a scale to evaluate T(2) /FLAIR (fluid attenuated image recovery) images: grade 1 = little or no white matter hyperintensity; grade 2 = limited periventricular hyperintensity; and grade 3 = diffuse white matter hyperintensity. RESULTS: Patients treated with WBRT and SRS had a significantly greater incidence of delayed white matter leukoencephalopathy compared to patients who underwent SRS alone (P < .001). On final imaging, 36 of 37 patients (97.3%) treated by WBRT developed leukoencephalopathy (25% with grade 2; 70.8% with grade 3). Only 1 patient treated with SRS alone developed leukoencephalopathy. CONCLUSIONS: Risk of leukoencephalopathy in patients treated with SRS alone for brain metastases was significantly lower than that for patients treated with WBRT plus SRS. A prospective study is necessary to correlate these findings with neurocognition and quality of life. These data supplement existing reports regarding the differential effects of WBRT and SRS on normal brain structure and function.

Nagai, A., et al. (2010). "Increases in the number of brain metastases detected at frame-fixed, thin-slice MRI for gamma knife surgery planning." Neuro Oncol **12**(11): 1187-1192.

For gamma knife planning, 2.4-mm-slice MRIs are taken under rigid frame fixation, so tiny tumors become visible. This study evaluated differences in the numbers of brain metastases between conventional contrast-enhanced MRI (6 +/- 1 mm slice thickness) taken before patient referral and contrast-enhanced MRI for gamma knife planning. The numbers of metastases on the 2 images were counted by at least 2 oncologists. For gamma knife planning, spoiled gradient-recalled echo images were obtained after 0.1 mmol/kg gadolinium administration using a 1.5-T system. Images from 1045 patients with an interval between the 2 MRI studies of 6 weeks or less were analyzed. Increases in the number of metastases were found in 33.7% of the 1045 patients, whereas the number was identical in 62.3%. In 4.0%, the number decreased, indicating overdiagnosis at conventional MRI. These proportions did not differ significantly by the interval before gamma knife. An increase from single to multiple metastases was found in 16.0%. Meningeal dissemination was newly diagnosed in 2.3%. On planning images, the proportions of patients with 1, 2, 3, and 4 or more lesions were 37.6%, 19.3%, 9.3%, and 33.8%, respectively. In cases of colorectal cancer and hepatoma, the proportions of patients with a single metastasis (32 of 61 [52%] and 5 of 6 [83%], respectively) were higher than that of patients with other malignancies. In about one-third of the patients, an increased number of metastases were found on the thin-slice images. This should be kept in mind when deciding the treatment strategy for brain metastases.

Ojerholm, E., et al. (2014). "Gamma Knife radiosurgery to four or more brain metastases in patients without prior intracranial radiation or surgery." Cancer Med.

Data on stereotactic radiosurgery (SRS) for four or more metastases are limited. Existing studies are confounded by significant proportions of patients receiving prior whole-brain radiation therapy (WBRT) or concurrent WBRT with SRS. Furthermore, published results disagree about the impact of tumor volume on overall survival. A retrospective review identified 38 patients without prior intracranial radiation or surgery who received Gamma Knife (GK) as sole treatment to >/=4 brain metastases in a single session. Twenty-eight cases with follow-up imaging were analyzed for intracranial progression. Prognostic factors were examined by univariate (log-rank test) and multivariate (Cox proportional hazards model) analyses. Common primary tumors were non-small cell lung (45%), melanoma (37%), and breast (8%). Cases were recursive partitioning analysis class II (94%) or III (6%). Patients harbored a median five tumors (range 4-12) with median total tumor volume of 1.2 cc. A median dose of 21 Gy was prescribed to the 50% isodose line. Patients survived a median 6.7 months from GK. Local treatment failure occurred in one case (4%) and distant failure in 22 (79%). On multivariate analysis, total tumor volume >/=3 cc was significantly associated with distant failure and worsened overall survival (P = 0.042 and 0.040). Fourteen patients (37%) underwent salvage WBRT at a median 10.3 months from GK and seven patients received repeat GK. GK as sole initial treatment for four or more simultaneous metastases spares some patients WBRT and delays it for others. Increased total tumor volume (>/=3 cc) is significantly associated with worsened overall survival.

Padovani, L., et al. (2012). "gamma knife radiosurgery of brain metastasis from breast cancer." Progress in neurological surgery **25**: 156-162.

The incidence of brain metastasis in patients with metastatic breast cancer ranges from 14 to 16%.Age, number of metastatic sites, short disease-free survival and molecular subtypes are associated with the occurrence of brain metastasis. Patients classified in the triple-negative group more frequently presented brain metastasis as the first site (26%) than those in the human epidermal growth factor receptor 2 (HER2)-positive (6%) or luminal (12%) subtypes. Whole brain radiation therapy (WBRT) is still the standard treatment for breast cancer patients with brain metastasis. The 1- and 2-year survival rates of patients with brain metastasis were 25 and 10%, respectively, with a median survival of 6 months. In selected patients with single brain metastasis, majority of lung cancer, three randomized controlled trials underlined the significant survival benefit in adding local treatment such as surgery or stereotactic radio surgery to WBRT. Similarly, the upfront stereotactic radiosurgery (SRS) alone did not affect survival rate in three other randomized studies and represents an alternative treatment for patients with stage 1-4. Metastatic breast cancer patients with Karnofsky Performance Scale >/=70, single or oligometastatic brain metastases and well-controlled extracranial disease or favorable disease-specific graded prognostic assessment group presented a median overall survival of 16 months. Delaying WBRT could spare patients of neurocognitive toxicity due to full-dose whole brain irradiation. Nevertheless, the real WBRT neurocognitive impact is still unclear. These patients should be followed with serial magnetic resonance image every 3 months and treated with WBRT or additional SRS at recurrence to control brain disease.

Park, Y. S., et al. (2011). "The efficacy of gamma knife radiosurgery for advanced gastric cancer with brain metastases." Journal of neuro-oncology **103**(3): 513-521.

The aim of this study was to retrospectively investigate the efficacy of gamma knife radiosurgery for brain metastases from advanced gastric cancer (AGC) comparing whole brain radiotherapy (WBRT). Between January 1991 and May 2008, 56 patients with brain metastases from AGC, treated with GKR or WBRT, were reviewed to assess prognostic factors affecting survival. Most brain metastases were diagnosed based on MRI, both metachronous and synchronous brain metastases, adenocarcinoma and signet ring carcinoma were included, but excluded cases of gastric lymphoma. Fifteen patients with a median age of 54.0 years (range, 42-67 years) were treated with GKR: 11 were treated with GKR only, 2 with surgery plus GKR, 1 with repeated GKR, 1 with GKR plus WBRT, and the other 1 with WBRT plus GKR. Forty-one were treated with WBRT only. The median number of metastatic brain lesions was 3 (range, 1-15), and treatment involved 17.0 Gy (range 14-23.6 Gy), or 30 Gy with fractionated radiotherapy. The median survival after brain metastases for GKR treatment was 40.0 weeks [95% confidence interval (CI) 44.9-132.1 weeks] and WBRT was 9.0 weeks 95% CI, 8.8-21.9 weeks). The progression free survival of 15 GKR treated patients was 56.5 weeks (95% CI 33.4-79.5 weeks). The recursive partitioning analysis (RPA) (class 2 vs. class 3) and use of GKR were correlated with prolonged survival in univariate and multivariate analyses. Age, sex, pathology, leptomeningeal seeding, tumor size (>/=3 cm), extracranial metastases, single metastasis, chemotherapy, and synchronous metastases were not correlated with a good prognosis in both univariate and multivariate analysis. Based on our study, the use of GKR and RPA class 2 resulted in more favorable clinical outcomes in patients with brain metastases from AGC.

Patchell, R. A., et al. (1986). "Single brain metastases: surgery plus radiation or radiation alone." Neurology **36**(4): 447-453.

We reviewed the records of patients treated for single brain metastases from non-small-cell lung cancer for 1978 through 1982. Forty-three patients received surgical treatment, including 37 who had surgery plus postoperative whole-brain radiation therapy and 6 patients who had surgery after failing to respond to radiation therapy. The surgically treated patients were matched with 43 patients treated with radiation therapy alone. The combined therapy group had significantly longer survivals than those treated with radiation therapy alone (19 months versus 9 months). The rates of local recurrence and neurologically related deaths were significantly higher in the radiation therapy-alone group. Patients treated with combined therapy survived longer, and the increased survival was due to lower recurrence of brain metastases after surgery and fewer neurologically related deaths.

Patchell, R. A., et al. (1990). "A randomized trial of surgery in the treatment of single metastases to the brain." N Engl J Med **322**(8): 494-500.
To assess the efficacy of surgical resection of brain metastases from extracranial primary cancer, we randomly assigned patients with a single brain metastasis to either surgical removal of the brain tumor followed by radiotherapy (surgical group) or needle biopsy and radiotherapy (radiation group). Forty-eight patients (25 in the surgical group and 23 in the radiation group) formed the study group; 6 other patients (11 percent) were excluded from the study because on biopsy their lesions proved to be either second primary tumors or inflammatory or infectious processes. Recurrence at the site of the original metastasis was less frequent in the surgical group than in the radiation group (5 of 25 [20 percent] vs. 12 of 23 [52 percent]; P less than 0.02). The overall length of survival was significantly longer in the surgical group (median, 40 weeks vs. 15 weeks in the radiation group; P less than 0.01), and the patients treated with surgery remained functionally independent longer (median, 38 weeks vs. 8 weeks in the radiation group; P less than 0.005). We conclude that patients with cancer and a single metastasis to the brain who receive treatment with surgical resection plus radiotherapy live longer, have fewer recurrences of cancer in the brain, and have a better quality of life than similar patients treated with radiotherapy alone.

Roberge, D. and L. Souhami (2010). "Tumor bed radiosurgery following resection of brain metastases: a review." Technology in cancer research & treatment **9**(6): 597-602.
There is a growing interest in adjuvant radiosurgery following resection of hematogenous brain metastases. We have identified 12 series reporting on a total of 480 patients treated to a tumor bed following microsurgery. These cases fall into 3 paradigms: adjuvant radiosurgery as an alternative to whole-brain radiotherapy (WBRT), radiosurgery as an intensification of adjuvant WBRT and adjuvant radiosurgery for patients having failed prior WBRT. For these paradigms the reported crude local control rates are 79%, 92% and 95%, respectively. The procedure appears well tolerate with approximately a 5% risk of late radiation necrosis. Prospective data is lagging behind clinical practice and plans for prospective trials are discussed.

Rush, S., et al. (2011). "Incidence, timing, and treatment of new brain metastases after Gamma Knife surgery for limited brain disease: the case for reducing the use of whole-brain radiation therapy." Journal of Neurosurgery **115**(1): 37-48.
OBJECT: In this paper, the authors' goal was to analyze the incidence, timing, and treatment of new metastases following initial treatment with 20-Gy Gamma Knife surgery (GKS) alone in patients with limited brain

metastases without whole-brain radiation therapy (WBRT). METHODS: A retrospective analysis of 114 consecutive adults (75 women and 34 men; median age 61 years) with KPS scores of 60 or higher who received GKS for 1-3 brain metastases </= 2 cm was performed (median lesion volume 0.35 cm(3)). Five patients lacking follow-up data were excluded from analysis. After treatment, patients underwent MR imaging at 6 weeks and every 3 months thereafter. New metastases were preferentially treated with additional GKS. Indications for WBRT included development of numerous metastases, leptomeningeal disease, or diffuse surgical-site recurrence. RESULTS: The median overall survival from GKS was 13.8 months. Excluding the 3 patients who died before follow-up imaging, 12 patients (11.3%) experienced local failure at a median of 7.4 months. Fifty-three patients (50%) developed new metastases at a median of 5 months. Six (7%) of 86 instances of new lesions were symptomatic. Most patients (67%) with distant failures were successfully treated using salvage GKS alone. Whole-brain radiotherapy was indicated in 20 patients (18.3%). Thirteen patients (11.9%) died of neurological disease. CONCLUSIONS: For patients with limited brain metastases and functional independence, 20-Gy GKS provides excellent disease control and high-functioning survival with minimal morbidity. New metastases developed in almost 50% of patients, but additional GKS was extremely effective in controlling disease. Using our algorithm, fewer than 20% of patients required WBRT, and only 12% died of progressive intracranial disease.

Salvetti, D. J., et al. (2013). "Gamma Knife surgery for the treatment of 5 to 15 metastases to the brain: clinical article." Journal of Neurosurgery **118**(6): 1250-1257.

OBJECT: It has been generally accepted that Gamma Knife surgery (GKS) is an effective primary or adjunct treatment for patients with 1-4 metastases to the brain. The number of studies detailing the use of GKS for 5 or more brain metastases, however, remains minimal. The aim of the current retrospective study was to elucidate the utility of GKS in patients with 5-15 brain metastases. METHODS: Patients were chosen for GKS based on prior MRI of these metastatic lesions and a known primary cancer diagnosis. Magnetic resonance imaging was used post-GKS to assess tumor control; patients were also followed up clinically. Overall survival (OS) from the date of GKS was used as the primary end point. Statistical analysis was performed to identify prognostic factors related to OS. RESULTS: Between 2003 and 2012, 96 patients were treated for a total of 704 metastatic brain lesions. The histology of these lesions varied among non-small cell lung cancer (NSCLC), breast cancer, melanoma, renal cancer, and other more rare carcinomas. At the initial treatment, 18 of the patients (18.8%) were categorized in Recursive Partitioning Analysis (RPA) Class 1 and 77 (80.2%) in RPA Class 2; none were in RPA Class 3. The median number of treated lesions was 7 (mean 7.13), and the median planned treatment volume was 6.12 cm(3) (range 0.42-57.83 cm(3)) per patient. The median clinical follow-up was 4.1 months (range 0.1-40.70 months). Actuarial tumor control was calculated to be 92.4% at 6 months, 84.8% at 12 months, and 74.9% at 24 months post-GKS. The

median OS was found to be 4.73 months (range 0.4-41.8 months). Multivariate analysis demonstrated that RPA class was a significant predictor of death (HR = 2.263, p = 0.038). Number of lesions, tumor histology, Graded Prognostic Assessment score, prior whole-brain radiation therapy, prior resection, prior chemotherapy, patient age, patient sex, controlled primary tumor, extracranial metastases, and planned treatment volume were not significant predictors of OS. CONCLUSIONS: In patients with 5-15 brain metastases at presentation, the number of lesions did not predict survival after GKS; however, the RPA class was predictive of OS in this group of patients. Gamma Knife surgery for such patients offers an excellent rate of local tumor control.

Siomin, V. E., et al. (2004). "Posterior fossa metastases: risk of leptomeningeal disease when treated with stereotactic radiosurgery compared to surgery." Journal of neuro-oncology **67**(1-2): 115-121.

INTRODUCTION: Leptomeningeal disease (LMD) represents a diffuse form of central nervous system metastatic disease that is often associated with poor quality of life and prognosis. Our objective was to compare the incidence of LMD in patients with posterior fossa metastases (PFM) following stereotactic radiosurgery (SRS) versus surgical resection. METHODS: The medical records of 93 patients aged 57.9 +/- 10.8 years (mean +/- SD) with PFM treated at the Cleveland Clinic from 1995 to 2001 were analyzed retrospectively. Treatments consisted of surgery with whole brain radiation therapy (WBRT) or SRS with or without WBRT. The impact of age, Karnofsky performance status (KPS) at presentation, Radiation Therapy Oncology Group, recursive partitioning analysis (RPA) class, status of extracranial disease, number, size, volume, pathology of brain metastases and steroid use were studied using univariate and multivariate analyses. RESULTS: There were 80 evaluable patients (10 lost to follow-up and three excluded for supratentorial surgery with subsequent LMD). LMD occurred after the surgical removal of the PFM in 9 of 18 patients (50%), whereas LMD occurred after SRS in 4 of 62 patients (6.5%) (p = 0.0028). Multivariate analysis also showed that patients who had surgery were more likely to develop LMD compared to patients treated with SRS (p = 0.0024). Patients had a median KPS decline of 30 points after LMD was diagnosed. There was no statistically significant difference in survival of patients with LMD and the rest of the patients (13.5 vs. 11.7 months, p = 0.7659). Patients treated surgically had significantly larger lesions (3.43 +/- 0.74 vs. 1.96 +/- 0.95 cm maximum diameter, p < 0.0001). All surgical patients belonged to RPA class II at diagnosis. Their survival was not different from the RPA class II patients in the SRS group. Surgery and SRS had comparable complication rates (8.1% vs. 5.6%, p = 0.99), although the surgical complications were more serious (e.g. hemorrhage, CSF leak). The duration of steroid use was longer after SRS compared to surgery (2.1 +/- 3.6 vs. 1.3 +/- 2.4 months); however, the difference was not statistically significant. Myopathy and psychosis in one patient after SRS, were the only steroid-related complications. There was no statistically significant association between the primary tumor type and the presence of LMD. CONCLUSIONS: In this retrospective analysis of patients with PFM, SRS was associated with a lower incidence of LMD than was surgery. Although LMD was associated with rapid and considerable decline in the quality of life, it did not influence the overall survival. SRS was associated with less serious complications than surgery. Surgery in this study was performed on patients with larger lesion sizes and a trend toward poorer initial performance status, which could bias these results. A prospective study directly comparing surgery and SRS and further evaluating the significance of LMD in PFM is warranted.

Skeie, B. S., et al. (2011). "Gamma knife surgery in brain melanomas: absence of extracranial metastases and tumor volume strongest indicators of prolonged survival." World neurosurgery **75**(5-6): 684-691; discussion 598-603.

OBJECTIVE: To review a series of patients who underwent Gamma Knife surgery (GKS) to identify prognostic factors for local growth control and survival. METHODS: During the period 1996-2006, 77 patients (42 men and 35 women) with a total of 143 metastases underwent GKS. A solitary lesion was present in 40 patients (51.9%). RESULTS: Growth control was achieved in 114 of 128 (89.1%) tumors and 59 of 70 (84.3%) patients. The median survival was 7 months (range 0-73 months) after GKS and 67 months (range 4-327 months) from the time of diagnosis. Patients with absence of extracranial disease lived longer than patients with more widespread disease-median 16 months (range 3-52 months) versus 6 months (range 0-73 months; P = 0.014). A total tumor volume of less than 5 cc was associated with longer survival (P = 0.041). Survival was significantly longer in recursive partitioning analysis (RPA) class 1 (22 months) than RPA class 2 (7 months) and RPA class 3 (3 months; P = 0.008). Even in cases of treatment failure with tumor growth or appearance of new metastases, GKS slowed down the cerebral disease with no significant reduction in the duration of survival. CONCLUSIONS: GKS for melanoma brain metastasis provides a high rate of local tumor control. Survival is longest for well-functioning patients with absence of extracranial metastases or with an intracerebral total tumor volume less than 5 cc.

Soltys, S. G., et al. (2008). "Stereotactic radiosurgery of the postoperative resection cavity for brain metastases." International journal of radiation oncology, biology, physics **70**(1): 187-193.

PURPOSE: The purpose of this study was to analyze results of adjuvant stereotactic radiosurgery (SRS) targeted at resection cavities of brain metastases without whole-brain irradiation (WBI). METHODS AND MATERIALS: Patients who underwent SRS to the tumor bed, deferring WBI after resection of a brain metastasis, were retrospectively identified. RESULTS: Seventy-two patients with 76 cavities treated from 1998 to 2006 met inclusion criteria. The SRS was delivered to a median marginal dose of 18.6 Gy (range, 15-30 Gy) targeting an average tumor volume of 9.8 cm(3) (range, 0.1-66.8 cm(3)). With a median follow-up of 8.1 months (range, 0.1-80.5 months), 65 patients had follow-up imaging assessable for control analyses. Actuarial local control rates at 6 and 12 months were

88% and 79%, respectively. On univariate analysis, increasing values of conformality indices were the only treatment variables that correlated significantly with improved local control; local control was 100% for the least conformal quartile compared with 63% for the remaining quartiles. Target volume, dose, and number of sessions were not statistically significant. CONCLUSIONS: In this retrospective series, SRS administered to the resection cavity of brain metastases resulted in a 79% local control rate at 12 months. This value compares favorably with historic results with observation alone (54%) and postoperative WBI (80-90%). Given the improved local control seen with less conformal plans, we recommend inclusion of a 2-mm margin around the resection cavity when using this technique.

Soon, Y. Y., et al. (2014). "Surgery or radiosurgery plus whole brain radiotherapy versus surgery or radiosurgery alone for brain metastases." Cochrane database of systematic reviews **3**: CD009454.

BACKGROUND: The benefits of adding upfront whole-brain radiotherapy (WBRT) to surgery or stereotactic radiosurgery (SRS) when compared to surgery or SRS alone for treatment of brain metastases are unclear. OBJECTIVES: To compare the efficacy and safety of surgery or SRS plus WBRT with that of surgery or SRS alone for treatment of brain metastases in patients with systemic cancer. SEARCH METHODS: We searched MEDLINE, EMBASE and The Cochrane Central Register of Controlled Trials (CENTRAL) up to May 2013 and annual meeting proceedings of ASCO and ASTRO up to September 2012 for relevant studies. SELECTION CRITERIA: Randomised controlled trials (RCTs) comparing surgery or SRS plus WBRT with surgery or SRS alone for treatment of brain metastases. DATA COLLECTION AND ANALYSIS: Two review authors undertook the quality assessment and data extraction. The primary outcome was overall survival (OS). Secondary outcomes include progression free survival (PFS), local and distant intracranial disease progression, neurocognitive function (NF), health related quality of life (HRQL) and neurological adverse events. Hazard ratios (HR), risk ratio (RR), confidence intervals (CI), P-values (P) were estimated with random effects models using Revman 5.1 MAIN RESULTS: We identified five RCTs including 663 patients with one to four brain metastases. The risk of bias associated with lack of blinding was high and impacted to a greater or lesser extent on the quality of evidence for all of the outcomes. Adding upfront WBRT decreased the relative risk of any intracranial disease progression at one year by 53% (RR 0.47, 95% CI 0.34 to 0.66, P value < 0.0001, I2 =34%, Chi2 P value = 0.21, low quality evidence) but there was no clear evidence of a difference in OS (HR 1.11, 95% CI 0.83 to 1.48, P value = 0.47, I2 = 52%, Chi2 P value = 0.08, low quality evidence) and PFS (HR 0.76, 95% CI 0.53 to 1.10, P value = 0.14, I2 = 16%, Chi2 P value = 0.28, low quality evidence). Subgroup analyses showed that the effects on overall survival were similar regardless of types of focal therapy used, number of brain metastases, dose and sequence of WBRT. The evaluation of the impact of upfront WBRT on NF, HRQL and neurological adverse events was limited by the unclear and high risk of reporting, performance and detection bias, and inconsistency in the instruments and methods used to measure and report results across studies. AUTHORS' CONCLUSIONS: There was no clear evidence of an effect on overall and progression free survival. The impact of upfront WBRT on neurocognitive function, health related quality of life and neurological adverse events was undetermined due to the high risk of performance and detection bias, and inconsistency in the instruments and methods used to measure and report results across studies.

Yaeger, K. A. and M. N. Nair (2013). "Surgery for brain metastases." Surg Neurol Int **4**(Suppl 4): S203-208.

The use of surgery in the treatment of brain metastases is controversial. Patients who present certain clinical characteristics may experience prolonged survival with resection compared with radiation therapy. Thus, for patients with a single metastatic lesion in the setting of well-controlled systemic cancer, surgery is highly indicated. Stereotactic radiosurgery (SRS) alone can provide a similar survival advantage, but when used as postoperative adjuvant therapy, patients experience extended survival times. Furthermore, surgery remains the only treatment option for patients with life-threatening neurological symptoms, who require immediate tumor debulking. Treatment of brain metastases requires a careful clinical assessment of individual patients, as different prognostic factors may indicate various modes or combinations of therapy. Since surgery is an effective method for achieving tumor management in particular cases, it remains an important consideration in the treatment algorithm for brain metastases.

Yamamoto, M., et al. (2014). "Stereotactic radiosurgery for patients with multiple brain metastases (JLGK0901): a multi-institutional prospective observational study." The lancet oncology.

BACKGROUND: We aimed to examine whether stereotactic radiosurgery without whole-brain radiotherapy (WBRT) as the initial treatment for patients with five to ten brain metastases is non-inferior to that for patients with two to four brain metastases in terms of overall survival. METHODS: This prospective observational study enrolled patients with one to ten newly diagnosed brain metastases (largest tumour <10 mL in volume and <3 cm in longest diameter; total cumulative volume </=15 mL) and a Karnofsky performance status score of 70 or higher from 23 facilities in Japan. Standard stereotactic radiosurgery procedures were used in all patients; tumour volumes smaller than 4 mL were irradiated with 22 Gy at the lesion periphery and those that were 4-10 mL with 20 Gy. The primary endpoint was overall survival, for which the non-inferiority margin for the comparison of outcomes in patients with two to four brain metastases with those of patients with five to ten brain metastases was set as the value of the upper 95% CI for a hazard ratio (HR) of 1.30, and all data were analysed by intention to treat. The study was finalised on Dec 31, 2012, for analysis of the primary endpoint; however, monitoring of stereotactic radiosurgery-induced complications and neurocognitive function assessment will continue for the censored

subset until the end of 2014. This study is registered with the University Medical Information Network Clinical Trial Registry, number 000001812. FINDINGS: We enrolled 1194 eligible patients between March 1, 2009, and Feb 15, 2012. Median overall survival after stereotactic radiosurgery was 13.9 months [95% CI 12.0-15.6] in the 455 patients with one tumour, 10.8 months [9.4-12.4] in the 531 patients with two to four tumours, and 10.8 months [9.1-12.7] in the 208 patients with five to ten tumours. Overall survival did not differ between the patients with two to four tumours and those with five to ten (HR 0.97, 95% CI 0.81-1.18 [less than non-inferiority margin], p=0.78; pnon-inferiority<0.0001). Stereotactic radiosurgery-induced adverse events occurred in 101 (8%) patients; nine (2%) patients with one tumour had one or more grade 3-4 event compared with 13 (2%) patients with two to four tumours and six (3%) patients with five to ten tumours. The proportion of patients who had one or more treatment-related adverse event of any grade did not differ significantly between the two groups of patients with multiple tumours (50 [9%] patients with two to four tumours vs 18 [9%] with five to ten; p=0.89). Four patients died, mainly of complications relating to stereotactic radiosurgery (two with one tumour and one each in the other two groups). INTERPRETATION: Our results suggest that stereotactic radiosurgery without WBRT in patients with five to ten brain metastases is non-inferior to that in patients with two to four brain metastases. Considering the minimal invasiveness of stereotactic radiosurgery and the fewer side-effects than with WBRT, stereotactic radiosurgery might be a suitable alternative for patients with up to ten brain metastases. FUNDING: Japan Brain Foundation.

Yang, H. C., et al. (2011). "What factors predict the response of larger brain metastases to radiosurgery?" Neurosurgery **68**(3): 682-690; discussion 690.

BACKGROUND: Approximately 20 to 40% of patients with systemic malignancies develop brain metastases. OBJECTIVE: To assess the potential role of stereotactic radiosurgery (SRS) for larger metastatic brain tumors, we reviewed our recent experience. METHODS: Between 2004 and 2008, 70 patients with a metastatic brain tumor larger than 3 cm in maximum diameter underwent Gamma knife SRS. Thirty-three patients had received previous whole brain radiation therapy (WBRT) and 37 received only SRS. RESULTS: The overall median follow-up was 8.1 months. At the first planned imaging follow-up at 2 months, 29 (41%) tumors had >50% volume reduction, 22 (31%) had 10 to 50% volume reduction, and 19 (28%) were stable or larger. We also evaluated brain edema using MRI T2 images. In 11 patients (16%) the peritumoral edema volume was reduced by more than 50%, in 25 (36%) it was reduced by 10 to 50%, in 21 (30%) it was stable, and in 13 (19%) it was increased. Twenty (36%) discontinued corticosteroids by the time of first imaging follow-up. Because of persistent symptoms, 7 patients (10%) required a craniotomy to remove the tumor. Tumor volume reduction (>50%) was associated with a single metastasis (P=.012), no previous WBRT (P=.002), and a tumor volume<16 cm3 (P=.002). The better peritumoral edema volume reduction (>50%) was associated with a single metastasis

(P=.024), no previous WBRT (P=.05), and breast cancer histology (P=.044). CONCLUSION: Surgical resection remains the primary approach for larger brain metastases if feasible. Tumor volume is a better indicator than maximum diameter. Tumor volume and edema responded better in patients who underwent SRS alone.

Yoo, T. W., et al. (2011). "Gamma knife radiosurgery for brainstem metastasis." Journal of Korean Neurosurgical Society **50**(4): 299-303.

OBJECTIVE: Brainstem metastases are rarely operable and generally unresponsive to conventional radiation therapy or chemotherapy. Recently, Gamma Knife Radiosurgery (GKRS) was used as feasible treatment option for brainstem metastasis. The present study evaluated our experience of brainstem metastasis which was treated with GKRS. METHODS: Between November 1992 and June 2010, 32 patients (23 men and 9 women, mean age 56.1 years, range 39-73) were treated with GKRS for brainstem metastases. There were metastatic lesions in pons in 23, the midbrain in 6, and the medulla oblongata in 3 patients, respectively. The primary tumor site was lung in 21, breast in 3, kidney in 2 and other locations in 6 patients. The mean tumor volume was 1,517 mm(3) (range, 9-6,000), and the mean marginal dose was 15.9 Gy (range, 6-23). Magnetic Resonance Imaging (MRI) was obtained every 2-3 months following GKRS. Follow-up MRI was possible in 24 patients at a mean follow-up duration of 12.0 months (range, 1-45). Kaplan-Meier survival analysis was used to evaluate the prognostic factors. RESULTS: Follow-up MRI showed tumor disappearance in 6, tumor shrinkage in 14, no change in tumor size in 1, and tumor growth in 3 patients, which translated into a local tumor control rate of 87.5% (21 of 24 tumors). The mean progression free survival was 12.2 months (range, 2-45) after GKRS. Nine patients were alive at the completion of the study, and the overall mean survival time after GKRS was 7.7 months (range, 1-22). One patient with metastatic melanoma experienced intratumoral hemorrhage during the follow-up period. Survival was found to be associated with score of more than 70 on Karnofsky performance status and low recursive partitioning analysis class (class 1 or 2), in terms of favorable prognostic factors. CONCLUSION: GKRS was found to be safe and effective for management of brainstem metastasis. The integral clinical status of patient seems to be important in determining the overall survival time.

NATIONAL KLINISK RETNINGSLINJE FOR BEHANDLING AF HJERNEMETASTASER Review

Table of contents

Evidensens kvalitet – de fire niveauer
Excellent selection of tools enabling an accountable analysis of the described available data.

Inledning - Kirurgisk resektion eller stereotaktisk strålebehandling

Stereotaktisk strålebehandling

1. Lokalisation i hjernestamme, thalamus, optiske nerver taler imod stereotaktisk strålebehandling

Remarks

Brainstem feasible for GKRS apart from optic nerve vicinity when administering in single dose regimen.

SRS, particularly Gamma Knife Radiosurgery (GKRS) can be an effective treatment modality for metastases within the brainstem and in close vicinity to other critical structures apart from the optic apparatus achieving high local control rates and low treatment-associated morbidity. [32] [7,8,10,17,19,22,36]

2 Betydning af operativ resektion og helhjernebestråling af solitær hjernemetastase

Compelling, well-structured assessment

3 Betydning af operativ resektion eller stereotaktisk strålebehandling ved solitær hjernemetastase

Compelling, well-structured assessment

Remarks
When utilizing SRS, particularly GKRS, the option of various modalities is still preserved closely timed or in the later course of the patients' history.
When utilizing microsurgery, the timing of the post-op MRI may play an important role in distinguishing between residual tumor and postoperative changes.
In the following overviews of respective studies show that GKRS may represent a feasible treatment option for intracranial metastases from various primary tumors including so called radioresistant metastases.

Metastases local control after treatment (in series > 1000 pat)	single/ multiple	number of patients	local tumour control
Gaudy-Marqueste C, Regis J-M, Muracciole X, Laurans R, Richard M-A, Bonerandi J-J, et al. *Int. J. Radiat. Oncol. Biol. Phys. 65:809–816, 2006*	**both**	**106**	**83,7%**
Simonová G, Roman L *Expert Rev Anti Infect Ther 3:879–890, 2003*	**both**	**400**	**90%**
Hasegawa T, Kondziolka D, Flickinger JC, Germanwala A, Lunsford LD *Neurosurgery 52:1318–26– discussion 1326, 2003*	**both**	**172**	**87%**
Chen JCT, O rsquo Day S, Morton D, Essner R, Cohen-Gadol A, MacPherson D, et al *Stereotact Funct Neurosurg 73:60–63, 1999*	**both**	**190**	**89%**

[5,11,15,37]

breast cancer metastases	Treatment modality	Number of patients	median survival Months	local tumour control
Goyal S, Prasad D, Harrell F, Matsumoto J, Rich T, Steiner L *J. Neurosurg. 103:218–223, 2005*	GKRS	43	13	
Muacevic A, Kreth FW, Tonn J-C, Wowra B *Cancer 100:1705–1711, 2004*	GKRS	151	10 34.9 (RPA class I) 9.1 (RPA class II) 7.9 (RPA class III)	94%
Kenneth J Levin, Emad F Youssef, Andrew E Sloan, Rajiv Patel, Rana K Zabad, Lucia Zamorano *J Neurosurg, 97(5 Suppl):663-5, 2002*	GKRS	12	11.5	
Amendola BE, Wolf AL, Coy SR, Amendola M, Bloch L *The Cancer Journal 6:88–92, 2000*	GKRS	68	7.8	94%
Firlik KS, Kondziolka D, Flickinger JC, *Lunsford LD Ann. Surg. Oncol. 7:333–338, 2000*	GKRS	30	13	93%

1,9,12,21,27

malignant melanoma metastases	Treatment modality	Number of patients	median survival Months	local tumour control
Powell JW, Chung CT, Shah HR, Canute GW, Hodge CJ, Bassano DA, et al. *J. Neurosurg. 109 Suppl:122–128, 2008*	GKRS	50	5.1	63% 12-month rate for freedom from local progression
Brown PD, Brown CA, Pollock BE, Gorman DA, Foote RL *Neurosurgery 62 Suppl 2:790–801, 2008*	GKRS	23	14.2 23.5 (RPA class I) 10.5 (RPA class II+III)	
Mathieu D, Kondziolka D, Cooper PB, Flickinger JC, Niranjan A, Agarwala S, et al. *Neurosurgery 60:471–81– discussion 481–2, 2007*	GKRS	244	5.3	86,2%
Gaudy-Marqueste C, Regis J-M, Muracciole X, Laurans R, Richard M-A, Bonerandi J-J, et al. *Int. J. Radiat. Oncol. Biol. Phys. 65:809–816, 2006*	GKRS	106	5.09	83,7%
Radbill AE, Fiveash JF, Falkenberg ET, Guthrie BL, Young PE, Meleth S, et al. *Cancer 101:825–833, 2004*	GKRS	51	6.5 14.25 (RPA class I) 5 (RPA class II+III)	81%
Yu C, Chen JCT, Apuzzo MLJ, O'Day S, Giannotta SL, Weber JS, et al. *Int. J. Radiat. Oncol. Biol. Phys. 52:1277–1287, 2002*	GKRS	122	7	
Mingione V, Oliveira M, Prasad D, Steiner M, Steiner L *J. Neurosurg. 96:544–551, 2002*	GKRS	45	10.4	82%
Lavine SD, Petrovich Z, Cohen-Gadol AA, Masri LS, Morton DL, O'Day SJ, et al. *Neurosurgery 44:59–64– discussion 64–6, 1999*	GKRS	45	8	97%
Grob JJ, Régis J, Laurans R, Delaunay M, Wolkenstein P, Paul K, et al. *European Journal of Cancer 34:1187–1192, 1998*	GKRS	35	22 (for solitary brain metastasis) 7.5 (for single brain metastasis and metastases elsewhere) 4 (for multiple brain metastases)	98.2% (at 3 months)
Mori Y, Kondziolka D, Flickinger JC, Logan T, Lunsford LD *Cancer 83:344–353, 1998*	GKRS	60	7	90%
Seung SK, Sneed PK, McDermott MW, Shu HK, Leong SP, Chang S, et al. *Cancer J Sci Am 4:103–109, 1998*	GKRS	55	8.75	77%

4,11,14,20,24-26,28,30,34,38

4 Betydning af stereotaktisk strålebehandling i behandling af oligometastaser i hjernen

Compelling, well-structured assessment

Stereotaktisk strålebehandling har kun effekt på påviste metastaser. Der er ikke forebyggende effekt på udvikling af nye metastaser andre steder i hjernen, som der kan være ved

helhjernebestråling. Dette bør man derfor tage med i overvejelserne når der vælges stereotaktisk strålebehandling og ikke helhjernebestråling.

Remarks
In in this context it is important to mention that WBRT does not hinder distant recurrences.
Distant metastases in 41.5 % 12-month actuarial rate after (WBRT +SRS)[2]
Distant metastases in 34% 12 months after WBRT[31]

Patients treated with SRS experience distant mets in up to 52% of cases.[6,35]

Shirato H, Takamura A, Tomita M, Suzuki K, Nishioka T, Isu T, Kato T, Sawamura Y, Miyamachi K, Abe H, Miyasaka K. Stereotactic irradiation without whole-brain irradiation for single brain metastasis. Int J Radiat Oncol Biol Phys. 1997 Jan 15;37(2):385-91

Chidel MA, Suh JH, Reddy CA, Chao ST, Lundbeck MF, Barnett GH : Application of recursive partitioning analysis and evaluation of the use of whole brain radiation among patients treated with stereotactic radiosurgery for newly diagnosed brain metastases. Int J Radiat Oncol Biol Phys 2000 Jul 1;47(4):993-9).

However as for example GKRS as a SRS modality has its strengths in a high-precision focus on the lesion, distant control cannot be expected. A structured routine follow-up consisting of an MRI every three months would enable the detection of new metastases and subsequent treatment. GKRS can be utilized multiple times for distant metastases if warranted by the patients' clinical status.

When utilizing SRS, particularly GKRS, the option of various modalities as whole brain radiation therapy is still preserved closely timed or in the later course of the patients' history.

5 Betyding af stereotaktisk strålebehandling i forbindelse med helhjernebestråling af fem eller flere hjernemetastaser

Compelling, well-structured assessment

Remarks

SRS and in particular GKRS may be an option for 5 or more intracranial metastases with good local control and a low risk for adverse events. [3,13,33]

521 patients treated with Gamma Knife radiosurgery :

For both overall survival and neurological survival, the differences between a few (</=3) and many (4-10) brain lesions were not significant

Patients with more than 10 metastases had a significantly poorer prognosis than those with less than 10 tumours.[33]

Serizawa T, Saeki N, Higuchi Y, Ono J, Iuchi T, Nagano O, Yamaura A. Gamma knife surgery for brain metastases: indications for and limitations of a local treatment protocol. Acta Neurochir (Wien). 2005

Favourable subgroup:
total treatment volume <7 cc and
< 7 brain metastases
with a median survival of 13 months

This subgroup's survival was significantly better (p <0.00005) than the remaining patients (Class 2) (n=111) with a median survival of 6 months.[3]

Bhatnagar AK, Kondziolka D, Lunsford LD, Flickinger JC. Recursive partitioning analysis of prognostic factors for patients with four or more intracranial metastases treated with radiosurgery. Technol Cancer Res Treat. 2007

6 Betydning af helhjernebestråling af hjernemetastaser og dårlig prognose

Compelling, well-structured assessment

7 Betydning af kemoterapi i behandling af hjernemetastaser

Compelling, well-structured assessment

Remarks

Particularly this point may require close monitoring of current and developing therapies as for example ipilumumab showing interesting results in selected cases. [16,18,23,29]

8 Betydning af steroid ved hjernemetastaser uden neurologiske symptomer

Compelling, well-structured assessment

9 Betydning af steroid ved hjernemetastaser med neurologiske symptomer

Compelling, well-structured assessment

Remarks

Steroid administration should in any case be monitored due to described well documented adverse events.
Patients should undergo regular oncological status as foundation for eventual re-assessment in case of response to potential ongoing treatment regimens.

10 Behandling af recidiv af hjernemetastaser efter tidligere helhjernebestråling

Compelling, well-structured assessment

Remarks

RPA, all feasible treatment options, overall oncologic status and patient perspective should be taken into consideration.

Evidensen bygger på en blandet population af patienter med forskellige kræfttyper og forskellige kemoterapeutiske regimer.

Compelling and important assessment

Arbejdsgruppen anbefaler, at patienter med solitær hjernemetastase om muligt inkluderes i et randomiseret studie, der sammenligner operativ resektion og stereotaktisk strålebehandling.

Bedømmelsen

General remarks

1. Manuskriptets styrker
The manuscript illuminates the entire spectrum of treatment modalities based on an extensive analysis of available data. The quoted studies are weighed in an accountable fashion.

2. Manuskriptets væsentligste svagheder og mangler
Management of intracranial metastases may warrant a more detailed comparison of available treatment modalities in the field of SRS possibly emphasizing differences between various modalities in this context as LINAC and gamma knife radiosurgical strategies.

3. Eventuelle forslag til ændringer
A more detailed comparison of various LINAC modalities with GKRS in the context of SRS would complete the current extensive analysis.

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