

Radiation planning for image guided preclinical radiotherapy

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Valorisation

1 Societal value

The relevance of advanced and accessible radiation planning tools for image guided small animal radiotherapy research platforms has been outlined in the first chapter of this thesis. This is an invaluable link for the overall innovation in cancer therapy, albeit with indirect and deferred ultimate benefit for patients. The magnitude of current and future numbers of patients worldwide assures the societal impact of the work of this thesis in the long term. In addition, there is an important general trend to minimize the number of animals used for research to decrease overall animal burden and cost of studies, for which it is essential to maximise the quality and value of animal research data. New approaches and tools as presented in this thesis are then indispensable.

2 Innovation and knowledge utilisation

Simply defining a micro irradiator in a clinical TPS is insufficient to reach adequate planning accuracy for reasons discussed in chapter 1 and 7. During the early stage of the work for this thesis, there was no commercial software available for image guided treatment planning in this setting. Research groups were forced to use simpler tabular lookup calculations or develop their own tools. Both options entail that the advanced imaging and irradiation hardware would not be used to their full extent, or that a big investment of time and money are needed to create capable tools. The manufacturers of the X-RAD 225Cx and SARRP were still in the early stages of development of the hardware and had no resources, time or specific knowledge readily available for such developments.

Therefore, we implemented algorithms and knowledge in a user-friendly manner, to advance ongoing radiobiological studies. To achieve results fast with minimal resources, SmART-Plan was written in a high-level interpreted coding language. Its development and validation are the topic of chapter 3. The vast knowledge on Monte Carlo modelling and simulations for kilovolt x-rays was made accessible to users who did not have specific in-depth knowledge of radiation planning and verification. Big efforts were made to make the product available to other research groups who had purchased the same irradiation platform. For marketing and first line customer relations, a collaboration was established with PXi. SmART-Plan would be sold as an add-on for new customers of their X-RAD 225Cx, which later evolved into the X-RAD SmART. With this setup, we had created a unique setting in which we could rapidly apply any developed knowledge to about half of the research community in this specific field throughout the world, using remote software updates. Towards the end of

the work of this thesis, SmART-Plan was operational at about 20 institutes throughout Europe, North-America, Asia and Australia, and we had presented our work during several international scientific conferences in the Netherlands, Belgium, Spain, Milan, Switzerland, and Portugal. SmART-Plan has already been used for many published studies [1–21], and many more studies are currently in progress or planned. Such studies are difficult to track as discussed in chapter 7.

3 Commercialisation

Successful valorisation of the developed software means that many hours need to be dedicated to the project. Valorisation is encouraged, but a research group or institute is often not equipped for such activities. Therefore, SmART Scientific Solutions BV was created as mentioned in chapter 7, which is part of the Brightlands Maastricht Health Campus [22]. SmART Scientific Solutions BV licenses the rights for ongoing extension, expansion, and development of irradiation planning for image guided small animal radiotherapy and created the new product SmART-ATP from scratch.

Development of software means that there is a huge cost until the first invoice for the created product can be sent to a customer. Once a first version of the product is ready, it is relatively inexpensive to deploy the same version of the product to additional customers. However, for SmART-ATP, a thorough specific calibration and validation procedure must be completed for each customer before accurate radiation planning is possible. Also, costs for customer support grow with the customer database and there will be ongoing product development. Modern consumer or business software is often sold using a licensing model with recurring license fees which makes a lot of sense from the perspective of the commercial entity to assure continuity. However, in the specific market for SmART-ATP, such costs are difficult to budget for, as purchases are usually realized with money from research budgets. It is practically more feasible to include the purchase of additional software together with the purchase of the relatively expensive hardware.

4 Market

Despite the number of radiobiological studies being conducted worldwide, the potential market for dedicated small animal radiotherapy planning software is relatively small. In 2013, we estimated that there were about 800 academic medical centres in Europe and the USA combined, of which about three quarter had a radiation research line. Only a part of these research centres would be able to benefit or be interested

in precision irradiation. That means that the total worldwide market would be limited to a few hundred devices. This makes commercially viable products, and companies based thereon, difficult to realize. Developments must be carried out lean or using external funding. In comparison with clinical counterparts of hardware and software, the potential revenue is very small which is likely one of the main reasons the current established companies in the field do not seem to be keen to enter this market.

Currently, there are about 130 installed commercial devices from Xstrahl and PXi combined. It is expected that this market will be saturated relatively soon, after which revenue for new installs will minimize and new pools of revenue need to be generated from recurring license fees for ongoing updates, upgrades with new feature sets, optional add-ons, additional users, or replacement of current setups. More recently, some larger institutes have shown interest in additional small animal precision irradiation platforms, e.g. because they are physically scattered.

Nevertheless, this means that required investments for research and development have a high impact on the cost of the product. This slows down technical innovations that may otherwise be relatively straightforward to implement. The commercial platforms already cost well over half a million US dollars, and considerably more if a platform is extended with options such as bioluminescence imaging or a more advanced beam collimation system. This is of course an important reason why there have been numerous local non-commercial projects to assemble image guided small animal irradiation platforms as outlined in chapter 1.

The vast majority of the current preclinical radiation research platforms are being operated at academic institutes, and there are only a handful operational devices at e.g. pharmaceutical companies. Small companies that need animal research are often spin-offs from academic institutes and outsource such studies to their affiliate universities. Large companies often choose to outsource animal studies to bigger contract research organisations (CROs) because they would not only need to invest in the specific required hardware and software but would also need to set up a research laboratory with specific knowledge and skills.

Xstrahl developed the small animal radiotherapy planning system Muriplan for their SARRP, which is based on 3DSlicer [23, 24]. Currently, SmART-ATP can only be used in combination with the X-RAD SmART, and Muriplan can only be used in combination with the SARRP. At the end of 2017, the company RaySearch Laboratories announced their product μ -Raystation as discussed in chapter 7 [25]. μ -Raystation is currently in use at Institut Cancérologie de l'Ouest (Nantes, France) for irradiation

with their X-RAD 225Cx, and at OncoRay National Center for Radiation Research in Oncology (Dresden, Germany) in combination with their locally developed SAIGRT.

5 Future

The market for precision small animal irradiation is not yet saturated and the number of commercial and non-commercial research platforms will keep growing the coming years. The potential market size may grow considerably in the future if e.g. legislation for new therapy or compound approval would specifically demand targeted localized micro irradiation studies with clinically relevant organ at risk avoidance, which is not the case at this time. Another interesting development might be an increasing interest in therapeutic irradiation for companion animals. This is currently still very uncommon in Europe with only about 10-20 irradiation facilities for animals, but higher demands exist in e.g. the USA.

The modern age of commercial software has seen a tremendous move to server-side based software, leading to many products being offered as a service (-aaS). The worldwide internet connectivity improvements with lower latencies and higher bandwidths enabled clients to use CPU and data heavy applications on a server, or in the cloud, without the need for local installation and setup. Instead of purchasing a one-time perpetual software license, a recurring license fee is charged for using the service. Relevant examples in the field of radiotherapy are an online radiochromic film analysis tool [26], cloud-based radiomics analysis software [27], or the ESTRO online tissue contouring training tool FALCON [28]. Providing a product as a cloud-based service has the advantage that it is easier to maintain for the developer. Such a path could also be realized for small animal radiation planning. Prior to the radiation planning, the relevant imaging data would need to be uploaded to a server, but thereafter the calculation may use the more powerful computer resources from the server, and the irradiation plan is easily communicated using small data packages.

When irradiation hardware evolves, or when new software features are being developed, substantial feature sets such as automated contouring using machine learning, can be sold as add-ons, or as paid software upgrades instead of updates, in addition to e.g. training or educational services. Undoubtedly, the radiation planning software will need to be updated regularly to provide state of the art capabilities.

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