Aalto University

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Impact assessment of post-treatment options in nuclear medicine therapy:

Final report

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1 Introduction

1.1 Background

Radiation and Nuclear Safety Authority of Finland (STUK) is responsible for protecting people, society, the environment, and future generations from the harmful effects of radiation. The responsibilities of STUK in health care include for instance monitoring of occupational radiation exposure, regulatory control of radiation practices, and regulatory control of radioactive waste. The activities of STUK cover both non-ionising and ionising radiation. The radiation practices and protective actions in health care are justified if the overall benefits of the treatment exceed the detriment caused. The benefits of the treatment may be economic, society or health related as long as the benefits can be compared with the harm caused by the practice. (Radiation Act, 2018.) The aim of the project for STUK is to conduct an impact assessment of the post-treatment scenarios in nuclear radiation therapy by getting an insight into the most essential factors related to the justification of radiopharmaceutical therapy.

Radiopharmaceutical therapy is a medical treatment that uses radioactive substances to target and destroy tumour cells. In radiopharmaceutical therapy, the patient is given a dose of long-lasting radioactive isotope that drifts towards the cancer cells and radiates there, damaging the cancer cells. After the treatment, the patient remains radioactive and must be kept isolated for a given time. Even after the hospitalized isolation, there is some radioactivity left in the patient, and especially the secretions of the patient are radioactive and should be handled with caution. (Kyllönen et al., 2022.)

One of the benefits of the radiopharmaceutical therapy is that it controls the growth of cancer cells and as a result, gives the patient more lifetime (Vaalavirta, 2021). However, it also causes harm to the patient, persons in close contact with the patient, such as caregivers and family members, and to the society (Lassen et al., 2023). The patient gets a dose of radioactive isotope which exposes the patient to radiation. The side effects include skin and mucosal damages near the tumour, and increased risk of a new cancer, among others (Vaalavirta, 2021). The patient also has to be isolated in the hospital and possibly at home.

The isolation and the disposal of radioactive waste in the hospital have monetary costs. Radioactive waste is also generated at home from patient excreta (Kyllönen et al., 2022; Lassen et al., 2023). Ideally, this waste should end up in the water supply system. It can cause problems if the waste ends up in the waste management system. The waste treatment may have to be interrupted, or radioactive ash may be generated when the waste is incinerated (Kallio et al., 2023). When the radiopharmaceutical therapy is considered as a treatment option, these factors have to be taken into consideration. The benefits of treatment must outweigh the harms of radiation to justify the treatment (Lassen et al., 2023). This can be a difficult task to accomplish, as valuing for example the harm to the patient caused by isolation is complicated.

The number of nuclear medicine examinations and radionuclide therapy treatments has steadily increased over the past years. In recent years, especially the use of the radionuclide Lu-177 in isotope treatments has increased significantly (Kuurne, 2023). Therefore, the focus in this project is on assessing different post-treatment scenarios in nuclear medicine therapy on treatments using Lu-177. While in hospitalized isolation, compliance with radiation safety practices is well-defined and monitored. Still, monitoring the patient's compliance with the post-treatment guidelines at home after the hospitalized isolation is more complex.

1.2 Objectives

The objective of this project is to create a model to help assess the impacts of post-treatment options in nuclear medicine therapy. The project will focus on the justification of the Lu-

177 therapy by evaluating the overall benefits and detriments of the treatment. As already mentioned, it is crucial that the benefits of the treatment exceed the detriments. The project focuses in particular on treatments provided by public healthcare in Finland. In addition, we are especially focusing on the usage of the Lu-177 for treating prostate cancer, which is the most common cancer type among men. The main focus of the project is the post-treatment scenarios and, and the risks of the treatment itself are not assessed. In this project, the economic cost of treatment, expected benefits, isolation, potential harm to the economy, written patient guidelines and individuals' attitudes toward guidelines are considered. All above-mentioned features are not included in the model, but they are still discussed in the report.

The model is implemented in Excel. The model consists of an event tree that presents possible post-treatment scenarios. These scenarios are constructed based on scientific literature, meetings with client and the data received from experts. To implement the model, waste management institutes and hospitals are contacted. Using the data received from the experts, probabilities and monetary values are calculated for each event and the values are added to the event tree. The output of the model is the minimum value for one gained life-year needed to justify the treatment. Instructions for the use of the excel model are provided for the client if additional considerations need to be introduced.

The Excel tool is created in a way that the client can easily modify the model if needed. For example, the parameters of the model can be changed by the client if new more accurate data is received. Since the values of the parameters can be easily modified, the model can be adapted effortlessly to other radionuclides. This way the client is able to utilize the model for comparing Lu-177 with for example, I-131 that is used for diagnosing and treating thyroid cancer. In addition, new events can straightforwardly be added to the model by the user.

For some parameters, we provide ranges that are constructed within the team based on literature research and the knowledge gained from experts. Some of the parameter values are determined by the group due to lack of data. However, these parameters are clearly indicated in the documentation of the model, and in the report. After the model is implemented, sensitivity analysis is carried out for the parameters by changing the value of one parameter while keeping the other variables the same.

2 Literature review

2.1 Radiopharmaceutical therapy in cancer treatment

In radiopharmaceutical therapy, specific tumours are targeted by radiopharmaceuticals to treat or control tumour. Radiopharmaceutical therapy can be utilized for treating tumours, such as metastatic prostate cancer, neuroendocrine tumours, and thyroid tumours. (International Atomic Energy Agency (IAEA), no date.) Radiopharmaceuticals are given orally or intravenously to the patient after which the radioactive substance is drifted towards the tumour organ via metabolism and blood circulation to destroy the cancer cells. Radioactivity of the radioisotope can be measured using Scintigraphy (gamma scan) that detects the gamma ray emitted by the targeted organ or tissue.

One of the most important benefits of the treatment compared to other medical treatments, such as radiation therapy, is that the radioisotope radiates locally and therefore, causes less damage to normal healthy tissue and organs. Radiation therapy can effectively kill or slow the growth of cancer cells, but it can also damage healthy cells (National Cancer Institute (NIH), 2022). The use of radiopharmaceuticals for treating cancer reduces potential side effects that may occur from the use of other cancer treatments. In general, common side effects of radiopharmaceutical therapy using the oral route involve chills, difficulty breathing, fainting, nausea or vomiting, fever, headache, and stomach pain depending on the type of the tumour and its location (Mayo Clinic, 2024). Other symptoms may also occur in some patients.

Generally, radiopharmaceutical treatments require healthy kidneys so that the majority of radionuclides and their carriers are eliminated through kidneys in a relatively short period of time. The medical record of the patient is checked every time before applying the treatment. For example, age, diabetes, hypertension, and other diseases that might affect the functionality of kidneys should be inspected before using radiopharmaceutical therapy. Treatments that utilize radioisotopes are not usually part of the last-stage treatment of frail patients. (Mäenpää and Tenhunen, 2012.)

The use of radiopharmaceutical therapies has increased steadily since 2009 according to research conducted by STUK in 2021 (Kuurne, 2023). Compared to 2009, the number of treatments has increased by over 1000 treatments in 2021. The increased number of treatments can be explained by the increased usage of Lu-177 PSMA therapy. (Kuurne, 2023.) New cancer treatments are developed constantly and especially the use of radioisotopes for cancer treatment has become more common.

The most common radionuclides, that have suitable physical properties to treat or control different diseases, are iodine-131 (I-131), yttrium-90 (Y-90), lutetium-177 (Lu-177), and Samarium-153 (Sm-153). However, the physical properties of the above-mentioned radionuclides differ from each other. These physical properties are for example half-time and disintegration energy. Physical and biological decay properties play an important role when choosing which radionuclide is used for specific cancer treatment. For example, I-131 is utilized in imaging the thyroid and treating thyroid cancer. It is also widely used for treating other conditions such as hyperthyroidism (Mäenpää, 2014). Yttrium-90 is used to treat liver cancer. On the other hand, Lu-177 is used for instance in treating metastatic prostate cancer and neuroendocrine tumours. Sm-153 can be used to treat bone cancer as well as other cancers that have already spread to the bone. Sm-153 is also used to relieve bone pain. (Sartor, 2004.)

Lu-177 has good physical properties for treating prostate cancer. Lutetium is a beta-minus emitter which emits gamma radiation when decaying. In addition, Lu-177 has a tissue range of about 2 mm. These properties make it possible for the beta-radiation to penetrate the cancer cells while affecting the surrounding cells minimally. This way normal cells and tissues are not damaged as much as in radiation therapy. In addition, the half-time of Lu-177 is 6.7 hours.

(Ohm et al., 2023.) This means that safety considerations need to be taken into consideration so that radioactivity does not cause harm to other people or the environment. For example, the patient must stay in the hospital for around 6 hours minimum so that the radioactive substance has enough time to break down.

In treating prostate cancer, Lu-177 targets prostate-specific membrane antigen (PSMA) on the surface of prostate cancer. In isotope treatment Lu-177 is bound to a ligand, that is specific to PSMA and seeks out cancer cells and destroys them with radiation. PSMA is a type II transmembrane glycoprotein with a large extracellular part that enables the ligands to bind to it. PSMA is an ideal binding target because PSMA levels are high in majority of prostate cancers and low in normal prostate tissue. In the kidneys, the small intestine and the salivary glands low levels of PSMA can be found and therefore, the radioisotope Lu-177 is also delivered to non-malignant tissues causing some damage to healthy tissues. (Ohm et al., 2023.) Before treatment, it is made sure that the metastases collect the Lu-177-ligand carrier by doing 18F-PSMA-PET-TT imaging using a F-PSMA tracer. This checks that the treatment does not cause serious damage to healthy tissues. In Finland, Palveluvalikoima has accepted the recommendation of using Lu-177- vipivotide tetraxetan in the treatment of metastatic castration resistant prostate cancer in their meeting at 1.2.2024 (Terveydenhuollon palveluvalikoimaneuvosto, 2024).

Prostate cancer is the most common cancer type among men. The risk of developing prostate cancer increases with age. The average age of diagnosis is 70. Typical symptoms of prostate cancer include troubles in urinating, blood in urine or semen, and urinary tract infections. (Saarelma, 2022.) Prostate cancer is usually treated or controlled using radiation therapy and surgery. However, new treatments are constantly being developed, and especially, treatments related to the use of radioisotopes have become more common. Prostate cancer cells typically need androgen hormones, such as testosterone, to grow. Androgen Deprivation Therapy (ADT) is a commonly applied treatment method for advanced and metastatic prostate cancer. In ADT, the levels of androgen hormones in the patient are reduced to control the growth of cancer cells and to shrink the tumours (Better Health Channel, 2023). In some cases, the prostate cancer will further develop into a metastatic, castration resistant prostate cancer (mCRPC), that does not respond to ADT (Ohm et al., 2023.). Metastatic, castration resistant prostate cancer means, that the cancer is incurable and different treatments can only prolong life and mitigate symptoms. The median overall survival for patients diagnosed with mCRPC is around one year and two years for patients diagnosed with CRPC (Aly et al., 2020). Since mCRPC is incurable and the common treatment options include only radiation and chemotherapy, Lu-177 PSMA offers a good alternative treatment method (Ohm et al., 2023). Lu-177 is also used for treating metastatic prostate cancer.

Lu-177 can also offer an alternative treatment option in cases where the patient has NETs in the gut and where the tumour has already spread to other parts of the body or where the patient cannot undergo surgery. Currently, surgery is the only potentially curative treatment for treating neuroendocrine tumours. NETs can develop nearly in any part of the body. The most common parts of body for developing tumour are, for example, the lungs, the small intestine, and the pancreas. Lu-177 has proven to be safe and effective in controlling the growth of NETs in the gut. Gastroenteropancreatic neuroendocrine tumours (GEPNETs) are tumours that can occur anywhere in the gastrointestinal tract. (Dullea et al., 2023.)

2.2 Patient guidelines in radiopharmaceutical therapy

Patient guidelines are written instructions for the patients and their relatives. The instructions intended to provide information about the patient's treatment pathway and to increase the patient's understanding of both the treatment and the post-treatment life. The purpose of the patient instructions is to promote patients' written guidance during radiopharmaceutical therapy.

By understanding the nuclear medicine therapy treatment, the patient can better understand the different steps in the treatment and its effects on the post-treatment life, which may help the patient to better manage his/her fear and uncertainty related to getting the treatment (Männynsalo, 2010). The patient guideline should be as practical as possible. Thus, it should answer any possible basic question that the patient might be having regarding the treatment such as how to arrive at the treatment, the course of the treatment, and post-treatment care as well as the hospital's contact information for getting answers to any additional questions or concerns. When the patient guideline is easy to understand, it is more likely that the patient carefully goes through the instructions and also follows them while getting treated (Kyllönen et al., 2022).

Although there is a wealth of information on nuclear medicine therapy available for patients, there is still a need for written patient guidelines as the radiation therapy treatments that the patients receive after often individually tailored to match the patient's needs. Therefore, not all of the generally available information may necessarily be correct regarding the patient's individually tailored treatment pathway. When the patient receives treatment-related instructions directly from the hospital that provides the treatment, the patient does not have to interpret whether the instructions apply to their treatment pathway. In addition, the information obtained from the hospital has been verified by professionals, and for that reason, the patient does not have to question the accuracy of the information provided. Also, the treatment methods regarding radiation therapy are constantly evolving, especially in radiopharmaceutical therapy using isotope Lu-177. Therefore, the patient guidelines obtained from the hospital ensure the patient receives updated information about their treatment. (Kyllönen et al., 2022.)

2.2.1 Patient guidelines in Lu-177 treatment

After getting radiopharmaceutical treatment with Lu-177 isotope, the patient should only be released from the hospital if the patient is deemed to follow the instructions given in the patient guidelines (Lassen et al., 2023). Typically the patient must be in isolation at the hospital at minimum for the half-time of Lu-177 isotope and after that the release of the patient is evaluated on an individual basis. There are several aspects that need to be considered when considering the release of patients from isolation after radionuclide therapy.

Firstly, there may be a potential risk of contamination and intake of radioactive material as the pharmaceutical passes from the body into excretion. Depending on the pathways of excretion, possible exposures can be, for instance, observed through saliva, urine, faeces, exhalation, or sweat (Lassen et al., 2023). Therefore, the patient must be able to follow hygiene instructions for seven days after being released from the isolation: Hands must be washed thoroughly after each visit to the toilet, the toilet bowl must be flushed twice after each visit, the release of radiating excreta into the environment must be minimized and if excreta gets on surfaces or textiles, the textiles must be immediately washed separately from other textiles and the surfaces cleaned immediately using disposable gloves (Kyllönen et al., 2022).

Secondly, the skin contamination of personnel and caregivers must be avoided. Skin contamination with only a droplet of radioactive excretion can lead to a significant skin equivalent dose. Many patients getting treated with Lu-177 treatment suffer from incontinence and need a catheter. For that reason, the caregivers of the patients who might need to perform tasks with the patients at home hold a significant risk of skin contamination. The risk of skin contamination should be minimized by minimizing bare skin during these tasks for instance by wearing long-sleeved aprons and appropriate disposable gloves. (de Bakker et al., 2023.) The caregivers and family members are also recommended to stand the farthest distance possible from the patients (Demir et al., 2016). However, as the patients getting treated with Lu-177 treatment often require intensive help, the exposure to radiation for the caregivers must be kept as low as possible concerning the standards and limits. Also, the potential impact on members of the public must be taken into consideration.

Lastly, after being released from isolation, the patients must be able to efficiently manage the radioactive waste at home. The generation of radioactive waste in the patient's home must be minimized and before releasing the patient from the hospital, the anticipated amount and activity of radioactive waste produced needs to be considered (Lassen et al., 2023). If the waste management instructions cannot be followed at home, the patient should stay at the hospital.

2.2.2 Likelihood of following the patient guidelines

After the treatment, compliance with radiation practices and protective actions such as control of the exposure pathways of persons in close contact with the patient and the management of radioactive waste can be ensured at the hospital isolation. When the patient is released from isolation, following the compliance of these becomes more complex. Therefore, when considering whether a patient should be released from isolation, the decisions must be determined based on patient questionnaires and interviews where the patient answers questions related to themes such as personal features, home conditions, working conditions, planned vacations/travel, the possibility to avoid close contact with children and pregnant women, and travel arrangements from the hospital. Based on the answers, relevant exposure scenarios can be identified which help the healthcare decision makers to consider who is likely to be exposed to the radiation and under which circumstances the exposure takes place and to conclude whether the patient can be released or not. (Lassen et al., 2023.)

The patient guidelines should be easy to read and understand so that the post-treatment guidelines become as straightforward as possible for the patient (Kyllönen et al., 2022). In post-treatment, the written patient guidelines will work as a reminder of what kind of instructions the patient must follow at home to ensure the minimization of radiation exposures and also as a reminder of what to expect the post-treatment life to be like. Before releasing the patient from isolation, the hospital should make sure that the patient understands the instructions thoroughly before leaving the treatment facility and also encourage the patient to seek clarification if something is unclear. Also, to ensure compliance with the patient's post-treatment guidelines, the patient must be encouraged to communicate any side effects or issues that they experience at home. This helps to address any problem early and prevent it from worsening.

2.3 Justification of radiation practices in medicine

Justification is an important principle in radiation protection that apply to the medical use of ionizing radiation (Ebdon-Jackson et al., 2021). In general, the justification requires that the benefits of the use of radiation outweigh the associated detriments (hazards and risks) (Ebdon-Jackson et al., 2021). In medicine, the International Commission on Radiological Protection (ICRP), has noted that there are three levels at which justification operates (Malone et al., 2012): At the first level, the use of radiation in medicine is accepted as doing more good than harm. At the second level, a specified radiological procedure with a specified objective is defined and justified. At the third level, the application of the procedure to an individual patient must be justified, meaning that the particular application should be judged to do more good than harm to the individual patient. In addition, in medicine, justification has well-accepted differences from other situations where it is also important (for example in nuclear power plants). These differences include the following three factors: the process of justification is evaluated with each individual, the consent of the individual is required for each and every radiation procedure, and exposures are not subject to regulatory dose limits (Malone et al., 2012).

In Finland, according to the Radiation Act (Radiation Act, 2018), radiation practices and protective actions are justified if the overall benefits achieved exceed the detriment caused (principle of justification). The Government Decree on Ionizing Radiation Government Decree on Ionizing Radiation (2018) further explains the details of justification in the case of ionizing radiation. According to the Decree, the justification assessment of a radiation practice and the optimization of radiation protection within a radiation practice shall take into account occupational exposure, public exposure, and medical exposure. In addition, the assessment must also consider the waste generated and the radiation exposure arising from the related waste management (Government Decree on Ionizing Radiation, 2018). The Decree also specifies which factors should be considered in the assessment of the overall benefits and detriments. An assessment of the overall benefit must consider the health benefit to the individual being exposed and the benefits to the society. An assessment of detriments must account for radiation exposure and the resultant health detriments, environmental detriments as well as detriments to property and the functionality of society.

It is important to note that with many procedures using ionizing radiation, the benefits are clear and well established, and generally well accepted within the medical profession and by society at large (Malone et al., 2012). This means that when a procedure that uses radiation is proposed, the expected benefits are often identifiable and sometimes quantifiable. On the contrary, the risks associated with the procedure are often difficult to estimate, require statistical techniques to infer, and may be difficult to quantify and communicate (Malone et al., 2012). The report on the IAEA (International Atomic Energy Agency) 2007 Justification Consultation states that the benefits should substantially outweigh the risks that may be incurred, in part because of the uncertainty of the risks (Malone et al., 2012). It is also important to emphasize the fact that while the medical benefit for the patient is a primary factor in the justification, it is not the only aspect to be taken into consideration. As was stated also in the Government Decree, the potential impact of ionizing radiation on persons in close contact with the patient as well as on members of the public and the environment must also be taken into account in the justification assessment (Lassen et al., 2023). These factors are important to consider especially when evaluating the release of patients from the hospital after the radiation procedure, to ensure that the post-treatment risks remain justified.

2.4 Impact assessment in health care and previously used models

To justify the model we will use in this project work, we reviewed previous evaluation models that are used to estimate the benefits of radiopharmaceutical treatments. We focused on monetary evaluation methods in more detail since we will use them in our own model. In general, many of the mathematical models found from literature focused to evaluate the progression of the treatment, and its effects to patients health, and not so much to potential post-treatment risks caused by radiation, e.g. errors in waste management or exposure of other people.

Our findings consisted of two model categories. First, there are general evaluation models that can be viewed as guidelines. From these types of models, health impact assessment (HIA) (Joffe and Mindell, 2005) and health technology assessment (HTA) (Mäkelä and Isojärvi, 2017) were used regularly. Second, we found more specific mathematical models that used probabilistic safety assessment (López, 2012), Markov model (Benedict et al., 2009), and event trees (Reed et al., 2009). Some of the studies, like Delea et al. (2013), used also partitioned survival-analysis to model patients health states, but the method is not relevant to our project.

HTA is used to evaluate methods like medicine, medical devices, treatments, and rehabilitation, and its aim is to support decision-making. HTA gives a multidisciplinary view of the evaluated method since it takes into account health-related, economical, social, organisational, ethical, and juridical perspectives. (Mäkelä and Isojärvi, 2017.) For example, Ohm et al. (2023) have conducted HTA for Lu-177 in prostate cancer treatment. HIA on the other hand, is more concerned with health in population level (Joffe and Mindell, 2005). Joffe and Mindell (2005) state that one of the aims of an HIA is to predict health policy's, program's, or project's health consequences before its implementation. HIA can also be conducted in a retrospect (Joffe and Mindell, 2005).

Cost-effectiveness analyses are commonly used in evaluations of radiopharmaceutical treatments. Cost-effectiveness analysis compares costs of the treatment to gained benefits. Pouwels et al. (2017) conducted a review of model-based economic evaluations in chemotherapy and targeted therapy for metastatic breast cancer. Articles studied in the review focused mainly on health state-transition analysis, and not on the external post-treatment risks. Pouwels et al. (2017) considered studies that used life years, quality-adjusted life years, and incremental cost-effectiveness ratio as output values. These we common indicators in other papers too. Quality-adjusted life years (QALY) takes other health factors into account (compared to only life years) (Mäkelä and Isojärvi, 2017). Since there is health-states between *death* and *very good life-quality*, QALY can be more suitable to analyse benefits of the treatments. The incremental cost-effectiveness ratio is expressed as costs per gained life year (or QALY).

As mentioned, Reed et al. (2009) used a decision tree in their study. The decision tree was used as a prespecified plan for cost-effectiveness analysis. Kamiński et al. (2018) argue that decision trees are models that help decision makers understand and communicate decision problems. A decision tree is a directed graph that has three kinds of nodes: decision nodes, chance nodes, and terminal nodes. Decision nodes describe decisions the decision maker must do. In chance nodes, the next step is selected randomly. Terminal nodes represent possible outcomes of the decision problem. (Kamiński et al., 2018.) Decision trees may contain lot of information but they can still be easily visualised. An event tree can be seen as a special case of a decision tree. It presents sequence of possible events caused by an initial event (Ostrom et al., 2012). Ostrom et al. (2012) claim that each event has two possible states: success or failure. That is the usual case, but event trees can also be constructed using more than two states.

López (2012) presents proactive methods for risk assessment in radiation therapy. One of them is probabilistic safety assessment. López (2012) introduces a study where probabilistic safety assessment is used in radiotherapy treatment with linear accelerators. First, possible failures and their frequencies in the treatment must be identified. Then, event trees are built: what kind of event chains can arise from each failure? The event trees contain the probabilities of failure of different safety features. Finally, probabilities of possible outcomes are quantified from the event trees. The results can be used for example to evaluate different risk reduction policies, analyse the importance of risks, and conduct sensitivity analysis. (López, 2012.)

2.5 Post-treatment impacts of radiopharmaceutical therapy

2.5.1 Impacts on the patient

Multiple post-treatment effects can negatively impact the patient after the radiopharmaceutical therapy. These effects can affect both the physical and psychological well-being of the patient. Therefore when assessing the post-treatment impacts and their effects on the post-treatment quality of life, it is important to highlight factors affecting both the physical and psychological well-being. The physical post-treatment symptoms are also often reflected in the mental well-being of the patient (Clark et al., 2003). The patient can for instance feel helpless and be ashamed of the physical post-treatment symptoms.

During the treatment period, up to 50-90 % of the patients suffer from fatigue and exhaustion. This is called "treatment fatigue" and it does not go away by resting and sleeping. One-third of the patients being treated with radiopharmaceuticals suffer from anxiety and many patients might feel depressed. In these cases, the patients might not only suffer from fatigue but also have over-tiredness and somnipathy. Typically the root cause for these symptoms is fear for the treatments and the disease (e.g. cancer). Especially when getting radiopharmaceutical therapy for cancer, the patient is facing a major life changes and must adapt to a completely new situation. Cancer can also affect the patient's self-image. Everyone deals with emotions differently and for that reason, understanding and openness are important for the patients both with the healthcare professionals and their relatives. (Kyllönen et al., 2022.)

After being treated with radionuclides such as Lu-177, there are usually no immediate side effects. The most common side effect for instance in the case of treatments using Lu-177 in the first 48 hours after the therapy was mild nausea that 12.5 % of the patients experienced. Other common side effects and complaints in the first 2 days were fatigue, dry mouth, headache, and hypogeusia. (Ahmadzadehfar et al., 2016.) the long-term effects of the Lu-177 treatments are still under investigation due to the majority of patients being elderly and the likelihood of them passing before the long-term effects are detected is high (Kyllönen et al., 2022) Generally, the post-treatment effects of radiopharmaceutical therapy are well tolerated.

2.5.2 Impacts on society

There are multiple scenarios post-treatment that can have a negative impact on society, which can be for example situations that result in economic losses or risking the health of other people in the society. Most of these scenarios and their probability are dependent on the patient's behavior, and how well they follow the patient instructions given to them. Some scenarios are not dependent on the patient's behavior but rather are mandatory due to legislation, such as the isolation of the patient in the hospital after the treatment. We have identified three different parties in society that can be affected negatively post-treatment: other people (members of the public, carers, and comforters), hospitals, and waste management companies.

The potential impact of the ionizing radiation on persons in close contact with the patient as well as on members of the public, is one of the main health-rated risks we have identified for society post-treatment, as this is also one of the factors that need to be evaluated when deciding on the release of the patient (Lassen et al., 2023). After the treatment, the radiation protection related to potential exposures of persons in close contact with the patient are considered and their evaluation varies according to the particular circumstances related to individual patients and may include both external and internal exposure. External exposure will typically arise from external radiation directly from the patient or the excreta, and in this case, the most important radiation protection measure is to keep a distance from the patient and to minimize the time spent near the patient and the patient excreta (Lassen et al., 2023). On the other hand, internal exposure, depending on the pathways of excretion for the radiopharmaceutical (e.g. through saliva, urine, feces, exhalation, regurgitation, sweat, breast milk), can result in potential risk and intake of radioactive material, especially in the case of incontinent patients (Lassen et al., 2023). The patient is kept in isolation in the hospital after the treatment to protect the rest of the population from radiation. The patient is released from the isolation when the radiation from the patient is low enough (under limits that are often provided by national legislation) (Kyllönen et al., 2022) and thus it can be assumed that the radiation directly from the patient to other people is not significant after the isolation (but still the patient should avoid spending long periods of time with children, pregnant woman and other people with a lower immune system). On the other hand, as the radiopharmaceutical passes into the urine and feces of the patient (Kyllönen et al., 2022), there is still a risk of significant radiation exposure to other people once the patient is released. The risk scenarios for people around the patient are significant when the patient's excreta is exposed to other people, for example, if urine or other body fluids are left on surfaces or saliva is left on bed linen. Thus, inefficient waste management, poor hygiene, and cleaning practices are factors that increase the health risks for other people post-treatment. Proper disposal of radioactive waste and efficient cleaning are crucial to prevent environmental contamination and minimize the risk of radiation exposure to waste management, hospital personnel, and the public.

In general, when assessing the relevant radiation exposures after the release of the patient, the relevant modes of exposure (internal or external) as well as the physical and biological decay properties of the radionuclides should be considered (Lassen et al., 2023). When assessing the possible health risks to other people after the treatment (and when deciding whether the patient should be released from isolation), one should evaluate whether the radiation stays under the dose limit/constraint, which is specified in the national legislation. In radiation practices, the radiation dose of workers and members of the public may not exceed the dose limit (principle of limitation) (Radiation Act, 2018). The effective dose of members of the public attributable to radiation practices may not be higher than 1 millisievert a year and the effective dose of a radiation worker may not be higher than 20 millisieverts a year (Government Decree on Ionizing Radiation, 2018).

There are post-treatment economic risks associated with the treatment. As mentioned earlier the patient is kept in isolation after the treatment, to protect the rest of the public from radiation (Kyllönen et al., 2022). In the case of treatments using Lu-177, the patient is kept in the hospital for at least six hours, during which time the radioactive medication has had time to decay by half, meaning its activity has decreased enough for the patient to be released. Thus when evaluating the economic losses post-treatment, the cost of isolation should be taken into account. On the other hand, there are major benefits related to isolation, because it protects the population, and thus these benefits need to be taken into account when justifying the treatment. Also, hospitals have limited capacity for isolation facilities, but we can assume that the treatments will not be done if the safe release of the patient is not guaranteed after the treatment.

In addition to hospitals, also waste management companies can face economic losses after the treatment. The difference between the hospitals and waste management scenarios is that the isolation is mandatory, and thus hospitals will have economic losses in all cases but the possibility of economic losses to waste management companies is dependent on the patient's and hospital's behavior. As was stated before radioactive waste is one of the major risk factors post-treatment, and thus if waste management is not done properly by the hospital or the patient at home, there is a risk that this contaminated waste will end up with other household waste and contaminate them. The radioactive waste can be produced by the patient for example when the patient uses diapers after the treatment or uses sanitary towels to clean possible excreta spills. In proper waste management, waste contaminated with radioactive substances is packed in tight waste bags at the point of origin. Waste bags are put to expire in a lead-protected cabinet marked with a radiation danger sign and solid waste contaminated with radioactive substances is aged in a radiation-protected warehouse (Ekokymppi, 2024). Aged radioactive waste is treated according to its remaining properties among normal mixed waste (Ekokymppi, 2024). These management practices can be done by the hospitals as they have the resources for it, but the hospitals should also, based on an appropriate safety assessment, describe the safe management of radioactive waste in the patient's home (Lassen et al., 2023). If the derived instructions cannot be followed, the patient should stay at the hospital (Lassen et al., 2023).

On the other hand, without proper waste management, the radioactive waste is incinerated with the regular waste, which means that artificial radionuclides such as Lu-177 and I-131 can end up in the ash or slag from the incineration (Kallio et al., 2023), which can increase the radiation exposure to the public and waste management workers, and thus elevates the health risks for the public post-treatment. If the radioactive waste is detected in the regular waste before the incineration, the waste treatment may have to be interrupted or the radioactive waste will have to be isolated, to prevent the radioactive ash or slag, and this will result in economic losses due to the downtime of a waste facility or additional work that the isolation requires. According to the study made by Kallio et al. (2023) only one of the incineration facilities in the study had radiation monitors installed for the detection of radioactivity from incoming waste fluxes, and thus the identification of radioactive can be hard. More often the patient's excreta ends up in the sewage system as the excreta is disposed through the toilet, but radionuclides discharged from radionuclide therapy into modern sewage systems result in doses that are well below the limits for the sewer workers and the public (Lassen et al., 2023), and thus the sewage system can be disregarded in our study. To conclude, the probability of patients following the waste management instructions given by the hospitals as well as the probability of hospitals doing their waste management correctly are important factors in determining the possible economic losses for waste management companies as well as possible health risks to the public due to the contaminated ash and slag.

2.6 Evaluation of a treatment

2.6.1 Evaluation of quality of life

Considering the quality of life, quality-adjusted life-years (QALY) are often used when evaluating for example benefits of a treatment. When evaluating QALYs, the quality of life is rated between 1 and 0, where 1 is perfect health and 0 is death. Then the estimated number of life-years left is multiplied with this value.

Evaluating the quality of life can be a difficult task to accomplish, as the quality of life is a subjective measure. Additionally, people's attitudes are not necessarily rational, when health is considered: the loss in quality of life is considered greater than a gain, even if the change is the same. Approaches such as utility theory and utility theory under prospect theory have been used to tackle this challenge. In these approaches, the utility of quality of life is obtained through interviews, where the respondents are asked to for example directly rate different health statuses or choose between gambles of different health outcomes. Respondents may be patients with actual experience of the condition, or they may be a general sample of the population. The second approach should be used when research findings are used in social decision-making, but this can cause problems when people with no experience of a health condition are asked to assess it.

2.6.2 Assessment of the impacts of a cancer treatment

Health state-transition models and decision trees are commonly used models for assessing cost-effectiveness of a cancer treatment. QALYs are often used to represent the benefits of a treatment. To evaluate the cost-effectiveness, the QALYs are given a monetary value. The results of a cost-effectiveness analysis can vary quite a lot, depending, for example, on what costs are considered and what utilities the health states are given. (Pouwels et al., 2017.)

In case of prostate cancer and other local cancers, it is often considered that the life expectancy of the patient should be at least 10 years, in order to the patient to benefit from the treatment (Prostate cancer: Current Care Guidelines, 2023). The life expectancy depends most on other diseases that the patient has, and the age of the patient or the aggression of the tumor have less affect.

2.7 Isolation after isotope treatment

There is very little research on the effect of isolation on a patient after radiation therapy. More research is available on the longer isolation to prevent immunocompromised cancer patients from becoming ill, and on the isolation of cancer patients during Covid-19.

However, a study by von Müller et al. (2014) examines the fear of isolation patients have before and after a radioiodine therapy. The study is done in Germany, where after radioiodine therapy, the isolation is 24 hours. This is significantly longer than the 6 hour isolation after Lu-177 treatment.

In their study, von Müller et al. interviewed patients before and after the 24 hour isolation, and asked if they were anxious about the isolation before the therapy, and if they had problems with the isolation after the treatment. The results of the study showed that the patients partially agreed that they felt anxious of the isolation before the treatment. However, when asked after treatment whether they had problems with isolation, most of them disagreed partially or completely.

3 Data

3.1 Collecting the data

The data is collected by contacting various experts that might have information about the health hazards and waste management problems related to isotope treatments in Finland. For this project, HUS, Kuopio University Hospital, Docrates Oy, Fortum Waste Solutions Oy, Suomen kiertovoima Oy, Jätekukko Oy, Finnish Environment Institute, Ministry of Social Affairs and Health and STUK are contacted. Some of the above-mentioned institutes did not reply, and ultimately, answers were received from HUS, Kuopio University Hospital, Fortum Waste Solutions Oy, Suomen kiertovoima Oy, Finnish Environment Institute, Ministry of Social Affairs and Health and STUK.

To formulate comprehensive questions for different parties, a general understanding of the topic is formed through literature research. Separate questions are created for the hospitals and waste management institutes. The questions are chosen carefully so that it would be possible to identify the most important post-impact scenarios and obtain valid results. If the data from experts does not include the necessary numerical values for the event tree probabilities, some values or parameter ranges are chosen subjectively by the project team. These values are clearly marked so that it is clear, which parameters are not based on the opinions of the experts.

The questions are written in Finnish. In some cases, follow-up questions are sent to some parties to get more accurate data. Some of the experts are interviewed and some answers are gathered through email.

3.1.1 Data received from waste management institutes

The questions formed for waste management institutions are carefully constructed based on the knowledge gained from literature research and meetings with STUK. The questions are about the risks that are related to having radioactive waste being mixed with normal waste. According to the meetings with STUK, there is a significant risk that radioactive waste can cause problems when it is mixed with normal waste. Radioactive waste includes items that are contaminated with the secretions of the patient. These are for example diapers, catheters, linen, and tissues. STUK stated that the incineration process may have to be interrupted if waste causes a blockage in waste feeders. This also causes radiation exposure to workers. Based on the answers from the waste management institutions, the radioactive waste from households does not cause significant problems in terms of waste management because the mixed waste mixes with the waste of various individuals and the amount of radioactive waste is so small. However, waste from hospitals can affect the functionality of waste management institutions because the volume of waste from hospitals is large.

The following questions are example questions that are asked from different waste management institutions:

- How to prevent radioactive waste from ending up in normal waste?
- How does legislation in general affect your management of radioactive waste?
- How much radioactive waste comes from health care and how much from households?
- What measures are taken if waste containing radioactive material is found among normal waste? What are the costs?
- Is it necessary to stop the treatment of waste if radioactive waste is found? How often does this happen?

- Do the waste facilities/installations have separate equipment or other systems (or manual methods) for the identification of waste containing radioactive material from normal waste? If so, how often do these systems alarm and how often are the alarms incorrect?

Some other questions and follow-up questions are also asked. The experts did not give any evaluation of the costs that occur from radioactive substances mixing with normal waste. This means that the project team must construct a monetary value range for this parameter.

In the case of Lu-177 treatment, relevant waste types from the waste management point of view are: waste that is generated from patient care in hospitals, and waste that is produced in the patient's own home after receiving treatment. According to the experts from different facilities, waste produced in the patient's own home does not contain a risk for the waste management system. The patient is namely released from the hospital once the radioactive substance has already broken down below the acceptable limits. In addition, mixed waste generated by an individual is practically always packed in separate bags, and the waste from various individuals gets mixed together. Several experts considered it unrealistic that a patient would be discharged from the hospital even though special waste was being produced. It is namely not possible to provide special waste management for individuals who have gone through radiopharmaceutical therapy and produce radioactive waste as a result of undergoing the treatment.

Recycling and waste management companies do not accept waste with measurable levels of radioactivity. This policy is determined by the companies, and it is not due to legislation. There are many reasons why waste management companies do not want to accept even minor amounts of radioactivity. One of these reasons is most likely reputational. The reuse of recycled raw materials may not be accepted by the customer. For example, Fortum does not accept waste with even a low level of radioactivity in Riihimäki, since it also wants to reuse slag and ash as efficiently as possible. The municipal waste plant in Mustasaari, on the other hand, takes hospital waste which includes radioactive waste, but the amount of radioactivity in these cases is small. (Promaint, 2019.)

Waste incineration facilities cannot accept any radioactive waste that is classified as hazardous. Radioactive waste entering the incineration process may cause radiation exposure to workers for example in the event of incidents when blockages in waste feeders are opened. Radioactive material or objects that pass through the incineration process end up in the bottom ash or fly ash of the incineration, or they end up in the by-products of gas treatment. There have not been blockages in the feeders that had to be manually opened in the years 2022 and 2023. In general, these blockages are extremely rare. Therefore, the probability of having a blockage in the waste feeder is close to zero.

Radioactive waste is generated in healthcare and especially in certain sectors of industry. In households, radioactive materials may include pharmaceutical waste, electrical appliances, batteries, and accumulators. For household radioactive waste, it is important that residents dispose them in the right way. Waste containing radioactive material is prevented from ending up in normal waste treatment, for example by carefully instructing customers. For example, the waste must be classified. An EWC code for the waste is identified. If the waste is hazardous, a document is also prepared. Separate collection of hazardous waste is another way of avoiding radioactive waste being mixed with normal waste. It is not common for radioactive waste to get mixed with normal waste. Radioactive waste is typically noticed at the reception points of waste, such as at the waste collection stations where customers drop off waste in the hazardous waste collection containers. Observations of radioactive substances can also be made when waste loads are received at the treatment facilities. It is rare for radioactive waste from households to end up mixed with normal waste.

An environmental permit defines what waste can be received, how much, and with what characteristics. The permit also specifies how monitoring should be arranged. Waste legislation and environmental protection legislation state that radiation measurement is not required unless it is known that radioactive waste is being handled. Typically, scrap metal recycling plants have radiation measurements installed.

Waste treatment facilities can have radiation portals. For example, Fortum has two radiation portals in Riihimäki. Vehicles entering the plant site pass through the portals. Leaving vehicles also pass through the radiation monitoring equipment. The use of radiation portals does not cause significant operating or maintenance costs. An alarm from the monitoring equipment is signaled to the gate, where a guard will report the waste. Then a check measurement is performed on the vehicle with a portable dose rate meter. In Riihimäki, Thermon SPRD spectrometer is used. This device identifies nuclides. If something is suspected to be radioactive material, the load is set aside, and an investigation begins under the guidance of a Radiation Safety Officer. This causes additional costs that are paid by the customer.

3.1.2 Data from hospitals

Similarly, as for the waste management institutes, the questions for the hospitals are carefully formed based on the literature review and information provided to us by STUK. The questions are divided into five subsections focusing on different themes such as isolation periods, patient guidelines, Lu-177 treatment, incontinence of the patients, and financial estimates of the treatment. Some hospitals answered the questions by email and some preferred interviews.

The following questions are example questions that were asked from the different hospitals:

- How long does the patient on average spend at the hospital in isolation after the treatment?
- Before discharge after the treatment, how is the patient guideline reviewed with the patient?
- How many of the patients are incontinent (use diapers or catheters etc.) before starting the treatments?
- How much does it cost the hospital to treat a patient with Lu-177 isotope therapy (treatment alone + the cost of the treatment including isolation costs)?
- How is radioactive waste managed in the hospital? Have you had any cases where radioactive waste would have ended up as a part of the normal waste management system?
- What percentage of patients follow the patient guidelines at home? Which factors influence this percentage?
- How often is PSMA treatment not given to the patient and what are the reasons for this?

As stated in Section 3.1.1, there is a significant risk of problems if radioactive waste gets mixed with normal waste. For that reason, we also wanted to get the hospitals' view of this to better understand how often radioactive waste ends up in normal waste at the hospital. Based on the answers from the hospitals, dealing with radioactive waste is routine for the hospital workers, and therefore it can be assumed that no radioactive waste ends up in normal waste in the hospital due to the staff as the radioactive waste is treated in the hospital according to the radioactive waste safety instructions. These measures ensure that the radioactivity of the waste is under acceptable limits, in other words, classified as normal waste, before it is put to normal waste, and not following these measures at the hospital is extremely rare according to the expert. Also, according to the patient guidelines, the patients must return their waste to the hospital if the radioactivity of it is over the free limit. This can be a wearisome process for the patients but since the patients are often highly motivated towards getting treated with the Lu-177 PSMA treatment they will most likely not see this procedure as a problem.

The patients getting treated with the Lu-177 PSMA treatment are often highly motivated to get this type of treatment as they have often already gone through rounds of other types of treatment and therefore are hoping that this treatment will help. For that reason, following the sometimes strict guidelines is not a problem for the patients and there have very rarely been cases where the patients have not been following the guidelines. Also, before getting the treatment, the treating doctor will go through the guidelines with the patient to ensure that the patient is able to follow the guidelines. This pattern is also repeated before the patient is discharged from the hospital. Also, if the treating doctor assesses that the patient is unable to follow the patient guidelines at home, the patient might not be able to get the treatment or must stay longer at the hospital facilities as an inpatient until the radioactivity of the patient is low enough.

Lu-177 PSMA treatment can be administered either as an outpatient or inpatient treatment. Typically, outpatients spend approximately six hours at the hospital facilities together with other patients getting treated with PSMA treatment. During the six hours, in the morning they typically get treated with the radiation dose and in the afternoon they go through radionuclide imagining to ensure that the treatment has affected the patient. Similarly, inpatients spend around 24 hours at the hospital as the treatment is typically administered in the afternoon and the patients are discharged from the hospital the following morning. Incontinent patients are often treated as inpatients to ensure proper radioactive waste disposal. As mentioned earlier, PSMA treatment is often used for treating patients with prostate cancer. The disease is associated with a predisposition to incontinence and patients with incontinence might use urinary bags or catheters.

3.2 Monetary value ranges and probabilities for data from waste management institutions

During the years 2022 and 2023, Fortum's Riihimäki plant received radioactive waste once from a customer in the healthcare sector. This waste was Iodine-131. Iodine-131 has been found three times in municipal waste incineration plant deliveries of municipal waste. In 2022, the monitoring equipment alerted 80 times out of approximately 40000 loads passing through the monitoring equipment. Four of these 80 alarms were legitimate. In 2023, there were 56 alarms out of approximately 50000 loads passing through the monitoring equipment. Two of these alarms were legitimate.

Using the above-mentioned numerical values for the number of alarms, the probabilities can be estimated for the event tree. The probabilities for the year 2022 are calculated below and shown in a table 1.

$\mathbb{P}(\text{Correct alarm} \mid \text{alarm}) = \frac{4}{80} = 0.05$

$\mathbb{P}(\text{False alarm} \mid \text{alarm}) = 1 - 0.05 = 0.95$

$\mathbb{P}(\text{Alarm goes on}) = \frac{80}{40000} = 0.002$

$\mathbb{P}(\text{No alarm}) = 1 - 0.002 = 0.998$

Similar probabilities are calculated below for the year 2023. These values are shown in table 2.

$\mathbb{P}(\text{Correct alarm} \mid \text{alarm}) = \frac{2}{56} = 0.03571428$

$\mathbb{P}(\text{False alarm} \mid \text{alarm}) = 1 - 0.035714 = 0.9642857$

$\mathbb{P}(\text{Alarm goes on}) = \frac{56}{50000} = 0.00112$

$\mathbb{P}(\text{No alarm}) = 1 - 0.00112 = 0.99888$

Additional costs for the waste management institution will occur if it is suspected that there is a radioactive substance in the load. The costs incurred for the waste management institution

Table 1: Probabilities for waste management model in 2022

$\mathbb{P}$(Correct alarm | alarm)	0.05
$\mathbb{P}$(False alarm | alarm)	0.95
$\mathbb{P}$(No alarm)	0.998
$\mathbb{P}$(Alarm goes on)	0.002

Table 2: Probabilities for waste management model in 2023

$\mathbb{P}$(Correct alarm | alarm)	0.0357
$\mathbb{P}$(False alarm | alarm)	0.964
$\mathbb{P}$(No alarm)	0.999
$\mathbb{P}$(Alarm goes on)	0.00112

Table 3: Additional costs needed for investigation of the bulk load

Different costs	Working time	Cost	Total costs
Employing the Radiation Safety Officer	7.5	150	1125
Operating costs of measuring devices	1	200	200
Machine-hour costs	24	12.5	300
Man-hour costs	10	100	1000

will be paid by the customer. The costs consist of the cost of employing the Radiation Safety Officer, operating costs of the measuring devices, machine-hour costs and man-hour costs. In addition, the employees must be trained to be able to handle these kinds of scenarios which also causes additional costs. The expert from Fortum waste solutions Oy did not give any numerical estimate for these costs. Therefore, the project team has to construct a subjective estimate for the costs that is used in the model.

Table 3 shows the additional costs that are needed if it is suspected that there is radioactive substance in bulk load. It is estimated that the costs of employing the Radiation Safety Officer are 150 €/h and the working time is estimated to be 7.5 hours. Therefore, the total costs related to employing the Radiation Safety Officer is 1125 euros. The operating costs of measuring devices is approximated to be 200 €/h and the required working time is one hour. The total costs of operating costs add up to 200 euros. Machine-hour costs are expected to be 12.5 €/h and the working time is estimated to be 24 hours. As a result, the total costs for machine-hour are 300 euros. Man-hour costs are expected to be around 100 €/h and the working time is around 10 hours. Total costs for man-hour are 1000 euros. If all the above-mentioned costs are combined, we obtain that the additional costs are 2625 euros. Since the values are student's own estimation, we conduct sensitivity analysis in Section 5.2 by testing whether the estimation for additional costs affects the results.

3.3 Monetary value ranges and probabilities for data from hospitals

During 2023, HUS treated patients with Lu-177 PSMA treatment approximately 375 times. Out of these treatments, 60 % of patients were treated as inpatients and 40 % as outpatients. Similarly during 2023, at KUH (Kuopio University Hospital) approximately 140 treatments were conducted. KUH treats incontinent patients as outpatients and the percentage of incontinent patients is 10-15 % out of all patients getting the treatment. HUS estimated the percentage of its incontinent patients to be between 10-20 %. Both of the hospitals reported that during the past years, the number of PSMA treatments has increased and will also continue to increase in the coming years, and especially the number of policlinical (outpatient) treatments will be increasing. When constructing the monetary value ranges and probabilities for hospital data, having data received from multiple hospitals helped us validate the value ranges and probabilities used in the model. Still, the answers received from HUS and KUH varied rather widely, which indicates that each hospital has their own practices. As a result, we ended up mostly using data received from HUS.

Typically during the PSMA treatment cycle, the patient gets treated with the radiopharmaceutical treatment at most six to eight times to ensure the effectiveness of the treatment. The median of the rounds of treatment that the patient goes through during the PSMA treatment cycle is three. (Rahbar et al., 2018.) Before starting the treatment cycle, to justify the treatment, it needs to be checked that the Lu-177 isotope starts to accumulate in the tumor. This is checked using PET scan which costs approximately 1000-1500 € per scan. As the PET scan itself is quite expensive, sometimes the patient is given a few rounds of treatment at first and if there are no clusters visible on the imaging after the treatment, the treatment is discontinued. For outpatients, this imaging is part of the policlinical procedure and it costs approximately 200 €. Respectively, for inpatients, the cost of treatment procedure is approximately 400 € which includes the one night cost of isolation at the hospital.

Lu-177 product used in the treatment can be either purchased from a commercial producer or produced in-house at the hospital. HUS for instance uses both of these methods for ensuring the availability of the product for treatments given at different times. The cost of buying the product from a commercial producer is 15 000 € and producing one dose of the product costs 4500 €. At HUS, the products are mostly produced in-house at the hospital and for that reason, in the model, the use of in-house products is assumed. Thus, in the model, we estimated that the average costs for one cycle of PSMA treatment, which includes the costs for the PET scan and the product, is approximately 4563 €. This value is conducted by summing the costs of the Lu-177 product used in treatment with the cost of the pre-treatment PET scan multiplied by the probability of the patient being PET scanned before the treatment. Note that this value does not include additional costs such as the costs from the isolation nor the contamination from radioactive waste. Similarly, we estimated the cost of radioactive waste not being treated the right way at the hospital to be around 35 €. This value is conducted by multiplying the cost of other people's contamination € $/mSv$ with cumulative dose readings between hours 4-20 mSv. These costs related to the PSMA treatment at the hospital facilities are shown in Table 4.

Table 4: Hospital costs related to PSMA treatment in 2023

Cost of Lu-177 product used in treatment	4500 €
Cost of PET scan	1250 €
Average costs from the PSMA treatment (one cycle)	4562.5 €
One night in isolation at the hospital (inpatient)	400 €/night
Cost of policlinical procedure (outpatient)	200 €
Cost of radioactive waste not treated right at the hospital	34.8 €

It is estimated that the probability of radioactive waste not being treated right by the staff at the hospital is zero, as dealing with radioactive waste is a routine for hospital staff. On the other hand, there is a possibility that the patients will generate radioactive waste in the hospital, such as tissues, which are not noticed by the staff, and this can cause contamination to hospital staff. When building the model, we estimated that the probability of radioactive waste not being treated right at the hospital, which corresponds to the probability of contaminating hospital staff due to unnoticed radioactive waste generation by the patient, is 1 %. Scanning the patients with a PET scan before starting the PSMA treatment cycle is rather expensive. Therefore, in our model, it is estimated that the share of the patient being treated with PSMA getting PET scanned before the beginning of the treatment cycle is 5 %. Probabilities of the factors related to the likelihood of the events occurring during the hospitalization are shown in Table 5.

Table 5: Probabilities for hospital model in 2023

$\mathbb{P}$(Patients with incontinence)	0.13
$\mathbb{P}$(Inpatient PSMA treatment)	0.6
$\mathbb{P}$(Outpatient PSMA treatment)	0.4
$\mathbb{P}$(Radioactive waste not treated right at the hospital)	0.01
$\mathbb{P}$(Share of treated patients being PET scanned before PSMA treatment)	0.05

Table 6: Probabilities for events occurring at home after the treatment

$\mathbb{P}$(Radioactive waste generated at home)	0.169
$\mathbb{P}$(Radioactive waste not treated right at home)	0.20
$\mathbb{P}$(Other people contaminated | Radioactive waste is generated)	0.65
$\mathbb{P}$(Other people contaminated | Radioactive waste is not generated)	0.065

When building the model, we also constructed monetary values and probabilities for scenarios occurring at home after the patient has been discharged from the hospital. Experts stated to us that after being discharged from the hospital but still over the radioactive safe limit, the patient should return all of their radioactive waste to the hospital for appropriate recycling. As this procedure may be difficult for the patients that recover from the treatment, we estimated the probability of radioactive waste not being treated right at home to be 20 %. Also, it is assumed that if the patient is incontinent, radioactive waste is always generated. Similarly, if not, it is estimated that the probability of radioactive waste generated at home is 5 % as the hygiene-related patient guidelines are sometimes hard to follow at home. By multiplying these probabilities of the events with the percentage of patients with incontinence, we get that the probability that radioactive waste is generated at home is 16.9 %.

Based on our discussions with the Ministry of Social Affairs and Health, if radioactive waste is generated, other people living with the patient after treatment are automatically contaminated as the radiation spreads easily. They also stated that patients getting treated with Lu-177 PSMA are typically older men. In 2022, 35 % of over 60 years old man were living alone (Official Statistics of Finland, 2022). Thus, we estimate that the probability that other people are contaminated after the treatment at home when radioactive waste is generated is 65 %. In situations where at home no radioactive waste is generated, there are fewer ways to be exposed to radiation for others, and the probability of this occurring is estimated by us to be one-tenth of the contamination risk when waste is generated. Therefore, the probability of other people being contaminated is 6.5 %. These probabilities are shown in Table 6.

Table 7 shows the costs of other people's contamination. HUS stated that after 3-4 days, the

Table 7: Costs from other people's contamination

Cost from other people's contamination (4-6 h isolation, outpatient)	10.18 €
Cost from other people's contamination (24 h isolation, inpatient)	4.80 €

radiation falls below the exemption limit. We estimated the cumulative dose of radiation 3.5 days after treatment by using the half-time formula where we set that after 4 hours (patient treated as an outpatient), the dose rate is 14.0 $\mu Sv/h$ and after 24 hours (patient treated as an inpatient), the dose rate is 6.6 $\mu Sv/h$. By multiplying these by the average cost of other people's contamination, we received the costs for other people's contamination for both inpatients and outpatients. When the patient is treated as an outpatient, the cost from other people's contamination is estimated to be 10.18 €. Whereas, when the patient is treated as an inpatient, the cost from other people's contamination is estimated to be 4.80 €.

More detailed information on the calculations of the values and their references for waste management and hospital events can be found in the Excel model's data sheets.

4 The model

4.1 Event tree

To model the possible scenarios after the patient gets cancer, event trees are employed. These include the relevant scenarios in estimating the justification of the treatment after the patient is identified with cancer. Also, the probabilities of the different events as well as their corresponding estimated detriments and benefits are included. After all the probabilities and expected monetary values for the detriments and benefits are calculated, the different scenario paths can be used the evaluate whether the overall benefits exceed the overall detriments, which would justify using the treatment.

As mentioned in the literature review, an event tree presents sequences of possible events caused by an initial event (Ostrom et al., 2012). The event tree approach assumes that as each event occurs, there are only two possible outcomes, which are failure or success (Ostrom et al., 2012). In our model, we will also use events, where the outcome is different, but for the majority of events, only failure or success outcomes are considered. In the event tree analysis, the events following the initial event are identified, and their success and failure probabilities are estimated. By identifying all possible events before the chosen end state (outcome), the estimated probabilities can be assigned to the events and combined using the appropriate Boolean logic to develop an overall probability for the different paths identified in the tree (Ostrom et al., 2012). In addition, different paths will have different detriments and benefits, and therefore the overall expected benefit (detriment) of the tree is calculated by combining all the possible paths with their evaluated probabilities and estimated monetary values. For each path, the expected value of the outcome is the product of the probability of the path and its expected benefit/detriment in monetary value. The total expected monetary value of the tree is then the sum of the expected monetary values for the different paths.

In the model, it is assumed that the events occur in chronological order. This is not always the case, as in for example in the event tree for the patient's home the events that were identified could happen in a different order or multiple times instead of happening just once. This is neglected in the model, to keep the event tree simple, and thus the model has the assumption of chronological order and the assumption of single events.

4.2 Identifying relevant scenarios

The model focuses on events happening at a hospital, at the patient's home, and at waste management facilities. The following event trees are developed separately for the hospital, patient's home, and waste management facilities. They include all relevant events identified through the literature review and the interviews. In addition, we will describe which events were excluded from our model, and why

The first event tree focusing on the events in the hospital is in Figure 1. The initial event is the patient having an advanced stage prostate cancer. After the initial event, the treatment is either given or not given. This depends on the patient's age and their possible other diseases. If the patient's cancer is chosen to be treated with the radiopharmaceutical treatment the price of the treatment is seen as a detriment (cost) in the model during this event. The benefit of receiving the treatment is increasing the lifetime of the patient. If the treatment is not given, the patient will not get more lifetime, and thus, there are no gained life-years and there will be no future events in the model.

After treatment, the patient will stay in isolation at the hospital to protect other people from radiation. The length of the isolation may vary between patients. This depends on the patient's state of health, home situation, given dose, general practices of the hospital, etc. Keeping the patient in isolation will result in costs for the hospital, but the benefit is protecting other people from additional radiation, since after the pharmaceutical treatment, the patient will emit radioactive radiation. The patient can either stay in the hospital overnight (24 hours) or they can get the policlinical procedure which requires the patient to stay at the hospital for 4-6 hours after the treatment. The nurses in charge of taking care of the patient in isolation will possibly be exposed to radiation, but as they use safety equipment and there are several safety measurements, it can be assumed that this exposure is under the dose limit, and thus will not be included in the model. It is worth mentioning that, isolation may also have negative impacts on the patients' mental health, but as this is a complex issue and thus hard to evaluate, we will not include this in the model. The last event included in this event tree is connected to the treatment of radioactive waste. During and after the treatment, patients will produce radioactive waste, by for example contaminating the medical equipment used during the treatment and bedding used in isolation, etc., which have to be treated at the hospital. This means collecting the radioactive waste and storing it in a room where the radioactivity of it will decrease under the specified limits. If the radioactive waste is not treated right at the hospital, it will end up in regular waste and thus can contaminate it, resulting in possible hazards in the waste management facility and waste collection process. However, from the discussion with an expert from HUS, it was revealed that the probability of this happening is very low, as they had never heard of or witnessed such situations, so we will exclude this event from the model. Thus, the risk during this event is the possible radiation exposure to hospital faculty due to the radioactive waste generated by patients, such as tissues.

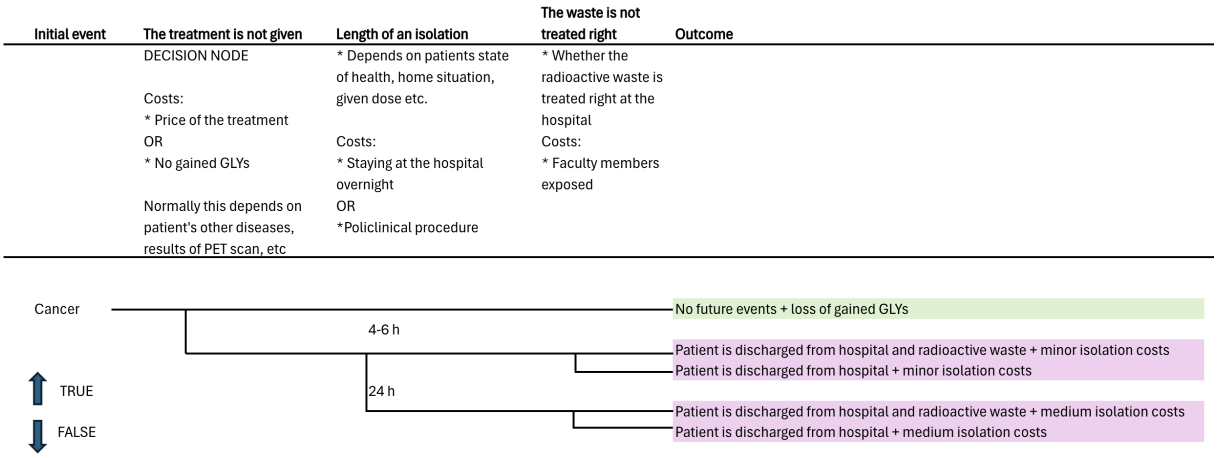

Figure 1: Event tree for hospital

After the isolation, the patient is released to home, which is the initial event for the next event tree. The event tree including the most relevant events in the patient's home is in Figure 2. In this tree, the focus is on the possibility of generating radioactive waste which can result in exposure and other hazards in the waste management facility, and the possibility to contaminate other people by spending a significant amount of time with them or contaminating them by exposing them to the radioactive excreta coming from the patient, which can happen if the patient does not follow the instructions from the hospital. The length of the isolation affects the amount of unsafe amount of radiation the patient will emit at home. It is assumed that after any isolation time, there is no significant radiation for other people when the patient spends only a short amount of time in their presence, and thus for example the transportation from the hospital to home will not be included in the model. In general, the patient is released from isolation when the radiation from the patient is low enough and thus it can be assumed that the radiation directly from the patient to other people is not significant. Therefore in the model, it is assumed that the unsafe radiation exposure is mostly caused by the patient's excreta, as the radiopharmaceutical passes into the urine and feces of the patient, and thus there is a risk of contamination when the patient's excreta is exposed to other people. At home, the patient can generate radioactive waste if, for example, they have to use diapers or a catheter, they have to clean their excreta with something, or they have to put their clothes or linen in normal waste.

As in the hospital, the radioactive waste must be treated correctly so that it does not end up as normal waste in the waste treatment facility. From the interview with HUS, it was discovered that patients should bring the radioactive waste to the hospital. It is assumed that if the radioactive waste is small, for example, just tissues, putting them in the normal waste will not result in significant hazards in the waste management facility, and thus bringing them to the hospital is not necessary, but rather this is the case only with diapers and catheters. If the patient disregards the instructions from the hospital and puts a significant amount of radioactive waste into normal waste, there is a possibility of hazards in the waste management facility. A patient without diapers and catheters can also generate a significant amount of radioactive waste if they produce an excessive amount of waste, for example, clothes, linen, and towels, but we assume that this is rare. It is assumed that incontinent patients will generate radioactive waste with certainty, but it is also assumed that the majority of people treat the waste appropriately, and return it to the hospital.

The final node in the event tree for patient's home is the possibility of contaminating other people. This can happen if other people are spending a significant amount of time with the patient, which can happen for example, if the patient sleeps in the same room with another person or attends events or gatherings where they are in close contact with other people for long periods of time. Also, the patient can contaminate other people if good hygiene is not maintained. This means that if the patient does not follow the instructions of cleaning their hands thoroughly (especially after going to the restroom) they can contaminate surfaces at home that other people use, thus possibly contaminating them. Therefore also cleaning one's environment regularly is important to avoid contamination if other people are living with the patient or visiting them. It is important that the toilet is cleaned carefully, to prevent contamination of other people using it. If the patient disregards cleaning, the possibility of contaminating other people is increased. An incontinent patient can increase the risk of other people's contamination since the radioactive waste generated by the incontinent patient will most likely be exposed to people in close contact with the patient. The model does not account for how the sewage system in Finland may affect the justification of the treatment, meaning that the model only considers cases where excreta is disposed by putting it in normal waste. More often the patient's radioactive excreta ends up in the sewage system as the excreta is disposed through the toilet, but this can be neglected in the model since radionuclides discharged from radionuclide therapy into modern sewage systems through excreta result in doses that are well below the limits for the sewer workers and the public (Lassen et al., 2023).

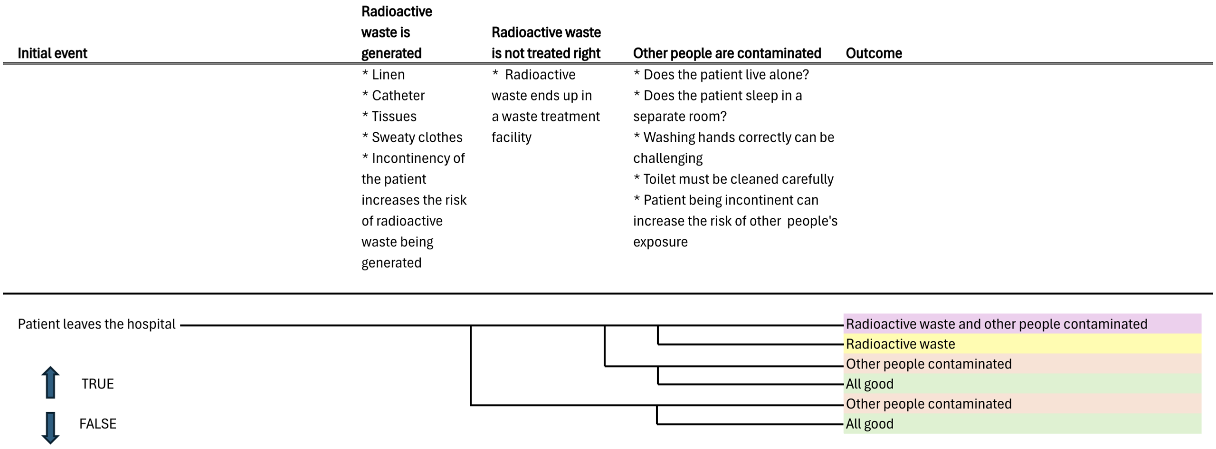

Figure 2: Event tree for patient's home

The final event tree is presented in Figure 3 and it illustrates the events in the waste management facility. In theory, radioactive waste can end up in waste management facilities from the hospital or the patient's home, but both of these events, especially the prior one, are very rare according to the data. The initial event in the waste management event tree is when the load goes through the radiation portal. Consequently, in the model it is assumed that the waste management facility will have a radiation portal, and all the waste loads coming to the facility will be driven through it. The radiation portal is a safety measurement used in waste management facilities, to detect radioactive substances in the waste load, and they do not generate significant costs for the facility. This procedure is used for example in the Fortum Waste Solutions Riihimäki waste management facility. If the alarm of the portal goes on, a waste management worker is alerted to the scene to investigate the load more carefully. In this case, the worker goes around the load with a portable dose rate meter and looks for a dose rate that is significantly different from the background radiation. In the Fortum Waste Solutions Riihimäki, a Thermon SPRD spectrometer is used, which also has a nuclide detection function. If something is found with the dose meter that gives reason to suspect that there is some radioactive substance in the load, it means that the alarm of the radiation portal was correct, and the load will be taken aside and further investigation will begin. This isolation of the load and further investigation of the load will create costs for the client sending the waste. Based on the interviews with waste management facilities, it is assumed that the possibility that a significant amount of radioactive waste ends up in waste incineration is very low. Thus the model does not include scenarios that would occur after the radioactive waste is spread in the fly ash or ends up in the slag. Additionally, the model will not consider possible radiation exposure to waste management workers in the case of disturbance, due to the assumption that the waste is very rarely radioactive. Also, the moving of the waste into the waste management facility is neglected in the model, as it is assumed that there is no significant possibility of radiation exposure in this case.

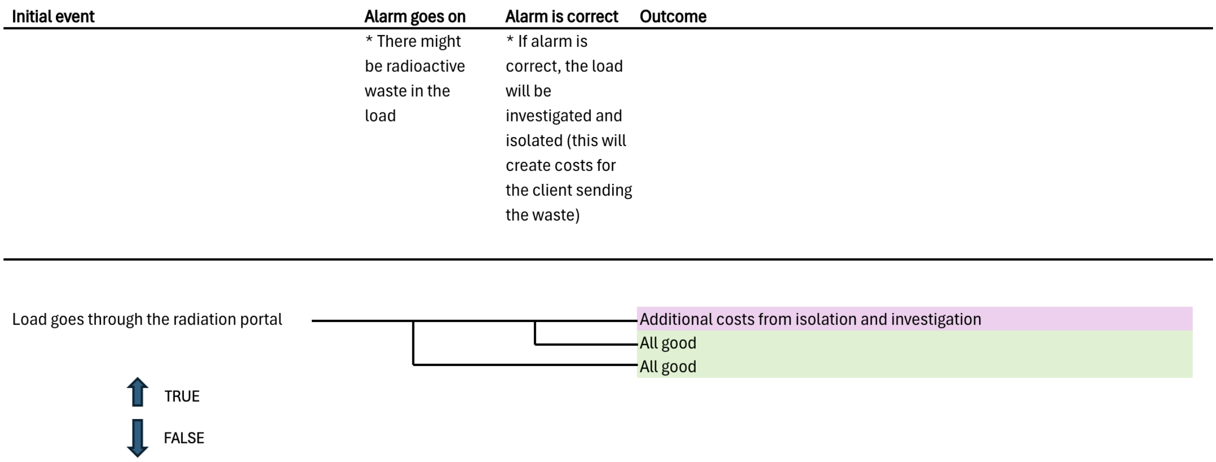

Figure 3: Event tree for waste management

4.3 Combining the trees

The above trees are next combined to obtain scenarios for all possible combinations of events. After each branch of the hospital events, branches of home events follow, and after them, the branches of events at the waste management. To each branch, we have attached the probability of the given event. At the end of the tree, on the right side, we have collected the probability of each combination of outcomes and their costs.

The branches following each hospital outcome are basically identical with each other, and similarly, the branches following each home outcome are identical. However, same outcomes at a certain stage might have different probabilities of happening, depending on the earlier events, as explained in Sections 3.2-3.3. Additionally, some events have a cost of 0 €, because the previous events actually prevent them from happening. Removing these branches would also take care of the same thing, and would be a more elegant option. However, as this is the first version of the model, such improvements can be made later.

5 Results

In this section, the results of the event tree are presented for different scenarios. The result of the model is the minimum value for one gained life-year (GLY) needed to justify the treatment. Further analysis of the results will be done in Section 6.1. Notice that we had to make some small adjustments to the Excel model after the results and analysis were written, and therefore the results differ slightly in the Excel model compared to the results presented in this report. The difference is very small, the adjustments only affect the expected costs coming from waste management, and thus the effect on the result is negligible. Therefore the analysis and the results presented in this report are valid.

5.1 Result with original values

The model is first constructed with values that are from expert interviews, literature review, and students' estimation. These values are called original values in this context. These values can be modified in Excel according to the instructions found in the first sheet of the Excel file. Furthermore, the Instructions sheet in the Excel file can be used to find where data sources, event trees, and other additional information used to construct the result can be found. The original values for the probabilities and costs used in the model are in Table 8.

Name	Value
P(Correct alarm | alarm)	0.044
P(False alarm | alarm)	0.956
P(No alarm)	0.998
P(Alarm goes on)	0.002
Costs of product used in treatment	4500
Costs of PET-scan	1250
One night in isolation	400
Costs from policlinical procedure	200
Share of patients with incontinence	13%
Share of PSMA treatments done with over night isolation (24 h)	60%
Share of PSMA treatments done as policlinical procedure (4-6 h)	40%
P(radioactive waste is not treated right at the hospital)	1%
Radioactive waste is not treated right at the hospital, cost	34.8
Costs from other people's contamination	
USD to € in 2021	1.18
Cumulative dose readings between hours 4-20	
Cumulative costs from other people's contamination between hours 4-20	34.8
Radioactive waste is not treated right at the hospital	1%
Share of treated people that are PET scanned before PSMA treatment	5%
Average costs from the PSMA treatment (one cycle)	4562.5
Costs from other people's contamination | 4-6 h isolation	10.18
Costs from other people's contamination | 24 h isolation	4.80
Additional investigation costs at waste management	2625
QALYs gained from the treatment	0.65
Assumed number of treatment cycles	3
P(radioactive waste is generated at home)	16.9%
P(Radioactive waste is not treated right at home)	20%
P(Other people are contaminated | radioactive waste is generated)	65%
P(Other people are contaminated | radioactive waste is not generated)	6.5%

Table 8: Original values used to construct the result. For the variables *Costs from other people contamination* and *Cumulative dose readings between hours 4-20* the original values are the estimates for minimum and maximum values. These are [38.0, 380.5] € / man-mSv and [0.03, 0.18] mSv, respectively.

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By using the values from Table 8 in the conjoined event tree, which is constructed by combining the individual event trees introduced in Section 4.2, we get the results illustrated in Table 9.

These results will be analyzed in Section 6.1.

Minimum value for one GLY needed to justify the treatment	22542 €/GLY
Costs from one cycle (€)	
Hospital	4883
Home	1.1
Waste management	0.008
Total	4884
Gained GLYs	
Gained GLYs	0.7
Needed cycles	3
Value of one GLY (€)	22542

Table 9: Result using the original values from Table 8

5.2 Results in different scenarios

In this part, we illustrate how the results change when we modify one of the variables to deviate from the original values. The results for different scenarios are in Table 10. In these scenarios always one variable is changed, while others remain as the original values illustrated in Table 8. This will allow us to analyze which events affect the result of the model significantly and which do not and why. This further analysis will be done in Section 6.1.

		Costs of product used in treatment = 15000	Additional investigation costs at waste management = 50000	Needed cycles = 6	P(Other people are contaminated | radioactive waste is not generated) = 0.4
Costs from one cycle (€)	Hospital	15383	4883	4883	4883
	Home	1.1	1.1	1.1	3.1
	Waste management	0.008	0.145	0.008	0.008
	Total	15384	4884	4884	4886
	Gained GLYs	0.7	0.7	0.7	0.7
	Needed cycles	3	3	6	3
	Value of one GLY (€)	**71003**	**22542**	**45083**	**22550**

Table 10: Results in different scenarios. The columns show which variable is changed and to which value, while other variables remain as the original values.

The scenarios illustrated in Table 10 are examples of the various scenarios and their corresponding results that can be generated using the Excel. The Excel allows for experimentation with different values to observe how the result changes. However, given the multitude of possible scenarios, only four additional scenarios, in addition to the original values, are included in this report as examples.

6 Discussion and future research

6.1 Discussion

6.1.1 Analysis of original result

In the original scenario, the minimum price for one gained life-year with the Lu-177 PSMA treatment is 22542 €, where the number of needed cycles is three and the GLYs from the treatment is 0.7 years. According to Engström et al. (2021), The National Board of Health and Welfare in Sweden has determined ranges for the costs for a QALY gained to be between 10 000 USD and 180 000 USD, where 10 000 USD is a low cost and 180 000 USD a very high cost for a QALY. The resulting minimum value for one GLY obtained from our model is within these ranges which supports that the result of the model is realistic. Still, when comparing the price of one GLY of the model to the range of price of a QALY, it should be noted that a QALY takes into consideration the quality of accumulated years. For this reason, the value of one QALY may be higher than the corresponding GLY value. This is one of the aspects that could be considered in the future development of the model.

The costs from one cycle in total are 4884 €, which mostly consists of the costs of the hospital treatment. It is reasonable that most costs of the treatment cycle come from the hospital costs: the costs include for instance the costs of Lu-177 product and costs related to the patient staying at the hospital. If the treatment is given, these costs are also certain, unlike the possible costs in later events.

Still, as a word of caution, it can be stated that many scenarios are left out of the range of the original model. We have excluded multiple scenarios from all three main localities both from the hospitals, patient's home, and waste management facilities which we have estimated to have relatively low probabilities of occurring. For instance, we estimated that the probability of hazards appearing in the waste management facility and waste collection system being interrupted due to radioactive waste from the hospital is extremely low, as the experts stated that they are highly familiar with their radioactive waste management procedures and the waste management institutes found the probability of this happening very low. In the interviews, we discussed the impact of sudden illnesses such as norovirus on the patient's ability to follow the patient guidelines at home. We estimated the likelihood of this happening to be so low that this scenario could be omitted. These kind of scenarios could have an impact on the results of the model but their probability of them taking place is extremely low. For this reason, they were left out of the model.

Similarly, we have left out of the current model themes and locations that most certainly have an impact on the outcome of the model. For instance, treatment itself and the need for isolation have an impact on the mental health of the patient. Also, when the patient transports from the hospital to home after the treatment, the driver's exposure to radiation increases, but this has not been included to the model. In the interviews, we have also discussed multiple possible upcoming events that might have effects on the model. For instance, the need for so-called delay tanks in the future might affect the hospital's and waste management institute's practices in dealing with radioactive waste. The new European regulation for waste incineration will affect the events in the future as well.

In the model, some monetary values and probabilities are our estimates. For instance, the likelihood of radioactive waste not being treated right at home is based on our estimation. We have sought to estimate these values to the best of our ability based on the literature review and discussions with the experts but since we are not healthcare professionals, these values may be inaccurate. For this reason, modifying the model and changing probabilities and the ranges of the monetary values is made effortless in the model.

In conclusion, the model seems reasonable and provides ranges similar to those for the models covered in the literature review. Still, when using and further developing the model, it is essential to note that the model is a simplified representation assessing the impacts on the post-treatment scenarios in nuclear medicine therapy and is still a work in progress that requires further development. Refining the ranges of monetary values and the likelihoods, and adding relevant scenarios is something that can be done in future research if more data becomes available.

6.1.2 Analysis of result in different scenarios

In this section, we consider the different scenarios in Table 10 in more detail. These scenarios are constructed by changing one variable at a time while keeping the other variables as the original values. We start by analyzing the scenario where the cost of the product used in a treatment changes from 4500 € to 15000 €. The 15000 € is used to construct a scenario where the commercial product used in the treatment is bought outside the hospital, rather than using a product that is done by the hospital themselves. In this case, the price of one GLY is 71003 €, which means that compared to the original result the value of one GLY triples. Thus if the patient goes to a hospital where the product is bought from outside, the value of one GLY needs to be significantly higher in order to justify the treatment. There is a clear link between the result and changing the price of the treatment, as roughly tripling the price of the treatment triples the result. Changing the price of the treatment impacts the costs in the hospital only, and does not affect costs in the patient's home or waste management. Therefore to conclude, the value of one GLY can change significantly in different hospitals depending on whether they use their own product in the treatment or have to buy it from a third party.

To establish a more accurate result for the value of one GLY, we would need more data from hospitals in Finland giving the isotope treatment, to evaluate what is the probability that a patient goes to a hospital using their own product, as this significantly affects the justification of the treatment. Unfortunately, due to the time limit in this project and lack of data received this is not included in our model, but this could be one of the aspects in future development of the model. In addition, while gathering the data we noticed that different hospitals give quite different probabilities for the hospital events, and have different practices with handling radioactive material. Therefore the result is dependent on which hospital the patient goes to, and in future development, the model could be modified to take this into account, instead of focusing on data from only one hospital.

We next analyze how the results change as a result of changing the cost in the waste management event tree. From Table 10 we can see that increasing the additional investigation costs at waste management from 2625 € to 50000 € keeps the value of one GLY at 22542 €. Therefore increasing the cost by 47375 € increases the result so insignificantly that it is not shown when rounded to the closest euro. Increasing the investigation cost drastically changes the expected costs coming from the waste management from 0.008 € to 0.145 €. This is due to the fact that the probability of additional investigation is very low in our model, and thus it affects the result very little. Due to the lack of data, the original value of 2625 € is an estimation made by the students, but as changing this value drastically does not affect the result significantly, the precise cost for this event is not required. To conclude changing the costs coming from the waste management tree, does not affect the result significantly.

Next, considering the impact of increasing the number of needed treatment cycles, Table 10 shows that by increasing the needed treatment cycles from 3 to 6, the value of one GLY changes to 45083 €. The costs for one cycle do not change in this case, but as the number of needed cycles doubles, also the value of one GLY doubles. Therefore the justification of the treatment is very dependent on the number of treatment cycles the patient goes through. Thus, to get more accurate results one would need more data about how many cycles there have been needed by the patients that have gone through the treatment in Finland. This way it would be possible to construct probabilities for different numbers of cycles that a future patient will have to go through, which would then give a more accurate value for one GLY for a patient that is needed to justify the treatment.

Finally, we analyze what happens to the result when the values in the patient's home event tree are changed. From Table 10 it can be seen that when the probability of the event that other people are contaminated at home given that radioactive waste is not generated is changed from 6.5% to 40%, the value of one GLY changes to 22550 €. This means that changing the probability of contamination quite drastically changes the result only by 8 €. The change in the probability concerning the patient's activity at home does not affect the expected costs for hospital or the waste management, but it increases the expected costs from the patient's home by 2 €. Therefore it seems that increasing the probability of unwanted events in the patient's home does not have a significant effect on the value of one GLY. This is because the model assumes that the consequences of contaminating a person with close contact with the patient, do not result in significant hazards for the contaminated person, due to the low radiation of the patient after the isolation. In other words, the amount of radiation coming from the patient is quite low after the isolation, and therefore the amount of radiation that persons near the patient are exposed to does not cause significant risks for them when there is no radioactive waste generated according to our model.

To conclude, the model is most sensitive to changing values regarding the events in the hospital compared to the events in the patient's home and waste management. This is because the events in the hospital in our model have larger probabilities and corresponding costs compared to the events at the patient's home and in waste management and thus changing their values impacts the result. On the contrary at the patient's home, the consequences of undesired events are small compared to the costs in the hospital, and thus changing the probabilities of the events does not affect the result significantly. In waste management, the probabilities for the events are very low, and thus changing the corresponding costs, does not affect the result significantly. It is possible that in the future the probability of hazards in waste management increases as the amount of treatments given in Finland increases, which would then make these events more significant factors when it comes to the result. This is something that can be tested in future research if more data becomes available.

6.2 Future research

6.2.1 New European regulation for waste incineration

From the discussions with our client, STUK, we learned that there has been a new European regulation for waste incineration. At the end of 2019, the European Commission reached the Best Available Techniques conclusions, under Directive 2010/75/EU of the European Parliament and of the Council, for waste incineration (Bertin, 2020). The main objective of the regulation is to improve the overall environmental performance of waste incineration, by planning and implementing necessary procedures as well as preventing and taking corrective actions to avoid environmental risks that can occur in waste incineration. The news article written by Bertin (2020) highlighted that one of the conclusions of this directive was the control of waste deliveries as part of waste acceptance procedures, which depends on the risk posed by the accidental presence of contaminated materials and orphan radioactive sources. The news article states that European incineration plants have to be equipped with a radiation monitoring system for the detection of very low radioactive contamination and orphan sources for example in municipal solid and other non-hazardous waste and clinical waste.

Most of the data used in the event tree for waste management was gathered from a waste incineration plant that has a radiation portal system, through which all the waste loads drive by. This data might not be the best estimate for justifying the treatment in Finland, due to the location of the plant being in Riihimäki rather than in the Helsinki Metropolitan area (or in some other area near hospitals where radiopharmaceutical treatments are used). Interestingly, the discussions with STUK revealed that in Finland these radiation portals are not yet used by all waste incineration plants. One future research topic could be why this is the case, and when the waste incineration plants are expected to comply with the directive. If the waste incineration plants in Finland start to comply with the directive in the future, it would be interesting to gather more data from waste incineration plants as they start to use different radiation measurement systems due to the directive. This will most likely affect the probability of alarms alerting about radioactive substances, as the waste incineration plants are legislated to measure the radioactivity of waste loads more carefully. Using estimates from multiple different plants with similar systems would give more reliable estimates for the waste management event tree, compared to the current implementation. Especially gathering data from waste incineration plants near hospitals would give more realistic results, as the current implementation most likely underestimates the probabilities related to the alarms in the waste management event tree. The probability of an alarm would most likely be larger in waste incineration plants that are located near hospitals that use radiopharmaceutical treatments or in the Helsinki Metropolitan area where the volume of waste is larger.

6.2.2 Effect of delay tanks on the justification of treatments

In our model, we decided to neglect how the sewage system affects the justification of the treatment. We came to this decision, as STUK stated that there was no need to focus on it, as the sewage system in Finland is very efficient, and therefore when the radioactive excreta of patients end up in the sewage water it does not result in hazards for the society. This was also confirmed in the literature review, as the report written by (Lassen et al., 2023) stated that more often the patient's excreta ends up in the sewage system as the excreta is disposed of through the toilet, but radionuclides discharged from radionuclide therapy into modern sewage systems result in doses that are well below the limits for the sewer workers and the public. This is the case now, but it is uncertain what will happen if the number of treatments increases. This is a perspective that was highlighted by one of the experts we interviewed during the project. During this specific interview, we learned that as the number of radiopharmaceutical treatments rises there might be a possibility that the sewage system in Finland will not be able to remain safe, meaning that the doses might increase over the allowed limits, and thus it would have to be added to the model.

In order to keep within the schedule, we decided not to incorporate this idea into our model. In addition, this is more of a question for future research, as currently there is not much data available, and it would be hard to estimate how the sewage system will be affected if the number of treatments rises. Our model is developed to estimate the current justification of the treatment, but if the sewage system becomes a hazard in the future, it should be added to the model to ensure that the model is accurate. During our interview with the expert, we learned that some other countries have started to use so-called delay tanks, to keep the sewage system safe from different radiopharmaceutical treatments. A delay tank is an underground system to reduce the radioactivity of contaminated I-131 clinical wastewater before it is discharged into an ordinary sewage system (Razab et al., 2020). Also, above-ground delay tanks are used. The report by Ravichandran et al. (2011) explains that liquid wastes (coming from outlets from isolation room toilets) generated from I-131 administrations are collected in the delay tank, and the isolation rooms have sewage connections to twin concrete tanks located in the garden area below ground level. The use of delay tanks seems to have improved hygiene and lowered radiation exposure to hospital and auxiliary staff, especially in hospitals where cancer patients used to be required to collect their urine (Goddard, 1999). The report written by Goddard (1999) states that when underground delay tanks were installed to delay the discharge of I-131 waste from the thyroid therapy unit to the on-site sewage treatment plant, the level of radioactivity discharged to sewage fell significantly.

The use of delay tanks will result in multiple new costs and risks which might affect the justification of the treatment in the future. Finnish hospitals do not yet use these delay tanks since the sewage system has remained safe enough with the current number of treatments, meaning that there is no data available for the use of delay tanks in Finland. In future research, it would be interesting to gather more information and data about the delay tanks and how they would affect the justification of the treatment. In addition, it would be interesting to evaluate whether an unsafe sewage system is actually a hazard in Finland, and should hospitals start to investigate the use of delay tanks or can the sewage system handle the possibly increased number of treatments in the future.

6.2.3 Mental health issues during treatment

We decided to neglect the possible mental health issues patients can have during the treatment. Realistically patients can have different mental issues due to cancer diagnosis and/or its treatment, which could be evaluated as a detriment in the model, and thus they would affect the justification of the treatment. Cancer is often a life-threatening disease, and thus it is understandable that many patients are anxious in response to the threat of cancer (Stark and House, 2000). According to Stark and House (2000), patients undergoing serial radiotherapy treatments experience high levels of anxiety, and these levels do not decrease for later treatments, as the threatening element is persistent, possibly because of the serial element of the therapy. In addition, the report states that patients ending radiotherapy experience a rise in anxiety, which may be due to the fact that they interpret it as a loss of a perceived protective effect. Therefore, in multiple different stages of the treatment, the patient can experience anxiety or other mental health issues, which could be seen as a detriment that should be taken into account in the justification of the treatment.

It is hard to estimate the monetary value of the possible mental health issues patients can have during the treatment, as it is a subjective issue with multiple, and often incomplete, perspectives. For example, Stark and House (2000) state that “It can be difficult to use all the current research criteria to define when anxiety is pathological, because they depend upon a subjective judgment as to the extent of actual threat, and rigorous studies defining the natural history of normal or adaptive anxiety are incomplete”. Since our model is aimed to evaluate the justification of the treatment in the most standard case, we assumed that due to the short isolation times, most people will not experience significant mental issues due to the treatment. This was also confirmed in an interview with a medical expert. During this interview, the expert stated that they doubt that a relatively short time in an isolation room, which usually has a television and other amenities, would result in significant mental health issues, that could be connected to the actual isolation. In addition, they stated that researching this problem would require a lot more time and resources than are available in this course. Nonetheless in the future, to make the model more accurate, it would be interesting to do research on how people evaluate their mental health issues during the treatment. To get as generic monetary values as possible for the possible mental health hazards during the treatment, it would be necessary to interview multiple patients and gather data on patient perspectives and preferences. This is most likely a very time-consuming project and requires access to patient information, and thus we decided not to incorporate this into our scope.

7 Conclusions

The aim of this project was to create a model that assesses the impacts of post-treatment options in nuclear medicine therapy by focusing on the justification of the Lu-177 therapy provided by public healthcare. We focused on the usage of the Lu-177 for treating prostate cancer, which is the most common cancer type among men. The model focuses on evaluating the overall benefits and detriments of the treatment because the benefits should exceed the detriments to justify the treatment. The risks of the treatment were not included in the model.

Section 3 presents the main findings from the literature research. The literature research allowed us to get familiar with the topic and made it possible for us to determine the post-treatment options for the model. Based on the literature research, Lu-177 can be used to treat prostate cancer and neuroendocrine tumours, and we chose to focus on the treatment of prostate cancer. Understanding the patient guidelines in Lu-177 treatment is necessary to determine the post-treatment options because neglecting the guidelines can cause unnecessary exposure to radioactivity. The justification of the treatment should be carefully considered for all patients because it is vital that the overall benefits of the treatment exceed the detriments. Based on the literature review of previously used model, event tree was chosen for this project. For the event tree, probabilities and monetary values for the detriments and benefits were estimated. We also focused on the post-treatment impacts of radiopharmaceutical therapy both on the patient and the society. For the patient, the effects can be physical and psychological meaning that the patient can suffer from e.g. fatigue, exhaustion, and anxiety. In the case of society, discussion focused on for example: the exposure of other people that are in close contact with the patient, and risks in terms of the waste management companies. Finally, the use of QALYs and the anxiety caused by isolation were briefly reflected.

Through scientific literature, a better understanding about the Lu-177 treatment and its post-treatment impact on individuals and society is gained. This way we were able to formulate appropriate questions for various parties related to health and waste management problems. Separate questions were created in Finnish for the hospitals and waste management institutes. In addition to STUK, the project team contacted HUS, Kuopio University Hospital, Docrates Oy, Fortum Waste Solutions Oy, Suomen kiertovoima Oy, Jätekukko Oy, Finnish Environment Institute and Ministry of Social Affairs and Health. We received answers from HUS, Kuopio University Hospital, Fortum Waste Solutions Oy, Suomen kiertovoima Oy, Finnish Environment Institute, Ministry of Social Affairs and Health and STUK.

We calculated the probabilities and monetary values for the benefits and detriments by using the received data. These values are presented in section 3. For some parameters, the team had to choose subjective values because the experts were not able to give us numerical data for all parameters. These values are clearly stated in the model and report so that they are not mixed with the answers of the experts.

We chose to focus on events at the hospital, the patient's home, and the waste management facilities. Section 4 shows the constructed event tree. The event tree includes all relevant events that were identified through the literature review and answers from experts. The event tree includes whether the treatment is given, the length of an isolation (6 h/24 h), waste is treated right, radioactive waste is generated, radioactive waste is not treated right, other people are contaminated, alarm in waste management facility goes on and the alarm is correct. Some events were excluded from the model due to low probability of occuring. For example, the model does not include the possibility that radioactive waste has not been properly treated in the hospital and therefore ends up in normal waste. We also excluded the event in which radioactive waste is spread in the fly ash or ends up in the slag from the model. In addition, disturbance in waste incineration due to radioactive waste is not included in the model. The negative impacts on mental health caused by the isolation and the risk of contamination due to the transportation to home from hospital are also excluded.

The result of the model is the minimum value for one gained life-year needed to justify the treatment. The results were shown in section 5. The minimum price for one gained life year by the Lu-177-PSMA is 22542 € where the number of needed cycles is three and the gained life year is 0.7 years. The total costs from one cycle were 4884 €. The smaller the price of one GLY is, the more easily justified the treatment is. The obtained result seems to be a reasonable value.

Since some of the values in the event tree were subjective opinions of the project team, we conducted sensitivity analysis by changing some of the values while keeping the other variables as the original values. Changing the additional costs at waste management significantly, the value of one GLY remains the same meaning that a change in additional cost does not have a meaningful affect on the results. Therefore, it does not matter that the project team assumed the value. The values of cost of product used in treatment, needed cycles and $\mathbb{P}$(Other people are contaminated | radioactive waste is not generated) were also changed to see how the result change. Based on the results, the model is the most sensitive to changing values of events in hospital compared to events in patient's home and waste management. This can be explained by the fact that the events in hospital have larger probabilities and costs meaning that the changes in those values affect the results more.

Further research could be conducted so that fewer assumptions are made. In addition, some events, that we have not included to our model due to lack of data and resources, could be added to obtain more realistic results. If the model is improved in the future, new European regulation mentioned in Section 6.2.1 could be considered in the model. If the number of Lu-177 treatments increase significantly in the future, there is a possibility that radioactive doses in the sewage system in Finland does not stay below the safety limits. Therefore, the use of delay tanks could be justified and included in the model. If data related to patients' mental health is gathered in the future, the negative impacts for mental health caused by the isolation could be added to the model .

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8 Self Assessment

How closely did the actual implementation of the project follow the initial project plan? Were there any major departures and, if so, what?

The implementation of the project followed relatively closely our original project plan and there were no major changes. In the interim report, we decided to extend the time needed for data collection because it turned out that it took more time to receive answers from the appropriate parties. We also started to implement the model even though we had not received all the data. We were able to stay on schedule because collecting the data and the implementation of the model overlapped slightly. We started to write the final report already while we were conducting the literature research, and we also wrote it while implementing the model. Therefore, we were not in a hurry at the last weeks of the project.

The scope changed slightly during the project because we had to narrow down the scope to finish the project on time. Initially, the scope was to focus on the Lu-177 treatments done in Finland in public healthcare. Due to the time limit, we had to prioritize some scenarios and neglect others, to be able to gather the data for the model and construct it in time. As already mentioned in the interim report, the risks changed slightly during the project. Our biggest risk in the project was identified after starting the data collection process and it was related to the fact that we had problems receiving help for narrowing down the scope because we had mainly obtained more topics to add to the model from the discussions with the experts. Therefore identifying a scope that was realistic enough to model the justification of the Lu-177 treatments, but at the same time be feasible in the given time frame, was identified as the main risk before the interim report submission. However, we were able to narrow down the scope such that the completion of the project on time was possible. Other risks stayed the same throughout the whole project, but the likelihoods changed slightly.

We managed to do most of the tasks we had planned to do. As the data collection process took a lot more time than anticipated, validating the data with the client was removed from the schedule, and more focus was put on constructing the Excel model. In hindsight, the validation of the data with our client could have been left entirely out of the schedule at the beginning of the project since the data was gathered from experts, and thus validating it with the client seems unnecessary. In our interim report we stated that if we would have spare time at the end of the project, we would try to extend our scope to include scenarios that were not seen as relevant to be included in the initial model. In the end, we did not have time to extend the scope and add any other scenarios to the model, but we included possible aspects for future research in the report.

In what regard was the project successful?

The primary objective for the project was successfully achieved meaning that we were able to conduct an impact assessment of post-treatment options in nuclear medicine therapy. However, the final product contains some parameter values that are chosen by the project team instead of experts. This means that the results are not necessarily that reliable. Fortunately, the Excel model was built to be dynamic and easy to use, and thus the model can be modified also by other people than the project team members which means that STUK can easily make alterations if needed. To improve the model, STUK can change the parameters and potentially add more scenarios.

The communication between the project team was successful. We had one meeting every week throughout the whole course. This way we were able to divide the workload equally between the team members. In these meetings, we often discussed the progress of our individual tasks, as well as decided on future responsibilities. In addition, these meetings were used to discuss our opinions and concerns about the project and the next steps, which resulted in the team having an open environment where everyone could voice their concerns, which helped us to identify potential pitfalls and problems before they happened (as someone might have noticed something that others did not). Having weekly meetings helped the team members to feel confident that the project was moving forward within the schedule, and everyone knew what they had to do for the team to reach the objective. In addition, we actively communicated via Telegram to get comments and clarifications from other team members as we worked on our individual tasks.

The communication with our client, STUK, was also successful. Sometimes it was slightly difficult to find a good timeslot for a Zoom meeting, but this did not create any bigger problems. There was a time when our main contact person was on holiday, and this delayed the validation of our model a bit, but no significant problems came from it. Our project manager communicated with STUK to find suitable times for the meetings, and most of the time we received answers relatively quickly. During our meetings, we were able to inform our progress and receive help for potential issues. The client showed interest in our project which made the communication with the client pleasant.

In addition, we spent quite a lot of time perfecting our project plan at the beginning of the project. This meant that throughout the project we had a clear vision of what tasks needed to be done at which time and which aspects were important to prioritize. This helped us to stay on schedule.

In what regard was it less so?

The results are not as reliable as they could have been if all the parameter values had been given by experts instead of creating our own subjective values. However, we were not able to receive more data from the hospitals and waste management institutions. We have mentioned in the report clearly which values are created by the team instead of experts. This way STUK can improve the model if in the future more data is available to make the model more reliable.

We could have received more help with narrowing down the scope or we could have tried to emphasize the challenge we had with it more in our discussion with the client and the experts. This was not easy to do as we sometimes obtained more topics to add to the model in some of the discussions with the experts even though we tried to emphasize ahead of the discussion and during it that we could not add every possible scenario to the model within the given time. It seemed that many of the experts were very keen on the project topic, and therefore they often had a lot of ideas to add to the model, which meant that they did not help us understand what could be left out of the model, which was our main concern during most of the discussions. However, despite the challenges, the team was able to narrow down the scope.

Another thing that was more challenging than expected was getting answers to our interview questions from the experts. Even though the team started to send the interview question very early on in the project, in some cases it took almost two months to receive the data which made it hard to follow the initial schedule of our project. The team could have reached out to the experts at the beginning of the project, to ask whether they had time to answer our interview questions that would be then sent to them in a couple of weeks. This way we would have known better when we would get the answers, and from whom, which might have worked better than just sending the interview questions straight to the experts without prior warning.

In addition, we noticed a small mistake in the Excel model just before the submission of the report, which was quite stressful. Fortunately, the mistake did not affect the value of the results significantly, and thus fixing the mistake did not affect the analysis, which meant that we did not have to rewrite the analysis. We fixed the Excel and added a few comments on it to the report. To avoid this kind of situation, it would have been better to investigate the Excel model more carefully, but as the model is very large, making these kinds of mistakes is almost inevitable.

What could have been done better, in hindsight?

As was already mentioned, the team could have sent the questions to hospitals and waste management institutions slightly sooner so that the data would have been received earlier. This way we could have potentially had time to add other scenarios to the model and to improve the model further. In addition, the team could have sent the questions to other institutions so that there would have been a higher chance of getting all the data that was needed instead of creating their own subjective parameter values, which would have made the model more reliable.

The deadlines for the reports could have been on Monday instead of Wednesday. This way there would have been more time to read the report of the opponent team and write the feedback. This would have helped a lot, especially with the final report because reading the report is time-consuming and there was only one day to read it and write the feedback. In addition, the presentation of the project plan could have been in February because this way the workload would have been divided more equally between the excursions/reports. The workload for the project plan was not as heavy and thus it could have been a couple of weeks earlier, to then ease the tight schedule later on in the spring. The workload for the final report was much more significant compared to the other two reports, and thus it could have worked out better if there had been more time between the excursions of the interim report and the final report.