

Proton versus photon therapy for oesophageal cancer – a trimodality strategy

Topic details

Action type	Research and Innovation Action (RIA)
Submission and evaluation process	2 stages
IMI2 JU Strategic Research Agenda - Axis of Research	Adoption of innovative clinical trial paradigms
IMI2 JU Strategic Research Agenda - Health Priority	Cancer

Specific challenges to be addressed by public-private collaborative research

Alongside chemotherapy and surgery, radiotherapy (RT) has evolved to become one of the essential therapies for the treatment of cancer. However, radiotherapy is not suitable for all cancer types, and when used, the potential for negative side effects to surrounding organs can limit the dose administered leading to longer treatment times and reduced effectiveness. By delivering a high radiation dose, more precisely focused on the tumour site, proton therapy (PT) has the potential to reduce these adverse events and provide better outcomes for cancer patients.

Although the number of patients treated annually with PT is increasing, the clinical evidence supporting its effectiveness remains limited due to the lack of large multi-centre studies. There is a critical need [1] for high quality evidence from multi-centre trials to determine the potential role of PT for various cancer indications and to allow a consensus to be reached across Europe on the most suitable indications.

A robust evidence base on the effectiveness of PT has the potential to open a new treatment modality for cancers with currently very low survival rates, for example oesophageal cancer. Oesophageal cancer is the seventh most common cancer worldwide, with more than 570 000 new cases per year leading to more than 500 000 cancer deaths annually [2]. Until recently, surgery was the main treatment for patients with localised disease. In 2012, the results of the Chemoradiotherapy for Oesophageal Cancer Followed by Surgery Study (CROSS) randomised trial demonstrated that adding neoadjuvant chemo-radiation to surgery results in a beneficial effect on pathological complete response (pCR) and survival compared to surgery alone [3][4]. However, with a pCR of 30 % and a five-year overall survival rate of 45-50 %, there is still a large unmet need.

The unique properties of PT allow oesophageal cancer patients the opportunity to receive more conformal radiotherapy with the possibility of reducing the dose to the surrounding normal organs including the lungs, heart and liver [5][6]. Treatment of oesophageal cancer patients with PT is under evaluation by several institutions. Recent publications present the role and the potential benefits PT offers to those patients [7][19] and could lead to better patient outcomes. Nevertheless, none of those publications provide level 1 evidence.

To build a robust evidence base to assess the potential of PT in oesophageal and other cancers, multi-centre international trials have to take place. The current diversity of reimbursement and coverage policies across the EU makes these trials difficult. A public-private collaboration of proton therapy oncologists, treatment centres, software developers and equipment manufacturers is needed to define a methodology to conduct clinical trials in PT at a European scale. In addition, a key factor is the generation of robust clinical evidence which is neutral and unbiased. A clinical trial conducted in a European framework, in a collaboration between industry and public partners, has an inherent degree of independence and neutrality required by the highest standards of clinical research.

Scope

The main objective of this topic is to examine the value of proton therapy as a treatment modality through a clinical study in oesophageal cancer. The study will compare outcomes between pencil-beam scanning proton therapy and intensity-modulated radiation therapy (IMRT). The study will determine if proton therapy in a trimodality (radiotherapy-chemotherapy-surgery) treatment;

- (i) reduces treatment-related cardio-pulmonary toxicity;
- (ii) increases loco-regional tumour control and pathological complete response and the influence of dose escalation;
- (iii) improves disease-free and overall survival.

Oesophageal cancer is chosen due to its relatively high occurrence in the population and the possibility to extend findings to other cancer types.

A second objective is to use the evidence generated during the oesophageal cancer study to reach a consensus on which methodology is most suitable to evaluate PT treatment for other indications. To facilitate this objective, cost-effectiveness data should be collected during the duration of the action. This objective should be supported by engaging with selected stakeholders as advisors such as the broader oncology community including oncologists (e.g. through relevant European networks), healthcare providers, health technology assessment (HTA) agencies, payers, and patient associations. In addition, the findings of the proposed project should be disseminated via publications, presentations at relevant conferences, and other suitable dissemination methods.

Expected key deliverables

To achieve the objectives, the proposed project should deliver:

- A **study protocol** for a non-blinded multi-centre randomised phase III study on a statistically significant number of oesophageal cancer patients. Patients should be treated with pre-operative concomitant chemo-radiation and randomised between irradiation to be delivered as either RT or PT. This protocol should include a rapid, clinically relevant primary endpoint to allow effectiveness to be demonstrated as early as possible.
- **Annual updates** on the progress of the study to include:
 - recruitment reports;
 - data collection reports;

- A final **dataset** collected in compliance with the FAIR principles;¹
- A proposal for a European methodology for multi-centric clinical trials in proton therapy;
- Publications & conference presentations on the results of the study;
- Publication and active dissemination of a **summary of results** to relevant authorities (e.g. healthcare providers, HTA bodies, payers).

Expected impact

In their proposals, applicants should describe how the outputs of the project will contribute to the following impacts and include wherever possible baseline, targets and metrics to measure impact:

- The outcome of this research is potentially practice-changing as it may define a new and improved standard for the treatment of oesophageal cancer patients and potentially patients with other cancer indications.
- The morbidity data from the study will allow better understanding of the dose-volume relationships for normal tissue complications, enabling refined selection of patients for proton therapy in the future.
- The results should allow health authorities and healthcare providers to improve the quality of care through better evidence of benefits and patient outcomes and support reimbursement decisions.

In their proposals, applicants should outline how the project plans to leverage the public-private partnership model to maximise impacts on innovation, research & development; regulatory, clinical and healthcare practices, as relevant. This could include a strategy for the engagement with patients, healthcare professional associations, healthcare providers, regulators, HTA agencies, payers, etc., where relevant. An advisory group including these stakeholders should be set up.

In their proposals, applicants should outline how the project will:

- Manage research data including use of data standards.²
- Disseminate, exploit, and sustain the project results. This may involve engaging with suitable biological and medical sciences research infrastructures.³
- Communicate the project activities to relevant target audiences.

Potential synergies with existing consortia

Synergies and complementarities should be considered with relevant national, European and non-European initiatives (including suitable biological and medical sciences research infrastructures^{Error! Bookmark not defined.}) in

¹ Findable, Accessible, Interoperable, Reusable, see: <https://www.force11.org/group/fairgroup/fairprinciples>

² Guidance on data management is available at

https://ec.europa.eu/research/participants/docs/h2020-funding-guide/cross-cutting-issues/open-access-dissemination_en.htm

³ <http://www.corbel-project.eu/about-corbel/research-infrastructures.html>

order to incorporate past achievements, available data and lessons learnt where possible, thus avoiding unnecessary overlap, and duplication of efforts and funding.

Industry consortium

The industry consortium includes the following IMI2 JU Associated Partners:

- Ion Beam Applications SA
- Varian Medical Systems Particle Therapy GmbH

The industry consortium plan to contribute the following expertise and assets:

- in-depth knowledge of proton therapy solutions, including equipment and treatment planning software;
- contribution to the development of dissemination and communication materials;
- a financial contribution (detailed in the indicative budget section) to cover study related expenses.

Indicative duration of the action

The indicative duration of the action is 60 months.

This duration is indicative only. At stage 2, the consortium selected at stage 1 and the predefined industry consortium may jointly agree on a different duration when submitting the stage 2 proposal.

Indicative budget

The financial contribution from IMI2 JU is a maximum of EUR 1 500 000.

The indicative in-kind and financial contribution from the IMI2 JU Associated Partners is EUR 1 500 000, which includes a financial contribution of EUR 1 000 000.

Therefore, the stage 1 applicant consortium is expected to allocate up to **EUR 2 500 000** (IMI2 JU financial contribution + IMI2 Associated Partner financial contribution) in the budget of their stage 1 proposal. The allocation of the IMI2 Associated Partner financial contribution of EUR 1 000 000 to cover study related expenses may be fine-tuned by the full consortium when preparing the stage 2 proposal.

Expertise and resources expected from applicants at stage 1

The stage 1 applicant consortium is expected, in the submitted short proposal, to address all the objectives and key deliverables of the topic, taking into account the expected contribution from the industry consortium which will join at stage 2 to form the full consortium. The stage 1 submitted short proposals should include suggestions for creating a full proposal architecture

This may require mobilising, as appropriate the following expertise:

- Extensive experience in the application of radiotherapy and proton therapy;
- Clinical expertise in the area of oesophageal cancer;

- Proven ability to design and conduct relevant studies to obtain high quality clinical data;
- Experience in dealing with the legal and ethical challenges associated with integrating multi-centre patient-derived data, as well as data-processing and management practices (e.g. privacy). Candidates should mention how they plan to integrate possible bias resulting from centre-specificity in the data analysis;
- Strong project management expertise;
- Access to HTA expertise and expertise from oesophageal patients or patient groups in an advisory capacity would be considered an advantage.

The size of the consortium should be proportionate to the objectives of the topic while ensuring its manageability.

It may also require mobilising, as appropriate, the following resources:

- Participating centres with the ability to include a statistically significant number of patients (with a minimum of 20 patients per centre) over the duration of the action;
- Applicants must demonstrate that they can secure access to:
 - relevant, state-of-the art radiotherapy and proton therapy equipment;
 - data centre and study monitoring infrastructure.
- Access to historical data that can be incorporated in the analysis would be considered an advantage. If relevant, applicants should indicate the volume and type of data they could bring to the project in their proposals.

Considerations for the outline of project work plan

In their stage 1 proposals applicants should:

- Provide the outline of a study protocol for the non-blinded multi-centre randomised phase III study. This should include a justified sample size of oesophageal cancer patients to ensure statistical significance. Applicants should also propose a rapid, clinically relevant primary endpoint to allow effectiveness to be demonstrated as early as possible.
- Give due visibility on data management; dissemination, exploitation and sustainability; and communication activities. This should include the allocation of sufficient resources for these tasks which will be further developed in stage 2 proposal.
- Consider including a strategy for ensuring the translation of the projects results to HTA settings (e.g. through scientific advice/ qualification advice /opinion, etc.), clinical and healthcare practices and/or decision-making processes.

Additional considerations to be taken into account at the stage 2 full proposal

At stage 2, the consortium selected at stage 1 and the predefined industry consortium jointly submit the full proposal developed in partnership. The full proposal is based upon the selected short proposal at stage 1.

In the spirit of the partnership, and to reflect how IMI2 JU call topics are built on identified scientific priorities agreed together with the IMI2 Associated Partners, these beneficiaries intend to significantly contribute to the programme and project leadership as well as project financial management. The final architecture of the full proposal will be defined by the participants in compliance with the IMI2 JU rules and with a view to the achievement of the project objectives. The allocation of a leading role within the consortium will be discussed in the course of the drafting of the full proposal to be submitted at stage 2. To facilitate the formation of the final consortium, until the roles are formally appointed through the consortium agreement, the proposed project leader from among IMI2 Associated Partners shall facilitate an efficient negotiation of project content and required agreements. All beneficiaries are encouraged to discuss the project architecture and governance and the weighting of responsibilities and priorities therein.

Data management

In their stage 2 proposal, applicants should give due visibility to data management including use of data standards. A full 'data management plan' (DMP) as a distinct deliverable must be delivered within the first 6 months of the project. The DMP needs to be kept up to date with the needs of the project and as such be updated as necessary during its lifetime.⁴

Dissemination, exploitation and sustainability of results

In their stage 2 proposal, applicants must provide a draft plan for dissemination and the exploitation, including sustainability of results. A full plan as a distinct deliverable must be delivered within the first 6 months of the project,⁵ and updated during the project lifetime and could include identification of:

- different types of exploitable results;
- potential end-users of the results;
- results that may need sustainability and proposed sustainability roadmap solutions.

Sufficient resources should be foreseen for activities related to dissemination and exploitation, including the plan for the sustainability of the project results. This may involve engaging with suitable medical sciences research infrastructures (RIs).⁶

Communication

The proposed communication measures for promoting the project and its findings during the period of the grant should also be described.

References

- [1] For example: H. Thomas, B. Timmermann. Paediatric proton therapy. *Br J Radiol.* 2019:20190601. <https://doi.org/10.1259/bjr.20190601>, M. Alahmari, Y. Temel. Skull base chordoma treated with proton therapy: A systematic review. *Surg Neurol Int.* 2019;10:96. <https://doi.org/10.25259/SNI-213-2019>

⁴ Guidance on data management is available at http://ec.europa.eu/research/participants/docs/h2020-funding-guide/cross-cutting-issues/open-access-data-management/data-management_en.htm

⁵ As an additional dissemination obligation under Article 29.1 of the IMI2 Grant Agreement will apply

⁶ <http://www.corbel-project.eu/about-corbel/research-infrastructures.html>

- [2] Global Cancer Observatory (GCO). <http://gco.iarc.fr>
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