May 11, 2023

Analysing workflows of high dose rate brachytherapy treatments for prostate cancer in the USA

BSc thesis
Industrial Engineering & Management

Stijn de Jong

Supervisors:
Daniela Guericke
Gréanne Leeftink
Ate Loonstra

UNIVERSITY OF TWENTE.

Elekta

This summary is intended for anyone who is interested in my bachelor thesis but does not have permission to read my confidential thesis. This summary will show what I have done for my thesis assignment during module 12 as part of the Industrial Engineering and Management educational program at the University of Twente.

UT/IEM-22.1101-11.05.23

University of Twente, Industrial Engineering and Management

PO Box 217, 7500 AE Enschede

Tel. +31(0)53489911

Bachelor thesis: Analysing workflows of high dose rate brachytherapy treatments for prostate cancer in the USA

Stijn Alexander de Jong – s2395908

First supervisor university: Gréanne Leeftink

Second supervisor university: Daniela Guericke

Supervisor company: Ate Loonstra

Publication date: 11 May 2023

1st edition

Number of pages: 15

Number of appendices: 0

This summary was written in module 12 of the Industrial Engineering and Management educational program as part of my bachelor thesis.

Glossary of terms

Abbreviation	Meaning
EBRT	External Beam Radiotherapy
HDR	High Dose Rate
LDR	Low Dose Rate
LINAC	Linear Accelerator
MCQ	Multiple Choice Question
MPSM	Managerial Problem-Solving Method
OAR	Organs At Risk
OEQ	Open-Ended Question
PCaBT(s)	Prostate Cancer Brachytherapy Treatment(s)
QA	Quality Assurance
RTT	Radiotherapy technologist
TNM	Tumour, Node, Metastasis
TPS	Treatment Planning System(s)
US	Ultrasound
USA	United States of America
UT	University of Twente

1. Introduction

Each year more than 160000 men get diagnosed with prostate cancer in the United States of America (USA) alone (Litwin & Tan, 2017). Around 1 out of 9 men get diagnosed with prostate cancer sometime during their lifetime (Porzycki & Ciszkowicz, 2020). Worldwide around 375000 men died in 2020 from the consequences of prostate cancer (Cancer Today, n.d.).

These numbers show that prostate cancer is a big health problem in the USA, but also worldwide. Brachytherapy can help improve the clinical outcome when treating prostate cancer, however, it is now being underutilized (Corkum et al., 2020). To help increase the adoption of brachytherapy we analyse workflows of high dose rate (HDR) prostate cancer brachytherapy treatments (PCaBTs) in the USA to find out how to increase the efficiency, reduce the complexity, and help to make it more popular. To start analysing HDR PCaBTs, we first discuss prostate cancer in more in detail in Section 1.1 and categorise HDR PCaBTs in Section 1.2.

1.1 Brachytherapy

There are multiple treatment options for prostate cancer, these are (combinations of) watchful waiting, active surveillance, radiotherapy, surgery, hormone therapy, chemotherapy, and experimental treatments that are still in clinical trials.

In this research, we will focus on a prostate cancer treatment called high dose rate proste cancer brachytherapy. This is a particular type of radiotherapy (Chargari et al., 2019).

1.1.1 HDR Prostate cancer brachytherapy treatment workflows

We categorized HDR PCaBTs into three workflows. These are:

- A non-Realtime workflow
- A Realtime workflow without image registration
- A Realtime workflow with image registration

(Mendez & Morton, 2018), (Mohnike et al., 2020), (Smith et al., 2018).

We discuss these three workflows in more detail, as they are the focus of our research.

1.1.1.1 Non-Realtime workflow

An HDR PCaBT can follow a non-Realtime workflow. Figure 1.1 shows a basic representation of a non-Realtime workflow. The main difference between this workflow and the others relates to the presence, or in the case absence, of immediate feedback on needle positions during insertion.

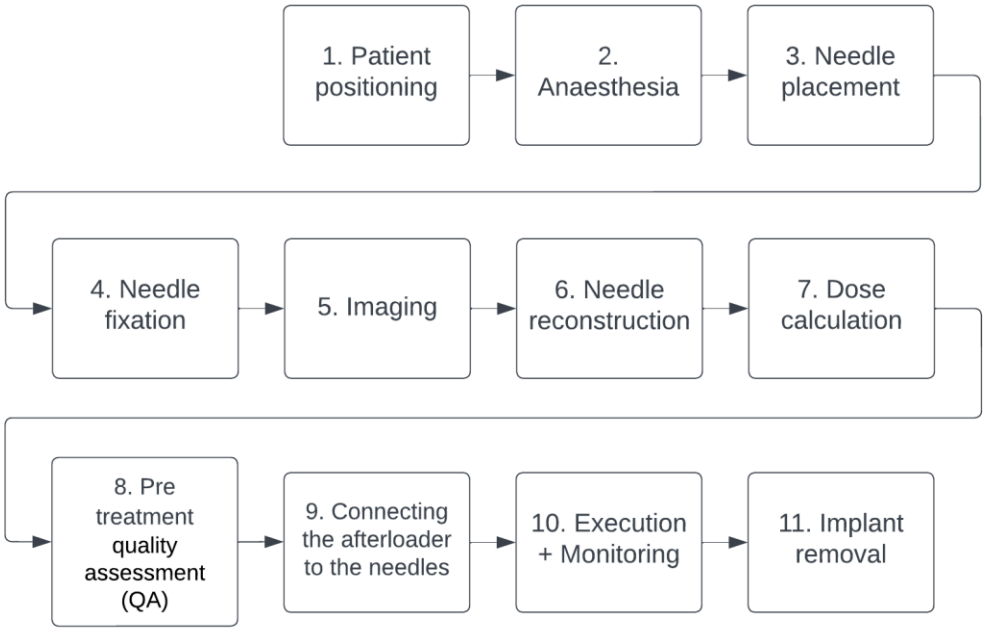

Figure 0.1: A basic representation of the steps of a non-Realtime workflow for prostate cancer brachytherapy treatments

Before a therapeutic intervention is selected, diagnostic images are made to determine whether the patient has prostate cancer, and in which stage the tumour is. Different kinds of images can be made depending on the equipment available. Often MRI images, CT scans, or a combination of both are used. These images are then used at the beginning of the PCaBT to determine the position and size of the volume to be treated and to plan how many and where the needles are going to be inserted. This plan is usually made before the patient arrives for his treatment.

When the patient arrives for the treatment, the following steps are taken:

Step 1: The usual preparations are done to make sure it is the right patient, whether the medication the patient takes will not interfere with the treatment, etc.

Step 2: If this is all okay, the patient will get anaesthesia (full, epidural, or a caudal block).

Step 3: When the patient has received anaesthesia, the area where the needles will be inserted is cleaned and the doctors can feel and look whether everything is as expected. If anything unexpected is found, the plan can still be adjusted. If the doctors agree on the plan, the needles are inserted. Afterwards, the needles are labelled, to be able to identify them correctly later during the treatment.

Step 4: When all the needles are inserted, they are fixated to ensure they do not move relative to the tumour/prostate.

Step 5: After this, new images are made to be able to determine the exact position of the needles relative to the tumour, prostate, and organs at risk.

Step 6: In these images, the needles, tumour, and organs are reconstructed/delineated to be able to see what their location is respective to each other.

Step 7: When these images are clear and checked, the dose can be calculated. This is done by deciding for how long the radioactive source should be in certain positions within the needles. Not all needles and/or positions in the needles (dwell positions) are used during a treatment. The calculation is done in a treatment planning system (TPS). The goal of the calculation is to design an optimal treatment plan and

make sure that the tumour gets enough radiation to destroy the malignant tissue but prevent the organs that are near from receiving too much radiation. Research is done to decide what these limits are (The Royal College of Radiologists, 2019). The treating physician can decide to do it all themself by adjusting the positions and/or dwell times of the source until the result is sufficient. As an alternative, the TPS can recommend treatment plans based on criteria filled in by the doctor. Often these suggested treatment plans need adjustments, but this can still save time compared to manually planning and optimizing the dose distribution.

Step 8: When the treatment plan is created, optimized, and then checked, the pre-treatment quality assurance (QA) can start. During this assessment, it is made sure that the patient is ready for the execution of the treatment.

Step 9: If everything is okay, the patient is brought to the room where the afterloader is located and then the needles are connected to this afterloader. The afterloader is the machine that contains the radioactive source and sends this source to the predetermined dwell positions for the planned dwell durations.

Step 10: When ready for treatment, all personnel leaves the treatment room and the treatment is started. During treatment, the afterloader sends the source one by one into the needles, according to the plan that was approved by the radiation oncologist. The patient and the treatment process are monitored using cameras in the treatment room.

Step 11: After the treatment execution, the source is retracted in the afterloader, the needles can be disconnected and removed, and depending on how the patient feels, he can go home again.

This treatment cycle, or parts of it, can be repeated to increase the dose, depending on the tumour and how the patient reacts to the treatment.

1.1.1.2 Realtime workflow without image registration

Figure 1.5 shows a basic representation of a Realtime workflow without image registration. During a Realtime workflow ultrasound (US) imaging takes place during the insertion of the needles.

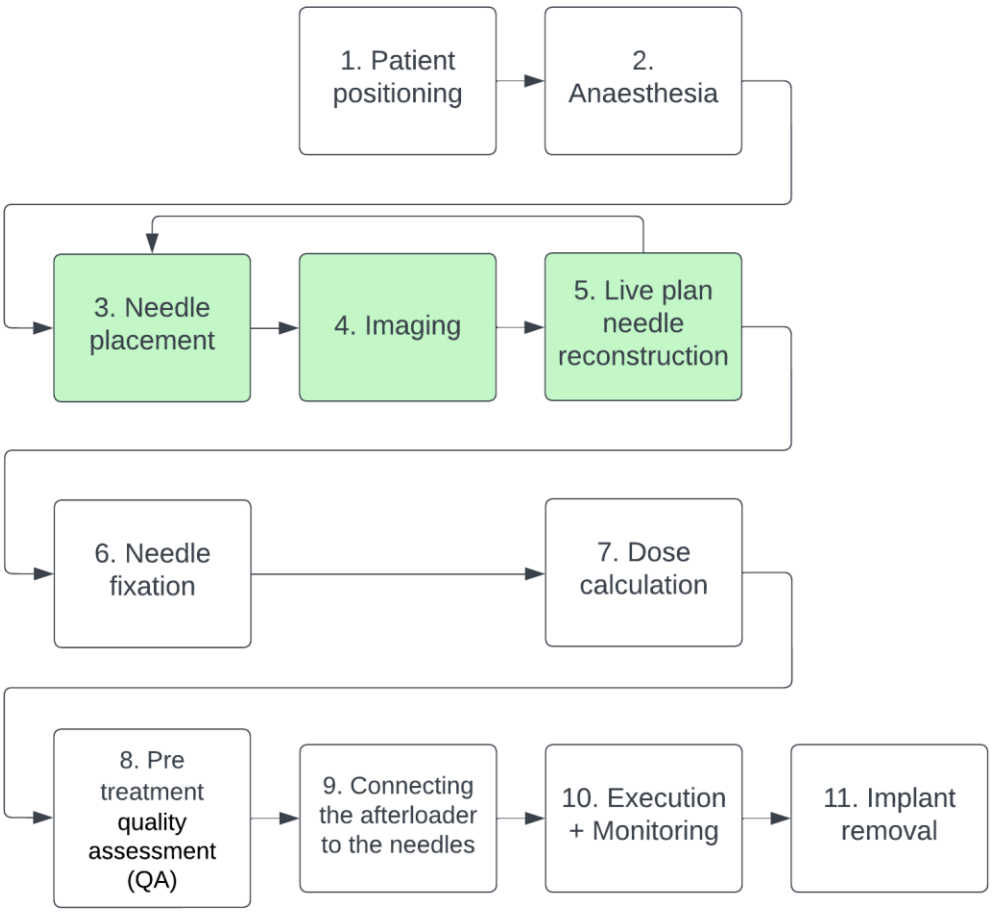

Figure 0.1: A basic representation of the steps of a Realtime workflow for prostate cancer brachytherapy treatments. The green steps are different than a non-Realtime workflow for prostate cancer brachytherapy treatments.

Step 1-2: A Realtime workflow without image registration starts with the same steps as a non-Realtime workflow. The differences start during the needle placement step.
Step 3: One or multiple needles are inserted.
Step 4: US images in real time are made. So, while the needles are inserted, the doctor can simutaneously see where the needle goes and what the impact is on the dose distribution.
Step 5: If a needle is inserted to a position that is not exactly as planned, the plan can be changed, and the effect on the planned dose can be corrected by inserting the rest of the needles differently than planned before.
Step 6-11: Due to the imaging being done during the insertion of the needles, this is not needed anymore afterwards (in between step 6 and 7). Other than that, the steps after the needle insertion are the same as a non-Realtime workflow.

1.1.1.3 Realtime workflow with image registration

Figure 1.6 shows a basic representation of a Realtime workflow with image registration.

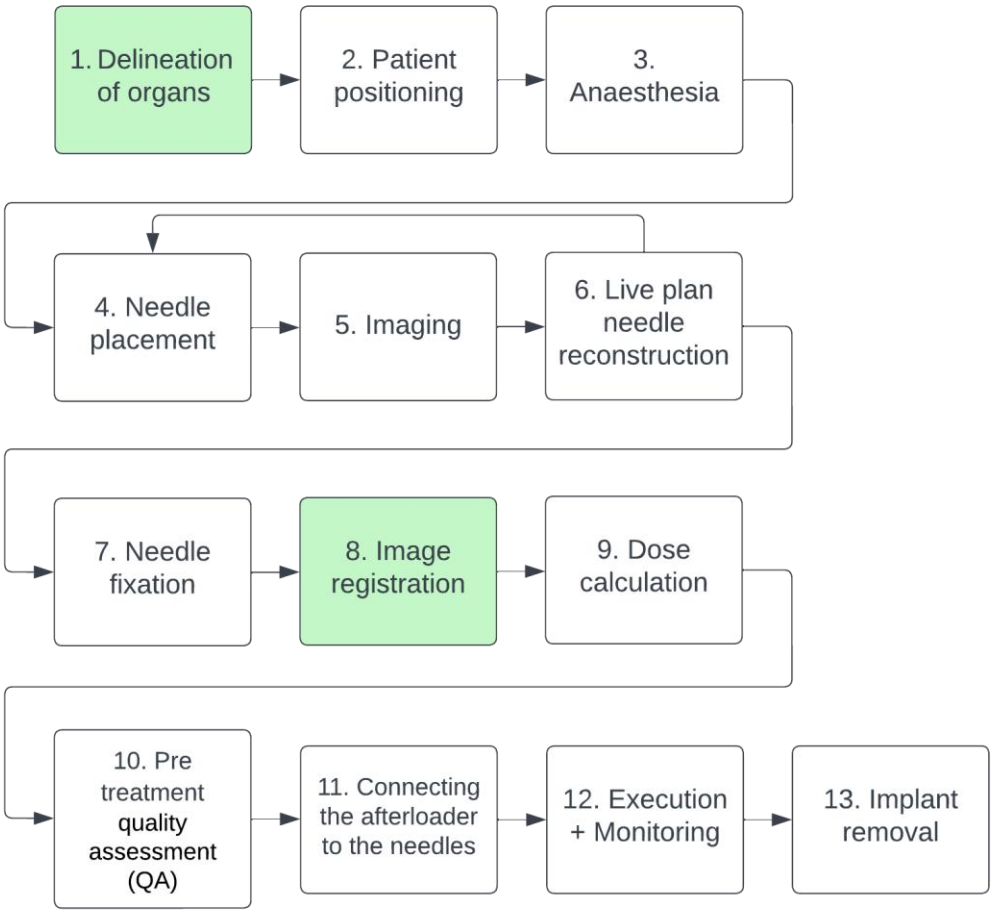

Figure 0.2: A basic representation of the steps of a Realtime workflow with image registration for prostate cancer brachytherapy treatments. The green steps are different than a Realtime workflow without image registration for prostate cancer brachytherapy treatments.

A Realtime workflow with image registration uses the diagnostic images made to determine whether the patient has prostate cancer and in which stage the tumour is, also later in the process. These diagnostic images are often obtained with MRI.

Step 1: To be able to use the images later, the organs and the tumour are already delineated in the 3D image before the operation starts.

Step 2-7: Then all the steps are the same as during a Realtime workflow without image registration, till after the needles are fixated.

Step 8: If image registration is used, the organs, the needles, and the tumour are delineated in the images made during the treatment. Later the diagnostic images made before the treatment are fused with the images made with a different imaging modality after needle insertion. To do so, the structures in the images need to have the same dimensions. So, the images can be combined by deforming one of the images until an organ or the tumour has the same shape as the other image. By doing this, the doctor can define the target more accurately and more precisely plan the treatment of the tumour.

Step 9-13: The steps after this are again the same as during a Realtime workflow without image registration.

1.1.1.4 Other workflows

Non-Realtime, Realtime without image registration, and Realtime with image registration are three examples of possible workflows that can be used to define how hospitals treat their prostate cancer patients with brachytherapy. However, there is a high chance that hospitals or clinics that both follow one of these workflows, still have their differences.

These differences can be caused by the equipment available, such as differences in imaging equipment available, and whether the patient is moved between rooms/departments during the treatment process or not.

It is also possible that there are differences due to the preferences and/or habits of the involved medical professionals, such as differences in how the needles are labelled, or when this labelling is done. The number of images used during a Realtime workflow with image registration can also differ due to preference or due to time pressures.

1.2 Problem identification

Even though brachytherapy is an established cancer treatment and has been available for several decades, the implementation in standard workflows is limited and market penetration is not complete. In addition, differences in market adoption exist between countries. The Managerial Problem-Solving Method (MPSM) was used to identify the reasons why brachytherapy is currently underutilized (Heerkens & Winden, 2021), (Corkum et al., 2020). Via interviewing Elekta employees and doing market research in combination with screening of literature, a list of potentially relevant problems was created. Relating the problems resulted in the problem cluster (Figure 1.1). From the problem cluster, we identified the following core problem:

It is unknown how to use brachytherapy efficiently in different hospital settings.

To be able to solve the core problem, it should be written in a way that the problem and the goal are clear. The method described in the book Solving Managerial Problems is used for this. Following this method results in the following statement:

There is insufficient knowledge available of the possible prostate cancer brachytherapy treatments and the time each step takes, while this knowledge is needed to document and improve the efficiency of the treatments.

An overview of the possible prostate cancer brachytherapy treatments and the time each step takes is needed to see which steps have opportunities for improvement. Due to the scope of the research and the limited time available for this research, it was decided to collect the required information in one country. This does eliminate the need for translation of questionnaires and multiple validation procedures and reduces the number of local Elekta representatives that must cooperate. We chose to collect data from centres in the United States of America. This region is chosen because the USA is a highly developed country and is currently one of the largest economies in the world. In addition, Elekta has a large installed base in the USA, and the USA is the leader in modern PCaBTs. After identifying steps that offer the largest opportunity for improvement, these steps can be improved to help solve the following problem:

On average, the procedure times for prostate cancer brachytherapy treatment are too long in hospitals/clinics in the USA.

However, improving a step of a prostate cancer brachytherapy treatment and then implementing the improvement is outside of the scope of this research. So, for this research the goal is to answer the following question:

Which step(s) of high dose rate prostate cancer brachytherapy treatments in centres in the USA gives the biggest opportunity for improvement relating to time?

To be able to answer this question, multiple sub questions need to be answered. These are:

1. *What is prostate cancer?*
    a. *What staging system for prostate cancer is used in the USA?*
    b. *Which treatment methods exist and how do they work?*
2. *Which different workflows can be used during an HDR PCaBT?*
3. *Which steps are taken in different workflows of HDR PCaBTs?*
4. *How long does each step of an HDR PCaBT take on average in hospitals/clinics from the USA?*

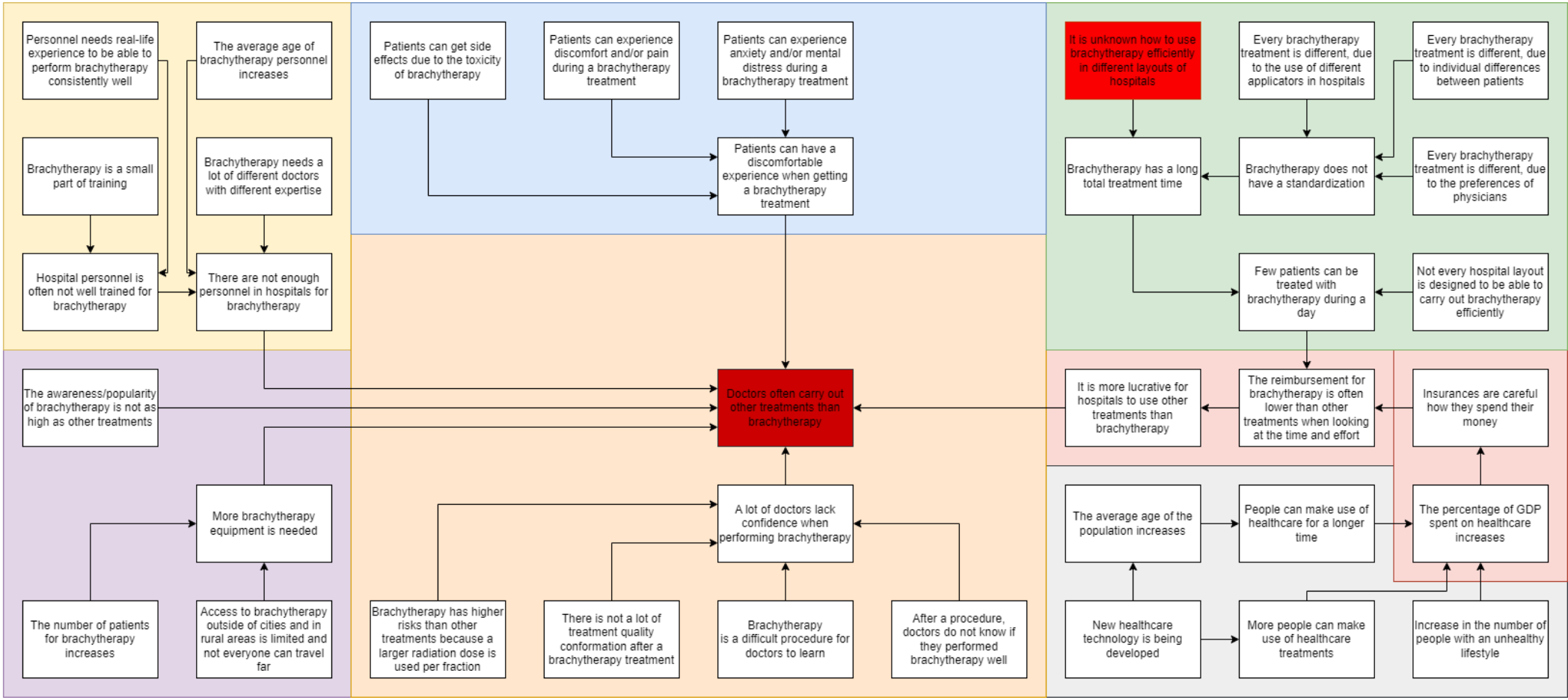

Figure 0.1: The problem cluster

2. Methodology

2.1 Methodology for gathering data about HDR PCaBTs

To answer the questions 1, 2, and 3 from section 1.2, a systematic literature review (SLR) was performed. Using this study, we wanted to find out how prostate cancer works, what the workflows and steps of HDR PCaBTs can be, and why these steps are performed.
We choose an SLR since the research is about all hospitals and clinics who perform HDR PCaBTs. So, looking into the workflow of an HDR PCaBT of only one hospital would not be enough, because different hospitals/clinics use different workflows. To make sure the data for the SLR is reliable, we used PubMed for our research (PubMed, 2023).
The answers to these questions are used as a steppingstone for creating the survey.

2.2 Methodology for gathering data from hospitals

A self-administered quantitative survey was made to find out how long each step of an HDR PCaBT takes on average in hospitals/clinics from the USA. This kind of survey has the following advantages:

- We do not need to physically travel to the USA to get data from the USA.
- Less people are needed to collect the data, which also saves costs.
- The survey can be filled out by doctors whenever they have time for it.
- It is easier to keep the participants anonymously.

While using a self-administered survey, multiple factors need to be kept in mind (Cooper & Schindler, 2013).

- Sensitive data is collected, so by using a program like Qualtrics the data can be collected safely (University of Twente, 2023).
- A self-administered survey could lead to more unclear answers, however, multiple validations helped to mostly prevent this.
- A self-administered survey often has a lower response rate, but the extra number of surveys that could be send out because we used this kind of survey meant that the quantity of completed surveys did not suffer from the low response rate.

The survey was sent out to 62 Elekta customers working in centres in the USA that perform HDR PCaBTs. The reasoning behind this can be found in Section 1.2.

3. Survey

To answer the research question, we decided that we needed to gather more data about how long each step of an HDR PCaBT takes on average in centres in the USA. We decided that a quantitative survey was the best way to collect these data due to time limitations and logistic restrictions. This survey was sent out to 62 Elekta customers from the USA. The survey asked, among other things, questions to figure out which HDR PCaBT workflow they use, how exactly they performed this workflow, and how much time they take on average to perform the steps of their workflow.

4. Results

The initial goal of the research was as follows:

Which step(s) of high dose rate prostate cancer brachytherapy treatments in centres in the USA gives the biggest opportunity for improvement relating to time?

Especially step X, is with 12 to 28% of the total treatment time a relatively time-consuming part of the procedure. Also, step Y takes a relative long time in the Realtime workflow without image registration. These steps, especially step X, have therefore the biggest opportunity for improvement relating to the total treatment time.
However, further research needs to be done to confirm this statement because these numbers are based on a survey with 12 fully completed responses, which means the data pool is limited for subset comparisons, and there are indications that the estimated durations may be different from actual durations in the real-life situation.

5. Conclusion & Recommendations

5.1 Conclusion

This research analyses the workflows of HDR PcaBTs as it is currently being executed by Elekta customers in the USA. The goal of the research was to answer the following question:

Which step(s) of high dose rate prostate cancer brachytherapy treatments in centres in the USA gives the biggest opportunity for improvement relating to time?

To answer the research question, we decided that we needed to gather more data about how long each step of an HDR PCaBT takes on average in centres in the USA. We decided that a quantitative survey was the best way to collect these data due to time limitations and logistic restrictions. The survey asked, among other things, questions to figure out which HDR PCaBT workflow they use, how exactly they performed this workflow, and how much time they take on average to perform the steps of their workflow. This survey was sent out to 62 Elekta customers from the USA.
There were 12 fully completed responses and from these responses 3 used a non-Realtime workflow, 7 used a Realtime workflow without image registration, and 2 used a Realtime workflow with image registration. These responses gave their self-reported duration estimates of all the steps from their workflow. With the help of these self-reported duration estimates, we show that step X and Y take relatively long. Step X can take up to 28% of the total treatment time on average and step Y can take up to 11% of the total treatment time on average. However, the time it takes for step Y takes a long time during Realtime HDR PCaBTs, but not during non-Realtime HDR PCaBTs. This could be explained by the different imaging techniques used during the workflows. Realtime workflows make use of US, while non-Realtime workflows make use of CT scans.
This research has thus shown that step X and Y should be the focus area for innovation, since these have the most impact on the total treatment time. Comparing this to existing literature about HDR PcaBTs is not possible, because data about this topic was not yet publicly known. However, the report from L. de Kraker (2023) showed that during a cervical cancer brachytherapy treatment the needle handling, imaging, and plan optimization & evaluation are points of improvement. This is similar to the conclusion of our research.

5.2 Impact in practise

Looking at the problem cluster from Figure 1.1, we can see which impact improving step X and Y will have. First, this will reduce the total treatment time, which can lead to more patients being able to be treated per day and/or reducing the workload of healthcare personnel. This would also mean that the reimbursement hospitals and clinics get for PCaBT would be relatively higher compared to the effort and/or time PCaBTs take. If this reimbursement would relatively increase, it would become more attractive for hospitals and clinics to offer PCaBTs instead of other treatments. This would positively impact patients with prostate cancer because PCaBTs often perform better than other prostate cancer treatments (Corkum et al., 2020).

5.3 Limitations

There were only 12 responses, which is a small data pool for subset comparisons. For Realtime HDR PcaBTs with image registration, there were only 2 responses. Having a small data pool could result in the averages not being a good reflection of the real-world situation.
A response rate of 19% could also mean there is a selection bias, so maybe only people who think they perform well filled in the survey or something similar. This could also result in the averages not being a good reflection of the real-world situation.
The survey is filled in with estimation, so the exact time certain steps take is never measured. Also,

there is a significant difference between the calculated and the estimated total treatment time. This suggests that either certain steps happen parallel or that the data is indeed not completely accurate. This data is only from hospitals/clinics from the USA and it is unknown if other countries have the same problems with HDR PCaBTs or not.

5.4 Recommendations

5.4.1 Recommendations to improve HDR PcaBTs

This research was the start of a bigger project to see what a good way of collecting and processing data was for HDR PcaBTs. During this research, we not only found out how to continue this research, but we also already have suggestions for further research into innovating brachytherapy. These are:

5.4.1.1 Shifting to using image registration

The collected data shows that Realtime HDR PcaBTs with image registration are the most efficient and that 2 out of the 9 centres that use Realtime HDR PcaBTs already use image registration. This could suggest a future shift to the use of image registration.

5.4.1.2 Share knowledge and offer trainings

Some hospitals perform certain parts of their workflows more efficient compared to other hospitals. By researching why they perform more efficient and sharing this knowledge, an efficient and possibly a standardized way of performing the different workflows can be defined. This knowledge can help hospitals to improve their efficiency, especially if they are now less efficient than the other hospitals. Elekta could help learn hospitals the most efficient way by offering trainings for the hospital personnel where they can practise on using Elekta equipment in a correct and efficient way.

5.4.1.3 Improving treatment planning systems

The time spent on making, optimizing, and evaluating the plan takes relatively long. There have also been multiple complaints about the planning system Elekta offers. So, improving this system could not only improve the efficiency of HDR PcaBTs but also improve customer satisfaction.
We found out that certain hospitals are already working on their version of the program that includes automatic dose calculations. By collaborating with them, Elekta could not lose its market share for the program, and they can make use of already completed research.

5.4.2 Recommendations for the continuation of the research

When more data on HDR PcaBTs will be collected, the research can follow the same steps as this research. However, some steps should be performed differently than during this research. The following points should be taken into consideration:

5.4.2.1 Who does the research?

As a bachelor student there was limited time to spend on the research. Due to not having a medical background, relatively much time was spent on getting to know how brachytherapy works. By either selecting people who have longer time for the research, selecting people with a medical background, or offering a quicker way to learn about brachytherapy, the time spent on getting to know brachytherapy can be reduced.

5.4.2.2 Which data to collect?

Only 12 out of 62 of the persons that received the survey of this research filled them in completely. If data from the other 50 can be (partially) collected, this could help evaluate the accuracy of this research.
Furthermore, extra data from other parts of the world, like Asia or places that are less developed can give different insights and can help find improvements that work worldwide. During our research we

heard that China and Japan are known for their efficient way of working, so their way of working could be valuable information for other hospitals/clinics. Different countries have also different reimbursements for HDR PCaBTs, which could influence the way of working. Furthermore, the way of working of an academic or private hospital also differs. So, these points should be kept in mind.
Doing more in-depth research about how each step of an HDR PcaBT works, can help find possible solutions for improving those. This research shows that needle handling and plan optimization & evaluation consume the most time, so these are logical areas for further research into innovation.

5.4.2.3 Making the survey

The survey used during this research can be used again, however, adaptations should be made. One of these adaptations is to find a better way to ask for the different workflows, instead of putting everyone into one of three categories. Furthermore, finding a better way to ask if steps are happening one after another or parallel could decrease the difference between the calculated and the estimated total treatment time. Including questions to see what the quality of the HDR PcaBTs performed by the hospitals/clinics gives relevant information. This helps to evaluate if other hospitals/clinics want to learn from more efficient workflows (while looking at time) or if the quality of the treatment reduces too much to want to adapt.
Something that should be kept in mind is that the survey should not have too many questions. This avoids people not filling it in due to them not wanting to put the time into it. Also, the survey and the email invitation should be adapted to the laws, regulations, culture, and language used in the area where the survey will be sent out.
The data safety should also be taken into consideration, so a program that can store the users' data safely must be used because the survey asks for sensitive data. Qualtrics was used during this research, and this program is a worldwide leading survey tool in terms of privacy measures (University of Twente, 2023). By following the General Data Protection Regulation (EU, 2018), the privacy of the participants will be guaranteed.

5.4.2.4 Validating the survey

The survey should be validated by multiple persons to avoid that people who fill in the survey do not understand or misinterpret the questions. And the survey and the email invitation should be validated by at least a person who knows the usual procedures from the area. This research got first validated by Elekta employees who are experts in the field of HDR PCaBTs, then it got validated by an Elekta employee that is an expert in surveys, and afterwards it got validated by an Elekta employee from the USA to make sure the survey was adapted to the customs, laws, and regulations of the USA.

5.4.2.5 Sending out the survey

The survey should be sent to as many relevant hospitals/clinics as possible, to increase the amount of data collected. However, it should be taken into account that there are limited number of hospitals/clinics that perform HDR PcaBTs in certain areas. The survey should be sent out by someone familiar to the persons filling out the survey to improve the chance they will fill in the survey. If he does not want to send the survey, try to see if it is okay to put him in the Cc of the email.
Once the survey has been sent out for a while, send out a reminder to the persons who have not reacted yet. This will increase the total response rate and lower the selection bias. If they still do not react, it could be checked if they ever received the survey by, for example, calling them. Furthermore, do not send the email around major holidays, because that is when people do not respond. And when they catch up on work accumulated during the holiday, their priority is often not on a survey.

5.4.2.6 Processing data

When the data is collected, it should not only be looked at which hospitals perform HDR PcaBTs quicker than others, but also why. Are they compromising on the quality of the treatment? And if

not, is the workflow from them easy to use in other hospitals? If this is the case, there workflow can be used to help standardize HDR PcaBTs.
To go to a hospital and time a treatment in real-life to validate the results of the survey could validate the data quality.
If the steps from HDR PCaBTs that have the most potential to reduce the total treatment time are found and validated with enough data, it should be researched why these steps are taking relatively long. If the cause is found, an improvement can be made.

References

Alasuutari, P., Bickman, L., & Brannen, J. (2008). The SAGE Handbook of Social Research Methods. In SAGE Publications Ltd.

American Cancer Society. (n.d.-a). *Chemotherapy for Prostate Cancer*. Retrieved February 11, 2023, from https://www.cancer.org/cancer/prostate-cancer/treating/chemotherapy.html

American Cancer Society. (n.d.-b). *Hormone Therapy for Prostate Cancer*. Retrieved February 11, 2023, from https://www.cancer.org/cancer/prostate-cancer/treating/hormone-therapy.html

Bager-Charleson, S., & McBeath, A. (2020). Enjoying Research in Counselling and Psychotherapy: Qualitative, Quantitative and Mixed Methods Research. Springer Publishing. https://link.springer.com/chapter/10.1007/978-3-030-55127-8_10

Cancer today. (n.d.). Retrieved March 4, 2023, from https://gco.iarc.fr/today/fact-sheets-cancers

Cancer World. (2019, March 18). *Brachytherapy: halting the spiral of decline*. https://archive.cancerworld.net/cover-story/brachytherapy-halting-the-spiral-of-decline/

Chargari, C., Deutsch, E., Blanchard, P., Gouy, S., Martelli, H., Guérin, F., Dumas, I., Bossi, A., Morice, P., Viswanathan, A. N., & Haie-Meder, C. (2019). Brachytherapy: An overview for clinicians. CA: A Cancer Journal for Clinicians, 69(5), 386–401. https://doi.org/10.3322/caac.21578

Cimadamore, A., Scarpelli, M., Raspollini, M. R., Doria, A., Galosi, A. B., Massari, F., Di Nunno, V., Cheng, L., Lopez-Beltran, A., & Montironi, R. (2019). Prostate cancer pathology: What has changed in the last 5 years. *Urologia Journal*, *87*(1), 3–10. https://doi.org/10.1177/0391560319876821

Cooper, D. C., & Schindler, P. S. (2013). Business research methods (12th ed.). McGraw-Hill

Education.Corkum, M. T., Morton, G., Louie, A. V., Bauman, G. S., Mendez, L. C., Chin, J., D'Souza, D. P., Dinniwell, R. E., Velker, V. M., Saskin, R., Warner, A., & Rodrigues, G. B. (2020). Is prostate brachytherapy a dying art? Trends and variation in the definitive management of prostate cancer in Ontario, Canada. *Radiotherapy and Oncology*, *152*, 42–48. https://doi.org/10.1016/j.radonc.2020.07.036

De Kraker, L. (2023). *Innovation Focus Areas for Cervical Cancer Brachytherapy Treatment in Academic European Hospitals*

Dinia, L., Frezza, F., & Marella, M. (2019). Parallelism between risk and perception of risk among caregivers during anesthesia delivery. *European Review for Medical and Pharmacological Sciences*, *23*(7), 3129–3141. https://doi.org/10.26355/eurrev_201904_17597

EU. (2018). General Data Protection Regulation GDPR. Intersoft Consulting. https://gdpr-info.eu/

European Commission. (2021, February 3). *Communication from the commission to the European Parliament and the Council*. https://eur-lex.europa.eu/legal-content/en/TXT/?uri=COM:2021:44:FIN

External beam radiation for prostate cancer - Mayo Clinic. (2021, July 29). https://www.mayoclinic.org/tests-procedures/external-beam-radiation-for-prostate-cancer/about/pac-20384743

Heerkens, H., & Winden, V. A. (2021). *Solving Managerial Problems Systematically (Routledge-Noordhoff International Editions)* (1st ed.). Routledge.

Hutchings, M. I., Truman, A. W., & Wilkinson, B. (2019). Antibiotics: past, present and future. *Current Opinion in Microbiology*, *51*, 72–80. https://doi.org/10.1016/j.mib.2019.10.008

Inverse square law - Energy Education. (n.d.). Energy Education. Retrieved February 11, 2023, from https://energyeducation.ca/encyclopedia/Inverse_square_law

Jackson, M. (2022). Brachytherapy for the future. *Journal of Medical Imaging and Radiation Oncology*, *66*(7), 977–979. https://doi.org/10.1111/1754-9485.13468

kanker.nl. (n.d.). *Hormonale therapie bij prostaatkanker*. Retrieved February 11, 2023, from https://www.kanker.nl/kankersoorten/prostaatkanker/behandelingen/hormonale-therapie-bij-prostaatkanker

Kuijper, K. (2021, September 29). *Miljoenennota 2022: dit zijn de gevolgen voor je zorgverzekering*. Zorgwijzer. https://www.zorgwijzer.nl/zorgverzekering-2022/miljoenennota-2022-dit-zijn-de-gevolgen-voor-je-zorgverzekering

Litwin, M. S., & Tan, H. J. (2017). The Diagnosis and Treatment of Prostate Cancer. *JAMA*, *317*(24), 2532. https://doi.org/10.1001/jama.2017.7248

Mayadev, J. S., Ke, G., Mahantshetty, U., Pereira, M. D., Tarnawski, R., & Toita, T. (2022). Global challenges of radiotherapy for the treatment of locally advanced cervical cancer. *International Journal of Gynecologic Cancer*, *32*(3), 436–445. https://doi.org/10.1136/ijgc-2021-003001

Mendez, L. C., & Morton, G. C. (2018). High dose-rate brachytherapy in the treatment of prostate cancer. Translational Andrology and Urology, 7(3), 357–370. https://doi.org/10.21037/tau.2017.12.08

Mohnike, K., Ricke, J., & Corradini, S. (2020). Manual on Image-Guided Brachytherapy of Inner Organs: Technique, Indications and Evidence. Springer Publishing. https://link.springer.com/book/10.1007/978-3-030-78079-1?source=shoppingads&locale=en-nl&gclid=CjwKCAiAu5agBhBzEiwAdiR5tJun_qksPisWO2BQ_DO22Hf1FQBfn-0YpO5lPLlSqbu3XukoRg3Q7hoCntgQAvD_BwE

Mukherji, A. (2018). Basics of Planning and Management of Patients during Radiation Therapy: A Guide for Students and Practitioners. Springer Publishing. https://pubmed.ncbi.nlm.nih.gov/33835403/

National Cancer Institute. (n.d.). *TNM staging system*. Retrieved February 26, 2023, from https://www.cancer.gov/publications/dictionaries/cancer-terms/def/tnm-staging-system

NHS website. (2022, November 30). *Treatment*. nhs.uk. https://www.nhs.uk/conditions/prostate-cancer/treatment/

Paner, G. P., Stadler, W. M., Hansel, D. E., Montironi, R., Lin, D. W., & Amin, M. B. (2018). Updates in the Eighth Edition of the Tumor-Node-Metastasis Staging Classification for Urologic Cancers. *European Urology*, *73*(4), 560–569. https://doi.org/10.1016/j.eururo.2017.12.018

Pecáková, I. (2016). Pitfalls of Quantitative Surveys Online. Acta Oeconomica Pragensia, 24(6), 3–15. https://doi.org/10.18267/j.aop.560

Petereit, D. G., Frank, S. J., Viswanathan, A. N., Erickson, B., Eifel, P., Nguyen, P. L., & Wazer, D. E. (2015). Brachytherapy: Where Has It Gone? *Journal of Clinical Oncology*, *33*(9), 980–982. https://doi.org/10.1200/jco.2014.59.8128

Porzycki, & Ciszkowicz. (2020). Modern biomarkers in prostate cancer diagnosis. *Central European Journal of Urology*, *73*. https://doi.org/10.5173/ceju.2020.0067r

Prostaatkanker in Nederland. (n.d.). Retrieved March 4, 2023, from https://iknl.nl/prostaatkanker-in-nederland

PubMed. (2023). PubMed. https://pubmed.ncbi.nlm.nih.gov/

Radiation Therapy Side Effects. (2022, January 11). National Cancer Institute. https://www.cancer.gov/about-cancer/treatment/types/radiation-therapy/side-effects

Saklayen, M. G. (2018). The Global Epidemic of the Metabolic Syndrome. *Current Hypertension Reports*, *20*(2). https://doi.org/10.1007/s11906-018-0812-z

Schad, M. D., Patel, A. K., Glaser, S. M., Balasubramani, G. K., Showalter, T. N., Beriwal, S., & Vargo, J. A. (2020). Declining brachytherapy utilization for cervical cancer patients - Have we reversed the trend? *Gynecologic Oncology*, *156*(3), 583–590. https://doi.org/10.1016/j.ygyno.2019.12.032

Smith, R., Hanlon, M., Panettieri, V., Millar, J., Matheson, B., Haworth, A., & Franich, R. (2018). An integrated system for clinical treatment verification of HDR prostate brachytherapy combining source tracking with pretreatment imaging. Brachytherapy, 17, 111–121. https://doi.org/10.1016/j.brachy.2017.08.004

Sturdza, A. E., Stephanides, M., Jurgenliemk-Schulz, I., Eriksen, J. G., Benstead, K., Hoskin, P., Vlad, S., Escande, A., Corradini, S., Knoth, J., Westerveld, H., Tagliaferri, L., Najari-Jamali, D., Konat-Bąska, K., Plesinac, V., Tan, L. T., Nout, R., Strnad, V., Niehoff, P., . . . Kamrava, M. (2022). Brachytherapy training survey among radiation oncology residents in Europe. *Radiotherapy and Oncology*, *177*, 172–178. https://doi.org/10.1016/j.radonc.2022.10.030

The Royal College of Radiologists. (2019). *Radiotherapy dose fractionation* (3rd ed.). https://www.rcr.ac.uk/publication/radiotherapy-dose-fractionation-third-edition

University of Twente (2023). Qualtrics. https://www.utwente.nl/en/bms/datalab/datacollection/surveysoftware/qualtrics/.

VTT, Stafford, D., Komonen, P., Kovanen, K., & Mäntylä, K. (2022). *Megatrends report: Leading towards a better future - VTT*. https://info.vttresearch.com/download-megatrends-report

Williams, V. M., Kahn, J. M., Thaker, N. G., Beriwal, S., Nguyen, P. L., Arthur, D., Petereit, D., & Dyer, B. A. (2021). The Case for Brachytherapy: Why It Deserves a Renaissance. *Advances in Radiation Oncology*, *6*(2), 100605. https://doi.org/10.1016/j.adro.2020.10.018