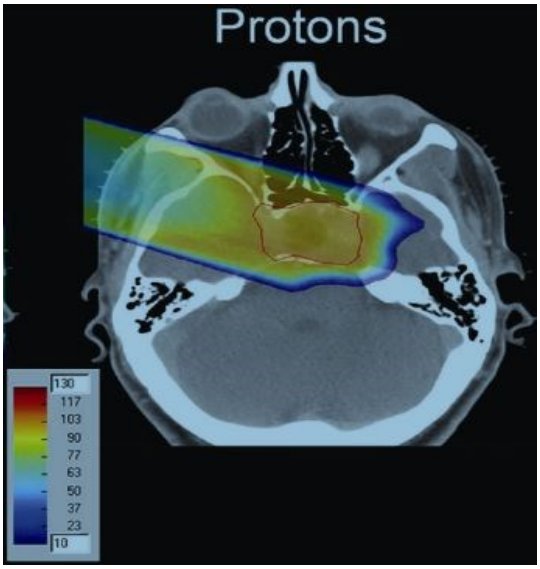
EFFECTIVENESS AND SAFETY OF CARBON ION BEAM RADIOTHERAPY (CIRT)

- *Original publication: Goetz, G, Mitic, M. Carbon ion beam radiotherapy (CIRT) for cancer treatment: a systematic review of effectiveness and safety for 12 oncologic indications. HTA Project Report No. 101; 2018. Vienna: Ludwig Boltzmann Institute for Health Technology Assessment.*
- *This **KCE has read for you** was prepared by Lorena San Miguel and Frank Hulstaert*
- *Published on 4 February 2019*

KEY MESSAGES OF THE ORIGINAL PUBLICATION

- Only 1 randomised, open label, pilot study (high risk of bias) focusing on safety and 3 case-control studies (moderate risk of bias)
- Overall, 54 indications were studied. No evidence was found for 41 indications, and insufficient scientific evidence was found for the remaining 13. .
- The technique should, to this date, be considered as "experimental".
- More research (RCTs) is needed to reach clear conclusions on the clinical value of CIRT for cancer therapy.



SUMMARY OF THE ORIGINAL PUBLICATION

Context

Contrarily to conventional radiotherapy (photon radiotherapy), which makes use of X rays, Carbon ion radiotherapy (CIRT) is a type of radiation which belongs, together with other charged particles such as protons, to the "family" of hadron therapy. The physical properties of CIRT enable a large fraction of energy to be delivered to the target (tumour), while being less invasive to the normal (healthy) tissue which surrounds it.

Compared to Proton beam radiotherapy (PBRT), CIRT has a higher relative biological effectiveness, which is good for tumour control but bad for healthy tissue toxicity. Therefore, while CIRT may offer a better alternative for deep located, radio-resistant tumours in adults, difficult to remove with surgery, PBRT remains the preferred hadron therapy option in children.

Method

The aim of this systematic review was two-fold: First, to identify via a systematic literature search the indications for which CIRT had been studied. Second, to assess the effectiveness and safety of CIRT for the 54 cancer indications, identified in the literature.

Outcomes for effectiveness were overall survival (OS), recurrence free survival (RFS), progression free survival (PFS), disease specific survival (DSS) and health related quality of life (HRQoL). For safety, both acute and late radiation morbidities were considered.

Four bibliographic databases were searched for publications up to the end of 2017. In addition to this, references of the included studies were consulted, and hand searches of the grey literature were performed.

The quality of the included RCTs was appraised using the Cochrane risk of bias assessment tool for RCTs. The quality of cases series (controlled or uncontrolled) was assessed by means of the IHE-18 checklist.

What is *KCE has read for you*?

KCE has read for you synthesises a recently published high-quality systematic review or health technology assessment with relevance for the Belgian health system.
The original publication was appraised and contextualised by KCE researchers.
KCE has read for you is not based on original research conducted by KCE.

More details on methodology can be found on the KCE website

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This document includes:

- **Key findings** of the publication under evaluation
- **A contextualisation** within the Belgian healthcare system

Not included:

- Recommendations
- Detailed descriptions

Trustworthy original publication

The methodological quality of the systematic review was assessed with the AMSTAR tool.

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Results

Included studies

Prospectively conducted studies with more than 10 patients, published between 2005 and the end of 2017, were included in this review. For case series, only those with a low to moderate risk of bias were retained. Overall, 27 studies were identified: Only 1 RCT, with a high risk of bias, was found. In addition to this, 3 case control studies and 23 case series reported on the efficacy and/or safety of CIRT.

Efficacy & safety

When assessing the superiority/inferiority of CIRT in comparison to standard radiation (photons), regarding efficacy and safety, no scientific evidence was found for 41 indications, and insufficient scientific evidence was found for the remaining 13 indications (See Table 1 for results grouped by body region).

Comparative data

The only RCT found consisted of an open label, phase II study, comparing toxicity and changes in HRQoL of CIRT versus PBRT, in 92 patients with prostate cancer. The study found no statistically significant differences in toxicity between treatment arms and comparable changes in HRQoL.

The first of the three case-control studies identified was on locally advanced adenoid cystic carcinoma of the salivary gland (1 study, 63 patients); while the other two were on non small-cell lung cancer (2 studies, 150 patients).

The study on locally advanced adenoid cystic carcinomas found no statistically significant differences in efficacy or safety between the combination of CIRT and standard (photon) radiotherapy versus standard radiotherapy alone.

The two studies on lung cancer found no statistically significant differences in efficacy or safety of CIRT versus proton radiotherapy. No comparisons were made between CIRT and standard (photon) radio therapy for lung cancer.

Conclusions

Overall, based on the available evidence on efficacy and safety of CIRT, the authors conclude that the technique should to this date be considered as “experimental”. More research (prospective controlled and randomised studies) is necessary to reach clear conclusions on its clinical value for cancer therapy.

Summary results from systematic review by the Ludwig Boltzmann Institute for HTA

Body region (may group more than 1 indication)	N of studies/N of patients	Type of study	Risk of Bias	Conclusion/Results*
Skull base	3/112	Uncontrolled case series	Moderate	Insufficient evidence (non-comparative) demonstrating superiority or inferiority vs conventional RT for chordomas and low-grade chondrosarcoma).
Eye	0	NA	NA	No evidence found
Brain	2/62	Uncontrolled case series	Moderate	Insufficient evidence demonstrating superiority or inferiority for WHO grade II-IV gliomas.
Ear-nose-throat	5/415	1 case control (n=63) , 4 uncontrolled case series	Moderate	Insufficient evidence demonstrating superiority or inferiority for sarcomas in the head and neck, tumours in the nasal cavity and paranasal sinus and adenoid cystic salivary gland
Lung	6/559	2 case control (n=150), 4 uncontrolled case series	Moderate	Insufficient evidence demonstrating superiority or inferiority for NSCLC.
Gastrointestinal tumours	2 /215	1 uncontrolled case series for oesophageal cancer and 1 uncontrolled case series for rectal cancer	Moderate	Insufficient evidence demonstrating superiority or inferiority for thoracic oesophageal squamous cell carcinoma and for rectal cancer without distant metastasis.
Bone and soft tissue tumours	1/17	Uncontrolled case series	Moderate	Insufficient evidence demonstrating superiority or inferiority for soft tissue sarcoma.

Prostate	8/2715	1 RCT (n=92), 3 pre and post studies, 4 uncontrolled case series	High (RCT) to moderate	Insufficient evidence demonstrating superiority or inferiority for prostate cancer
Breast	0	NA	NA	No evidence found
Kidney	0	NA	NA	No evidence found for nephroblastoma
Central nervous system	0	NA	NA	No evidence found for neuroblastoma
Hematologic cancer	0	NA	NA	No evidence found for non-Hodgkin's and Hodgkin's lymphoma
Other oncologic indications	0	NA	NA	No evidence found for liver metastasis in colorectal cancer, retroperitoneal metastases in primary tumours and oligo metastasis in controlled primary tumours for selected indications

RT: Radiotherapy; NSCLC: Non small-cell lung cancer

KCE COMMENTS

Quality of the publication

Two KCE researchers independently appraised the quality of this review using the AMSTAR tool. The score obtained was high (i.e. high quality).

Belgian context

A procedure is in place at RIZIV/INAMI to reimburse both carbon-ion and proton radiotherapy treatment, if delivered in a specialized center, for patients who meet certain conditions. More detailed information on the specific conditions needed to be fulfilled (and the clinical indications covered) is available on the RIZIV/INAMI website. Carbon ion or proton radiotherapy treatment requires for patients to be sent abroad, since no specialised centre is available in Belgium. Proton therapy but not carbon-ion therapy is nevertheless, expected to become available in Belgium, around the end of 2019, at a proton therapy centre in Leuven.

This KCE has read for you comes to complement two recent KCE reports. The first one published in 2015 on hadron therapy (i.e. proton therapy and carbon ion) indications in children. A more recent SR was published in January 2019 on the efficacy and safety of proton beam therapy for adults suffering form 6 cancer indications not yet reimbursed in Belgium.

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