Technoleg Iechyd Cymru
Health Technology Wales

Topic Exploration Report

Topic explorations are designed to provide a high-level briefing on new topics submitted for consideration by Health Technology Wales. The main objectives of this report are to:

1. Determine the quantity and quality of evidence available for a technology of interest.
2. Identify any gaps in the evidence/ongoing evidence collection.
3. Inform decisions on topics that warrant fuller assessment by Health Technology Wales.

Topic:	Intraoperative radiotherapy for the treatment of brain tumours or brain metastases
Topic exploration report number:	TER215

Introduction and aims

People who have surgery to remove a brain tumour (either a primary tumour or metastases) may also receive radiotherapy after resection of the tumour. This usually involves delivery of a course of external beam radiotherapy after surgery is complete. Intraoperative radiotherapy (IORT) is an alternative method of delivering radiotherapy: after the tumour has been removed, a miniaturised x-ray source is inserted into the tumour cavity and used to deliver a single dose of radiation directly to the tumour bed. This is done at the time of surgery, while the patient is still under anaesthesia, rather than requiring repeat visits for a course of treatment after surgery. Available technologies to carry out IORT include the Xoft Axxent Electronic Brachytherapy (eBx) System. This is designed to be used in the treatment of cancer anywhere in the body, but this report focusses solely on its used to treat tumours or metastases in the brain.

Health Technology Wales researchers searched for evidence on the effectiveness of IORT in the treatment of brain tumours, using the Xoft system or any other available technologies.

Summary of evidence

We identified six observational trials studying the clinical effectiveness of IORT in people with brain tumours or metastases. Across the six trials a total of 159 patients received IORT. Three trials compared IORT to other types of radiotherapy within a cohort of patients treated at a similar time, or to a historical control group. In two trials, the authors conclude that IORT improves length of survival, whilst the third trial did not find a difference in survival between IORT and control treatment. The design of the trials makes it difficult to draw reliable conclusions about the effectiveness of IORT compared to other forms of radiotherapy. Other trials did not include a control group and only report outcomes for IORT. These trials are listed in the Brief Literature Results section at the end of this report.

We did not identify any guidelines or technology assessments on the use of IORT as a method of delivering radiotherapy to people having surgery to remove a brain tumour, or any evidence on the cost effectiveness of this treatment in people with brain tumours.

We identified three studies that compared IORT to a control treatment (Fujiwara 1995, Nemoto 2002, Chan 2005) in people having surgery for glioma. One trial compared IORT to people treated with postoperative external beam radiotherapy alone; two trials compared IORT to historical controls and did not specify the exact treatment received. The number of patients treated with IORT was between 20 and 32.

All three trials reported overall survival. Fujiwara reported that median survival time in the IORT group was 14 months and that of the control group was 10 months, and that this difference was statistically significant. Nemoto reported no significant difference between survival rates in the IORT patients and control patients; results for anaplastic astrocytoma and glioblastoma were reported separately and also no significant difference in survival was found. Chan reported median survival after IORT of 9.1 months, and reported that this compared favourably to patients of similar recursive partitioning analysis (RPA) status taken from a historical database, although exact survival figures for this historical control group were not reported.

Chan reported that acute side effects from IORT treatment were mild and late complications were rare but did not report adverse events for a control group. Fuijiwara reported that 6 out of 20 patients experienced complications as a result of IORT but also did not report comparative outcomes from their control group.

We identified two ongoing studies of IORT, both in people with brain metastases. Both are single-arm studies that do not include a control group. Details of the trials are in the Brief Literature Results section.

Areas of uncertainty

The evidence identified compares IORT to control treatment in non-randomised studies, some of which used historical controls. These trials compared survival between treatments, but the design of the trials means the results are associated with considerable uncertainty. We did not identify any published or ongoing randomised controlled trials that would provide more reliable evidence about the effectiveness of IORT. We did not identify any evidence comparing adverse events of treatment from IORT with other treatments: two trials reported adverse events from IORT but did not report these for the control group. We did not identify any evidence on how IORT affects other outcomes that may be of importance, such as people's satisfaction with their treatment or their quality of life after treatment.

The evidence identified studied IORT in people with varying classifications and stages of brain tumour, both previously treated and recurrent. It is unclear whether there are particular groups or types of brain tumour that would benefit most from IORT over other treatments.

Conclusions

Evidence from observational studies reports mixed conclusions about the comparative effectiveness of IORT compared to other radiotherapy treatments in people with brain tumours. Outcomes reported focussed on survival; it is unclear based on the evidence found whether IORT could offer advantages to patients by reducing treatment toxicity and

treatment burden, or improving quality of life after treatment. Further trials of IORT are ongoing.

Brief literature search results

Resource	Results
HTA organisations	
Healthcare Improvement Scotland	We did not identify any relevant guidance from this source.
Health Information and Quality Authority	We did not identify any relevant guidance from this source.
UK guidelines and guidance	
SIGN	We did not identify any relevant guidance from this source.
NICE	National Institute for Health and Care Excellence. Brain tumours (primary) and brain metastases in adults NICE guideline [NG99]. Published date: 11 July 2018. Last updated: 29 January 2021. https://www.nice.org.uk/guidance/ng99 *This guideline does not include any recommendations on the use of IORT specifically.* We did not identify any other relevant guidance or advice on IORT.
Secondary literature and economic evaluations	
EUnetHTA	We did not identify any relevant published or ongoing guidance from this source.
Cochrane library	Hanna C, Lawrie TA, Rogozińska E, Kernohan A, Jefferies S, Bulbeck H, Ali UM, Robinson T, Grant R. Treatment of newly diagnosed glioblastoma in the elderly: a network meta-analysis. Cochrane Database Syst Rev. 2020 Mar 23;3(3):CD013261. https://doi.org/10.1002/14651858.cd013261.pub2 *This review does not include any evidence specifically on IORT.* Hu X, Fang Y, Hui X, Jv Y, You C. Radiotherapy for diffuse brainstem glioma in children and young adults. Cochrane Database Syst Rev. 2016 Jun 27;(6):CD010439. https://doi.org/10.1002/14651858.cd010439.pub2 *This review does not include any evidence specifically on IORT.*
Medline	Najafipour F, Hamouzadeh P, Arabloo J, Mobinizadeh M, Norouzi A. Safety, effectiveness and economic evaluation of intra-operative radiation therapy: a systematic review. Med J Islam Repub Iran. 2015;29:258. Published 2015 Sep 7. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4715414/ *Review of systematic reviews and economic evaluations of IORT (any indication). We identified some methodological flaws in the conduct of this review, and it does not report any evidence on the effectiveness of IORT for the treatment of brain tumours or brain metastases.*

Primary studies	
Cochrane library	*Comparative studies* Fujiwara T, Honma Y, Ogawa T, Irie K, Kuyama H, Nagao S, Takashima H, Hosokawa A, Ohkawa M, Tanabe M. Intraoperative radiotherapy for gliomas. Journal of neuro-oncology 1995; 23(1): 81-86. https://doi.org/10.1007/bf01058463 Nemoto K, Ogawa Y, Matsushita H, Takeda K, Takai Y, Yamada S, Kumabe T. Intraoperative radiation therapy (IORT) for previously untreated malignant gliomas. BMC cancer 2002; 2(null): 1. https://doi.org/10.1186/1471-2407-2-1 *Single-arm studies* Weil RJ, Mavinkurve GG, Chao ST, Vogelbaum MA, Suh JH, Kolar M, Toms SA. Intraoperative radiotherapy to treat newly diagnosed solitary brain metastasis: initial experience and long-term outcomes. Journal of neurosurgery 2015; 122(4): 825-832. https://doi.org/10.3171/2014.11.JNS1449 Epstein M, Khan S, Chen P, Kim B, Guerra L, Snyder L, Coleman C, Lopez J, MacKintosh R, DeLeon C, Silverstein M. 640 Patients treated with Intraoperative Radiation Therapy (IORT): initial report. Annals of surgical oncology. Conference: 17th annual meeting of the american society of breast surgeons, ASBS 2016. United states. Conference start: 20160413. Conference end: 20160417 2016; 23(3 Supplement 1): 359-360. https://doi.org/10.1245/s10434-016-5195-2 Brehmer S, Welsch M, Karakoyun A, Forster A, Seiz-Rosenhagen M, Clausen S, Schneider F, Wenz F, Hanggi D, Giordano FA. Intraoperative radiotherapy after resection of brain metastases (INTRAMET) - Initial safety/efficacy analysis of a prospective Phase II study. Neuro-oncology 2018; 20 (Supplement 3): iii310-iii311. https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01984731/full Giordano FA, Brehmer S, Mürle B, Welzel G, Sperk E, Keller A, Abo-Madyan Y, Scherzinger E, Clausen S, Schneider F, Herskind C, Glas M, Seiz-Rosenhagen M, Groden C, Hänggi D, Schmiedek P, Emami B, Souhami L, Petrecca K, Wenz F. Intraoperative Radiotherapy in Newly Diagnosed Glioblastoma (INTRAGO): An Open-Label, Dose-Escalation Phase I/II Trial. Neurosurgery. 2019 Jan 1;84(1):41-49. https://doi.org/10.1093/neuros/nyy018
Medline	Chan TA, Weingart JD, Parisi M, et al. Treatment of recurrent glioblastoma multiforme with GliaSite brachytherapy. Int J Radiat Oncol Biol Phys. 2005;62(4):1133-1139. https://doi.org/10.1016/j.ijrobp.2004.12.032
Ongoing primary or secondary research	
PROSPERO database	We did not identify any relevant ongoing secondary research.

Clinicaltrials.gov	Study of Intraoperative Radiotherapy for Patients With Large Brain Metastases Treated With Neurosurgical Resection. ClinicalTrials.gov Identifier: NCT04040400. First posted: July 2019. Recruitment status: recruiting. https://clinicaltrials.gov/ct2/show/NCT04040400 Focal Intraoperative Radiotherapy of Brain Metastases. ClinicalTrials.gov Identifier: NCT03789149. First posted: December 2018. Recruitment status: recruiting. https://clinicaltrials.gov/ct2/show/NCT03789149
Other	
Evidence provided by the topic proposer:	Krivoshapkin A, et al. Repeat Resection and Intraoperative Radiotherapy for Malignant Gliomas of the Brain: A History and Review of Current Techniques. World Neurosurgery (2019) 132: 356-362. https://doi.org/10.1016/j.wneu.2019.09.037

Date of search:	March 2021
Concepts used:	Intraoperative radiotherapy; brain tumours (primary); brain metastases