STUDY OF PLAN OF THE DAY ADAPTIVE RADIATION THERAPY VALIDITY

By

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Abstract

Radiation therapy is the use of radiation sources or generators to treat patients. The most common usage is in the treatment of cancers. Adaptive radiation therapy (ART) is the use of either multiple radiation therapy plans or adjusting a radiation therapy plan for daily anatomical changes. Soft tissue in the lower abdomen and pelvis can be greatly displaced depending on a variety of factors, especially bladder and rectum fill. This paper focuses on the creation of multiple plans prior to treatment to have options each day. Depending on the alignment and anatomical changes, clinicians can choose which one is most appropriate to maximize target coverage while minimizing organ at risk (OAR) toxicity. This type of ART technique is referred to as plan-of-the-day (POTD). A total of 12 bladder, prostate and gynecologic cases were retrospectively considered for viability in this study. For most patients, the POTD approach did not prove beneficial due to unpredictable and non-reproducible anatomical changes that could not be accounted for with 2-3 plans. In 1 patient, the anatomical changes were predictable enough to be modeled with 2 POTD plans, represented by (1) an empty and (2) a full bladder. This patient was selected for a full dosimetric analysis. Contours were made for empty bladder plans on past patient computed tomography (CT) images and evaluated against daily cone beam CT (CBCT) for viability. Radiation dose was calculated on every CBCT to determine the delivered dose to target and OARs. The delivered dose, POTD possible dose, and the original planned dose were all compared. Planning target volume (PTV) coverage was comparable for both the ART and original plans with the possibility of reduced bowel dose when using the POTD style treatment, especially at higher dose levels. There was also a trend showing that dose metrics were almost identical if bladder volume was above 250cc. This proves viability of traditional non-ART treatment style with appropriate patient coaching. If ART-style treatments are desired, online adaptive platforms, which have more

flexibility in accounting for daily anatomical changes, should be explored further for their viability and clinical benefits.

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List of Abbreviations

Boron Neutron Capture Therapy (BNCT)

Low Dose Rate (LDR)

High Dose Rate (HDR)

Organ at Risk (OAR)

Computed Tomography (CT)

Conebeam CT (CBCT)

Magnetic Resonance Imaging (MRI)

Planning Target Volume (PTV)

Plan of the Day (POTD)

Adaptive Radiation Therapy (ART)

Minimum Dose that 95% of the Structure Volume Received (D95%)

Volume of the Structure that received over 4000 cGy (V4000 cGy)

Volume of the Structure that received over 4000 cGy (V4500 cGy)

Cubic Centimeters (cc)

centiGray (cGy)

Fractions (fx)

Introduction

Small regional hospitals often must work with limited resources rather than having access to state-of-the-art technology. In the context of adaptive radiation therapy, there exists multi-million-dollar machines requiring specific staffing and significant resources. These machines enable daily adjustments to radiation plans to accommodate anatomical changes like bladder or stomach filling. Typically, these machines are acquired and utilized by large medical centers or research hospitals. However, for community hospitals, where the majority of treatments occur for the general population, acquiring such machines may be unfeasible. Assessing the value of these machines in terms of patient treatments and outcomes remains a relatively nascent and inconclusive field.

This project aimed to evaluate the feasibility of implementing a daily adaptive therapy program in the clinic using existing hardware and modifying clinical workflow, rather than relying on specialized machines or software. This approach would utilize existing standard hardware with modifications to clinical workflow, rather than introducing entirely novel methods. Theoretically, this approach could facilitate more precise treatments, particularly in cervix and endometrial cases where the uterus remains intact and is significantly influenced by adjacent soft tissue changes on a daily basis. The availability of multiple plans each day could potentially achieve comparable or improved target dosing while minimizing radiation exposure to adjacent healthy organs. Additionally, these treatments might obviate the necessity for patients to reposition or address alignment issues in soft tissue, thereby potentially reducing treatment duration and imaging exposure.

Background

History

Radiation therapy has a significant history dating back to the late 1800s when radioactivity and x-rays were discovered. Initially, radioactive materials were applied directly to skin lesions and skin cancers on the tip of the nose[1]. It was soon realized that generated x-rays could also treat cancers. This development led to the treatment of breast and stomach cancers, resulting in reduced pain and disease in patients[2]. Extensive research was conducted in the field until the 1950s and 1960s, during which Cobalt 60 teletherapy units emerged as the primary source of radiation treatment. These machines accurately aimed gamma rays, sparing healthy tissues that did not require treatment[3]. Continued research in the field led to advancements in science and technology, eventually resulting in the development of linear accelerators. Linear accelerators enabled the generation of radiation without the requirement of a high activity radioactive source. This eliminated the need to transport hazardous sources and allowed radiation to be turned off instead of simply being shielded.

The next step in modernization involved advancements in treatment planning for radiation machines. While machines could now output radiation very accurately, it remained challenging to determine how the dose was deposited. This paved the way for the modern treatment planning systems in use today. These treatment planning systems enabled the precise mapping of radiation dosage from the linear accelerator onto a patient's computed tomography (CT) scan. Technological advancements led to the development of improved aiming devices and dynamic treatment styles over time. Technological advancements led to the development of improved aiming devices and dynamic treatment styles over time. These advancements enabled increasingly complex and conformal treatments, allowing for the treatment of even the smallest visible targets with minimal side effects. This marks the modern age, characterized by excellent treatment conformity and the ability to focus on other factors[3]. Internal soft tissue can undergo significant daily changes within the same patient. Factors such as eating and drinking schedules, as well as daily activities like exercise, can affect internal soft tissue. Enter adaptive radiation therapy. Adaptive radiation therapy addresses the day-to-day differences in patient anatomy. It represents the next logical step in patient-specific conformal treatment planning. It involves not only patient-specific plans but also daily-specific plans, accounting for the imperfections of human anatomy.

Radiation Therapy Basics

Understanding the basics of radiation therapy is essential for comprehending modern treatment planning styles and future innovations. Radiation therapy is a medical discipline that employs radiation to destroy cancer cells while minimizing damage to healthy cells in the body. Initially, it is important to distinguish between two main types of radiation: ionizing and non-ionizing radiation. Ionizing radiation is considered potentially dangerous, while non-ionizing radiation is generally harmless. Non-ionizing radiation includes light, radio waves, and cellphone signals, which are present but lack sufficient energy to harm the body's cells. In contrast, ionizing radiation possesses sufficient energy to induce cellular damage. Examples of ionizing radiation include cosmic radiation from the sun and hazardous substances like Uranium. Additionally, there are various subtypes of ionizing radiation, X-rays/gamma rays, electrons (beta particles), alpha particles, neutrons, protons, and heavy charged particles.

The primary types of ionizing radiation used in radiation therapy are X-rays/gamma rays. X-rays/gamma rays are the most commonly used radiation in radiation therapy.

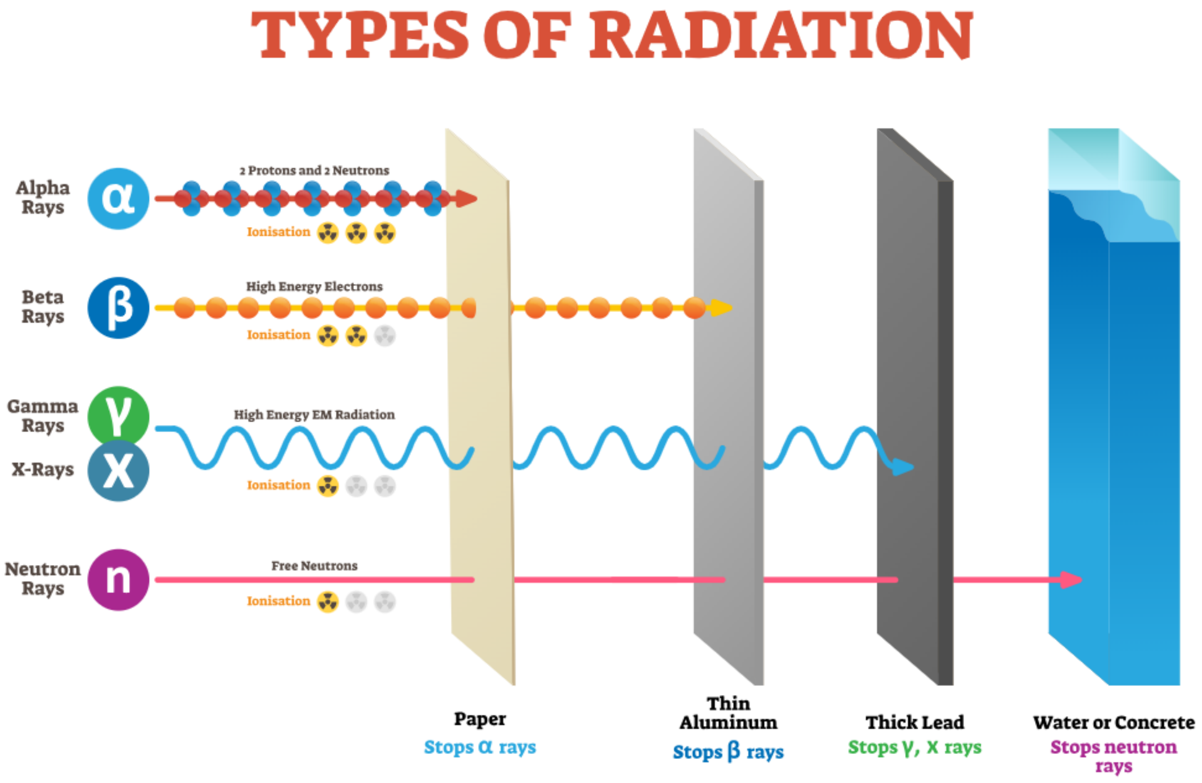


Figure 1. Different types of radiation and their shielding requirements [4].

X-rays/gamma rays have deep penetration capabilities and are cost-effective and easy to produce. There are two primary methods of production, highlighting the significance of naming conventions. X-rays are generated within a linear accelerator or an X-ray tube. The energy of X-rays can be altered and controlled through machine design. This capability facilitates the production of low-energy X-rays for applications such as dental X-rays and mammography, resulting in high-resolution images. Additionally, this enables the development of high-energy linear accelerators used in radiation therapy for cancer treatment. Gamma radiation shares the same properties as photons, but with a different source. Gamma radiation is emitted from radioactive isotopes like Cobalt-60. While gamma radiation has been utilized in radiation therapy, it is now more commonly associated with byproducts or hazardous waste. This radiation results from the decay of isotopes transitioning from a higher to a lower energy state.

Another primary type of radiation is electrons. Electrons are frequently employed for shallow dose distributions, such as in treating skin lesions or in brachytherapy, where precise shallow dose distributions are essential. Electrons can be produced either by a machine for external beam radiation therapy or, like gamma rays, can originate from radioactive materials such as strontium-90. Electrons emitted from radioactive materials are referred to as beta particles. Due to their specialized applications, electrons are not as commonly utilized as photons in radiation therapy. However, they are virtually indispensable for these specific applications.

Neutrons are neutral particles found in atoms, primarily produced in nature through large fission reactions such as those occurring in nuclear reactor rods. Neutrons have been utilized in radiation therapy either as a direct treatment, or through a technique called boron neutron capture therapy (BNCT). BNCT involves injecting a substance directly attracted to the tumor into the patient. This substance, primarily boron, reacts with neutrons to emit alpha particles (discussed later). The emitted alpha particles cause significant damage to a localized area less than a millimeter from the boron-enriched drug. This targeted approach ensures that the tumor receives the desired dose while neighboring tissues receives minimal to no dose. However, this technique has been shown to have significant limitations and, as such, it is only used in a few clinics worldwide.

Protons are the third most commonly used type of radiation in radiation therapy. Protons possess properties that are highly advantageous for tumor treatment. Unlike X-rays and gamma rays, protons have both mass and charge which results in a Bragg peak in materials, including tissues. The Bragg peak occurs when a proton enters a material and is minimally slowed down by surrounding particles, resulting in limited damage until it reaches deeper into the material and begins to decelerate. Subsequently, as the proton interacts more with nearby materials, it begins to decelerate more rapidly. This process continues until the proton rapidly releases all its energy over a short distance, resembling a depth charge effect. Consequently, tissue experiences minimal damage until the significant energy release occurs. The Bragg peak can be strategically positioned so that the significant energy release targets the tumor, with minimal damage to healthy tissue it passes through beforehand.

Alpha particles are another type of radiation utilized in radiation therapy. These particles are helium nuclei consisting of two neutrons and two protons. Due to their large size and charge, alpha particles typically have limited penetration in materials such as biological tissues. Consequently, they are frequently employed in treatments requiring short-range, high-damage effects, e.g., radiopharmaceutical treatments where alpha particles are injected directly into tumors. Another example is in treatments employing BNCT as discussed previously.

In the context of radiation therapy, heavy charged particles refer to particles with an electric charge that have significant mass compared to other types of radiation including X-rays/gamma rays and electrons. In addition to alpha particles and protons, the only other heavy charged particle that has found clinical use in the treatment of cancer is Carbon-13. These particles interact with tissues in a similar manner as protons, but are potentially more effective in localizing damage to tumors due to their larger mass. Due to their high cost, there are only about a dozen Carbon-13 treatment facilities in the world.

Types of Treatments

Radiation therapy can be divided into two types: brachytherapy and external beam therapy. "Brachy" is Greek for "short," which translates to "close" treatment. Brachytherapy involves treating with a source placed in close proximity to the treatment site. Common forms of brachytherapy include low dose rate (LDR) prostate seed implants, dating back to the late 1910s. In this procedure, typically iodine or palladium seeds are permanently implanted in the prostate, delivering the desired dose while decaying in place. Although this approach has been relatively successful, it has been replaced in most clinics with high dose rate (HDR) brachytherapy. In HDR brachytherapy, hollow needles are inserted into the prostate in a relatively evenly spaced pattern. These needles are connected to a machine called an afterloader via transfer tubes. The afterloader contains a single high-activity radiation source welded to a steel cable. The afterloader can extend the cable and position the radioactive source along the inside of the channel in small increments. The source remains at specific positions within the channel (which is placed inside the tumor) for a predetermined duration which determines the tumor dose. This enables a highly conformal dose distribution, with the tumor or target receiving a high radiation dose while nearby tissues receive minimal doses [5]. Additionally, this treatment approach avoids the need for radiation beams to penetrate thick layers of tissue to reach the tumor, thereby reducing the overall body dose. However, this treatment approach comes with the cost of an invasive procedure requiring pain management, anesthesia, and actual operating room time and preparation of the patient.

Compared to brachytherapy, external beam radiation therapy is a more commonly used treatment approach in the vast majority of clinics. In this method, the target is typically treated with a radiation beam generated by a high energy (MeV) linear accelerator. One advantage of this treatment is its non-invasiveness, and with modern techniques like modulated arcs, it can achieve a high level of conformity.

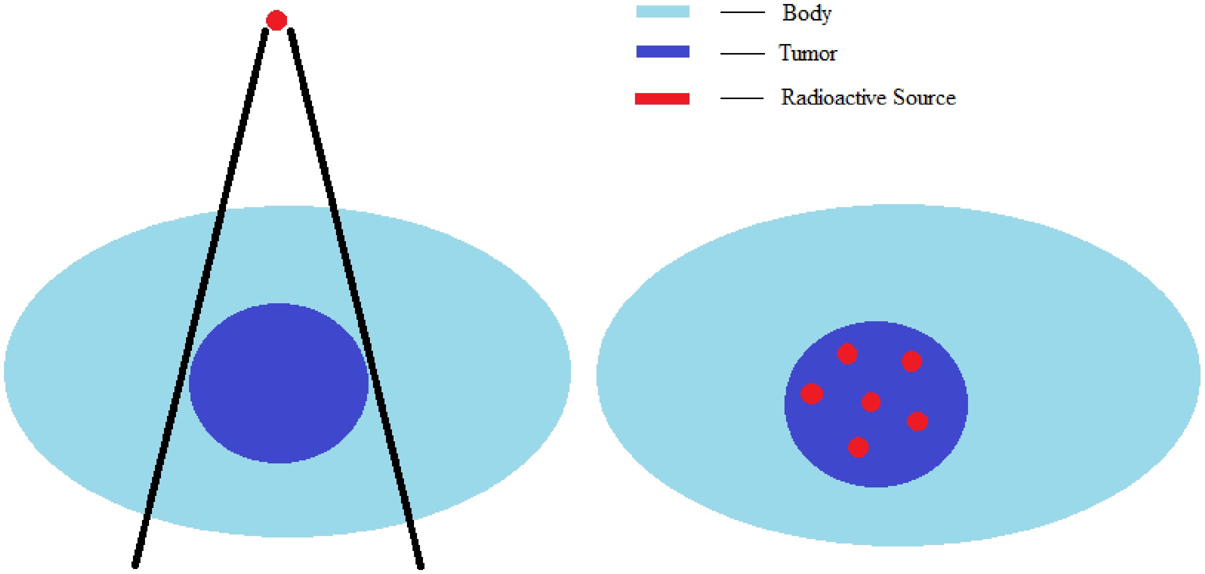


Figure 2. Illustration of the difference in brachytherapy (pictured right) and teletherapy or external beam radiation (pictured left).

However, a drawback is that the radiation must penetrate deeply into the patient, resulting in a higher dose to healthy tissues compared to brachytherapy. During these treatments, patients simply lie on a table for a few minutes, making it a comfortable and straightforward experience for them. The comfort and simplicity of this treatment have made external beam radiation therapy the preferred choice. Over the years, this approach has been refined to maximize conformity and minimize invasiveness.

Adaptive Radiation Therapy

Past Conformality Advances

Originally, external beam treatments were straightforward and typically consisted of two to four square fields, e.g. one field from the front, one from the back, and possibly two lateral fields – the so-called four-field box technique. Although this simplistic approach ensured even target coverage, and subsequent tumor control, high doses to normal tissues often resulted in significant complications. For example, when treating the prostate using the four-field box technique, parts of the rectum, small bowel femoral heads and bladder receive significant doses often resulting in frequent urination, diarrhea, abdominal cramping, intestinal blockage and fistulas. Therefore, the primary challenge in radiation therapy is to ensure the delivery of a tumor controlling dose while sparing surrounding normal tissues. Innovations in beam shaping and an increase in the number of beams (or beamlets) have played a key role in addressing this challenge.

The initial step involved shaping the beam. The beam was initially configured as a square or rectangle using radiation shielding collimators which prevented unintended radiation exposure to surrounding tissues. Unfortunately, most treatment fields are not simple squares or rectangles. To address this limitation, the use of customized cutout blocks were introduced to treat irregular fields. Block making is a time consuming procedure and involves a number of toxic metals. Furthermore, the blocks are heavy and must be inserted into the treatment gantry by the radiation therapist. Due to these limitations, blocks have been replaced with MLCs. A MLC is made of individual leaves made of tungsten that can move independently in and out of the treatment field (Figure 3). The function of MLCs is two-fold: they shape the radiation field and vary the intensity of the beam. Since irregular field shapes can be changed rapidly, MLCs have facilitated the use of a large number of fields resulting in a greater degree of conformality compared with treatment approaches using individualized blocks. Additionally, modern linear accelerators have the ability to dynamically adjust the MLCs while the gantry rotates around the patient thus faciliting the use of a larger number of fields and varying the beam intensity within the field: a treatment procedure termed modulated arc therapy. A comparison of a traditional four-field box plan and a modulated arc plan is illustrated in Figure 4.

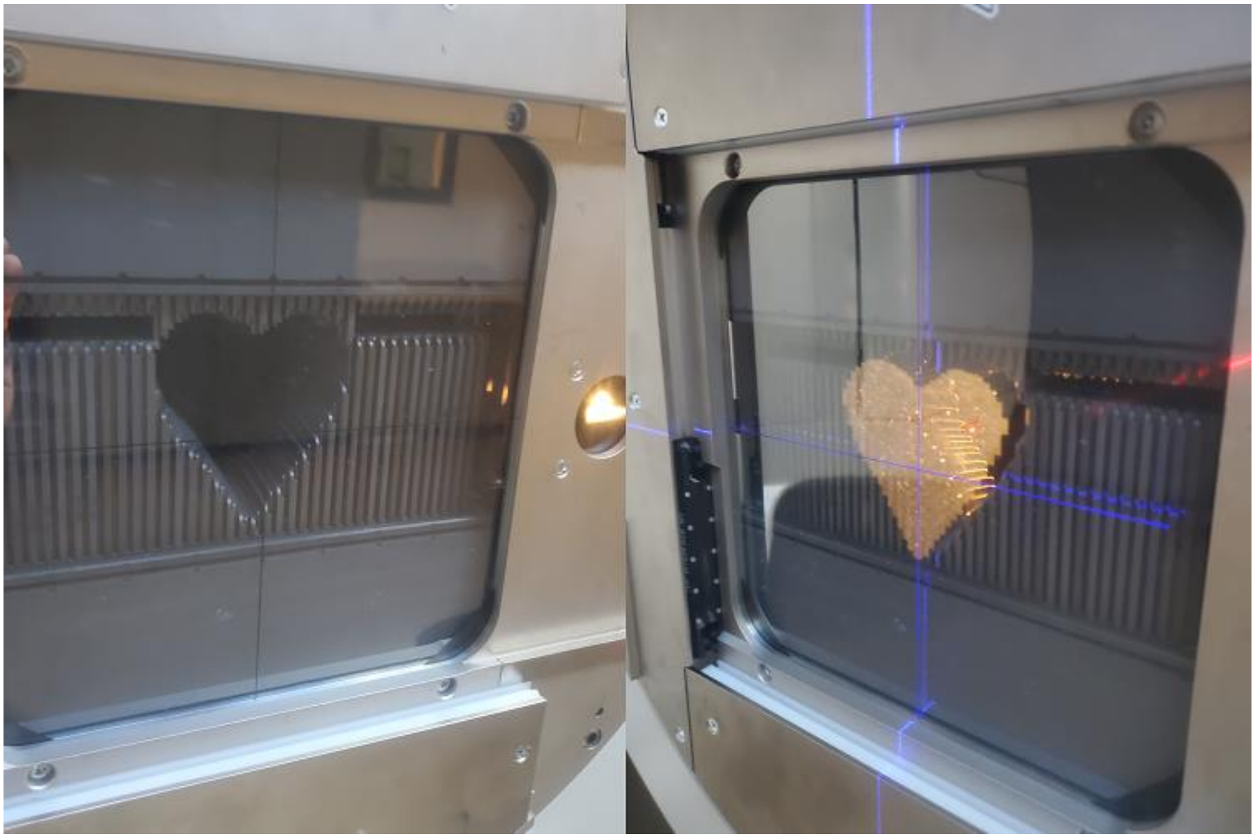


Figure 3. Example of multileaf collimator and its ability to shape output of radiation beams during treatment. MLCs are very versatile and can form very intricately, shown here by one forming a heart shape.

Another advancement in treatment precision and conformity occurred with the introduction of on-board imaging (OBI), enabling visualization of daily anatomical changes and alignment. This involved integrating x-ray sources and imaging panels into treatment machines giving rise to what is known as image-guided radiation therapy (IGRT). With imaging capabilities integrated into the machines, target volumes can be delineated more precisely, and patients aligned more accurately.

Modulated arc treatments have become the standard of care worldwide, delivering highly precise and customized doses to cancer patients on a daily basis. To achieve even greater treatment conformity, specific plans tailored to different days will be necessary to account for the day-to-day variations in soft tissue within a patient. With the integration of on-board imaging (OBI) and image-guided radiation therapy (IGRT), daily changes can be identified and appropriately addressed. This is where adaptive-style therapies play a crucial role.

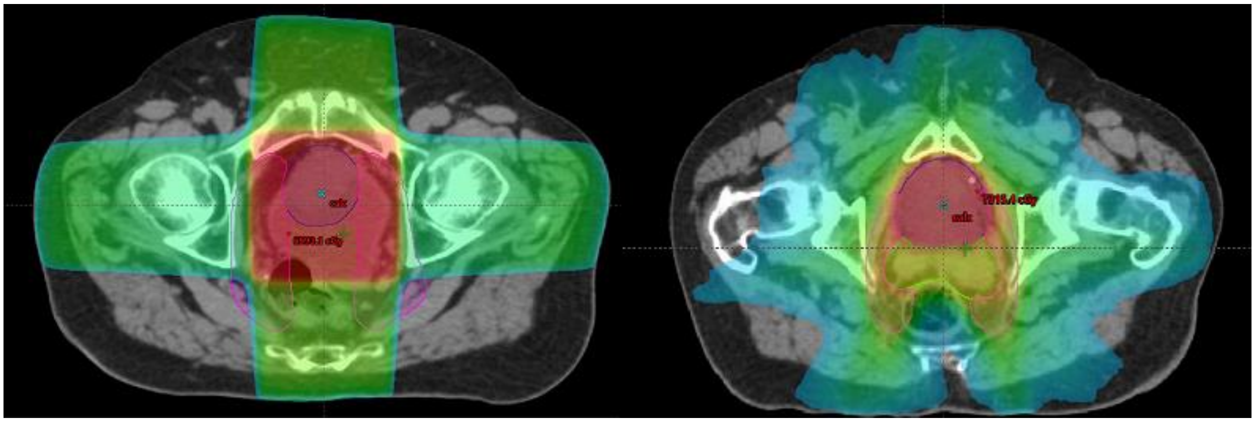


Figure 4. Comparison of traditional 4 field box technique (left) to modern modulated arc therapy plan (right) illustrating the higher degree of conformality with the arc plan.

Types of Adaptive Radiation Therapy

In traditional treatment approaches, the radiation plan is developed and calculated based on a CT scan typically acquired several weeks before the actual treatment. Implicit in this approach is the assumption that the internal anatomy remains relatively constant throughout the treatment period. Adaptive therapy has emerged as a significant topic of research in radiation oncology since the late 1990s [6]. It involves adjusting treatments to accommodate changes in patient anatomy on a weekly, daily, or even hourly basis. There are two primary approaches to adaptive radiation therapy: offline and online. Online adaptive therapy involves modifying the original treatment plan or creating a new one while the patient is on the treatment table, using onboard imaging. This allows for a highly customized plan tailored to the patient's anatomy each day. However, this approach demands substantial resources in terms of staffing and often requires specialized equipment and software. With online adaptive therapy, cone-beam CT (CBCT) or magnetic resonance imaging (MRI) is used to acquire images immediately before treatment, and these images are then aligned with the original CT scan used for planning. This enables examination of daily anatomical changes, such as bladder filling or the presence of air in the rectum or bowel. Based on these observations, decisions can be made to either re-plan completely, adjust the existing plan, or proceed with the treatment as planned. If adjustments are deemed necessary, the planning target volume (PTV) can be deformed or redrawn to better match the patient's soft tissue alignment for that day. The plan is then reoptimized and recalculated using the new target and contours from the day-of scan. Subsequently, the patient can be treated immediately with the newly customized plan, tailored to their anatomy at that precise moment. However, to execute this approach, a physician, physicist, and dosimetrist must be present at the treatment machine for each session. These treatments are more time-consuming, typically lasting 30-45 minutes compared to standard non-adaptive treatments which take 15-20 minutes. Nevertheless, this approach offers the greatest flexibility in accommodating anatomical changes in patients. Online adaptive therapy is effective for most treatment sites but yields the best results in patients with abdominal targets, where there is significant movement of surrounding soft tissues such as the stomach, intestines, or bladder.

Offline therapy represents another approach to adaptive therapies. It involves re-planning between treatments or having multiple plans prepared at the outset of treatment to choose from [7]. In this workflow, patient imaging from the treatment machine is compared with the original plan after each treatment session. Like online adaptive therapy, decisions can then be made to either proceed with treatment or re-plan in response to anatomical changes. This approach provides a 24-hour or 48-hour window for staff to conduct re-planning and secondary checks. It allows dosimetry and physics teams the necessary time to refine plans and ensure accuracy, without the time pressure and patient discomfort associated with on-machine re-planning. Offline therapy is commonly employed for lung tumors or head and neck patients, where tumors tend to shrink rapidly, and patients may experience weight loss during treatment, impacting dose distribution. Another technique in offline adaptive therapy is the "plan of the day" approach. This involves creating multiple plans at the outset of treatment to anticipate various scenarios that may arise during treatment. This provides radiation therapists with a library of plans to choose from on the treatment day, reducing the need to compromise on target coverage or OAR dose daily. Instead of relying on a single plan and adjusting it as best as possible, this approach offers the possibility of selecting a plan that fits the day's conditions optimally. These plans often consider factors such as bladder filling, which can significantly affect the positioning of abdominal organs. Offline adaptive therapy is particularly suitable for targets with predictable movement, such as bladders, prostates, and uteruses, where bladder volume can vary widely and impact the positioning of surrounding organs in the abdomen.

Methods

Patient Selection

Plan of the day (POTD) adaptive therapy feasibility was assessed with the intention of implementing the program at a small community hospital if proven viable. The initiative was initiated following difficulties experienced by multiple patients in achieving correct bladder filling during treatment. This prompted research into plan of the day adaptive treatment methods aimed at improving patient experience and streamlining therapist efficiency. Buschmann et al [8], provided a comprehensive overview of their capabilities and findings. Their study, conducted using equipment like that of Utah Valley Hospital, was deemed replicable. To assess whether the additional workload and workflow changes justified the outcomes, past patient data were analyzed to ascertain treatment viability. The abdominal treatment site for patients undergoing whole uterus treatment was chosen due to its similarity to the Buschmann et al [8] study and the observed degree of movement. When treating the uterus, consideration is already given to a patient's bladder fill, which can be a point of contention for some physicians. A full bladder reduces the volume being treated, thereby reducing bladder exposure to radiation while also pushing bowel higher into the abdomen and out of the treatment field. Some physicians insist on patients maintaining a specific bladder fill daily to ensure optimal treatment. At the onset of treatment, planning scans are evaluated for both full and empty bladders to determine the preferable patient setup. Typically, the scan with a full bladder is selected.

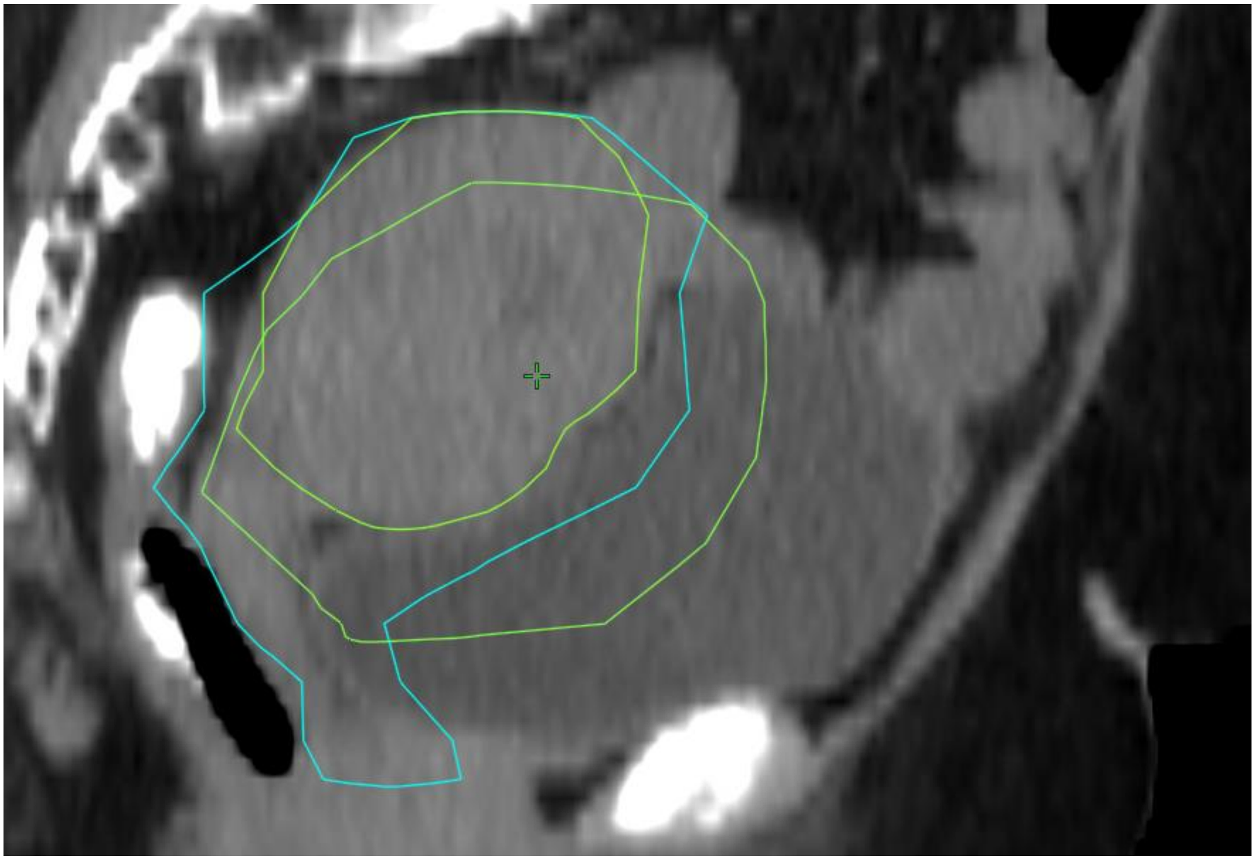


Figure 5. Patient case where uterus greatly increased in size during treatment. Green contours show the start and end size of uterus and the blue is the planned target with margin.

These scans serve as the basis for determining the viability of adaptive radiation therapy (ART) for the patient. Following the parameters outlined by Buschmann et al [8], patients exhibiting a uterine tip movement of 2.5 cm or greater were selected for analysis. To assess viability, the empty and full bladder planning CT scans were registered and aligned to bony anatomy. The pelvis, being a stable bone structure, serves as a reference point for alignment and supports the surrounding soft tissue. Aligning with the pelvis facilitates the identification and comparison of soft tissue deformations. The displacement of the uterine tip in the full bladder scan was then compared to that in the empty bladder scan to determine the extent of movement.

This analysis involved eleven patients previously treated at Utah Valley and the American Fork satellite hospital. Among these patients, one exhibited swelling that not only increased the PTV but also shifted it anteriorly and superiorly, altering its position relative to the lymph nodes rather than merely flexing in place. The volume of the uterus in this patient nearly doubled from 167.2 cc to 319.4 cc after the initial treatments, as depicted in Figure 5. This significant change warranted consideration for a full re-plan adaptive approach, given its consistent and repeatable nature over time. Another patient experienced minimal variation in bladder volume, with less than a 20cc difference between an empty and full bladder. Consequently, there was little anatomical change day to day, making standard treatment methods highly viable. Similarly, another patient exhibited minimal uterine movement regardless of nearby organ motion, indicating the effectiveness and repeatability of standard treatment techniques. However, the patient selected for ART analysis presented recurring issues during treatment days, albeit in a predictable manner. This patient demonstrated significant uterine flexion caused by a substantial difference in bladder volume—495.3 cc when full and 77.7 cc when empty. This resulted in a 4.88 cm shift in the position of the uterine tip, exceeding the threshold of 2.5 cm established by Buschmann et al. [8] and Seppenwolde [9] for categorization as a "mover" or a valid plan of the day candidate. Furthermore, in addition to the uterine movement, this anterior flexion created space behind the uterus and in front of the rectum, allowing the bowel to descend deeply into the original PTV. This observation underscores the complex interplay between anatomical structures and the implications for treatment planning and delivery.

This patient was then assessed as a suitable candidate for plan-of-the-day adaptive treatment analysis. Prior to creating treatment plans, the day-to-day anatomical changes needed to be identified and delineated. All 25 Cone Beam CTs (CBCTs) from each treatment session were manually contoured, excluding rigid structures such as femoral heads or spinal structures, which remained unaffected by soft tissue deformation. Contours were drawn for the PTV, rectum, bladder, and bowel bag. Manual contouring was chosen over automated contouring tools due to the latter's inaccuracies in contouring CBCTs. Once all CBCTs were contoured, the process of plan selection commenced. Based on the original contours, a full bladder reduced margin contour was created. In traditional treatments, an iterative target volume (ITV) is often utilized to accommodate tissue deformation, enlarging the target to ensure adequate irradiation while accepting increased dose to nearby OARs such as the bladder. Subsequently, an empty bladder contour was created based on the empty bladder scan to serve as the target for the reduced margin empty bladder plan. The planning CTs were then registered and aligned with each CBCT, focusing solely on soft tissue changes by aligning with bony anatomy. Uterine position was examined for each CBCT and compared to the planning scan's empty and full bladder PTVs, facilitating the selection of the appropriate plan for each treatment day. The chosen plan for each fraction was recorded, along with any instances where this approach prevented the need for the patient to adjust bladder fill mid-treatment. To justify the additional planning time from dosimetry, extra contouring time from physicians, and additional check time for physicists, a significant benefit was required. A target utilization rate of approximately 20% was selected, with the potential for even greater usage, as demonstrated in research papers such as Wang et al [10], which reviewed multiple sites' experiences with testing the validity of ART.

The contours created by the physician served as the reference for generating all other target volumes. The initial plan prescribed 180 cGy for 25 fractions (fx), totaling 4500 cGy, with a brachytherapy boost planned after the completion of external beam treatment. However, for the purposes of this analysis, the brachytherapy boost will not be considered as brachytherapy is already highly conformal and the focus is on personalizing the external beam treatment for improvement. The original plan utilized an iterative target volume (ITV) approach, wherein the physician delineated an area covering most of the uterine movement to accommodate day-to-day anatomical deformation.

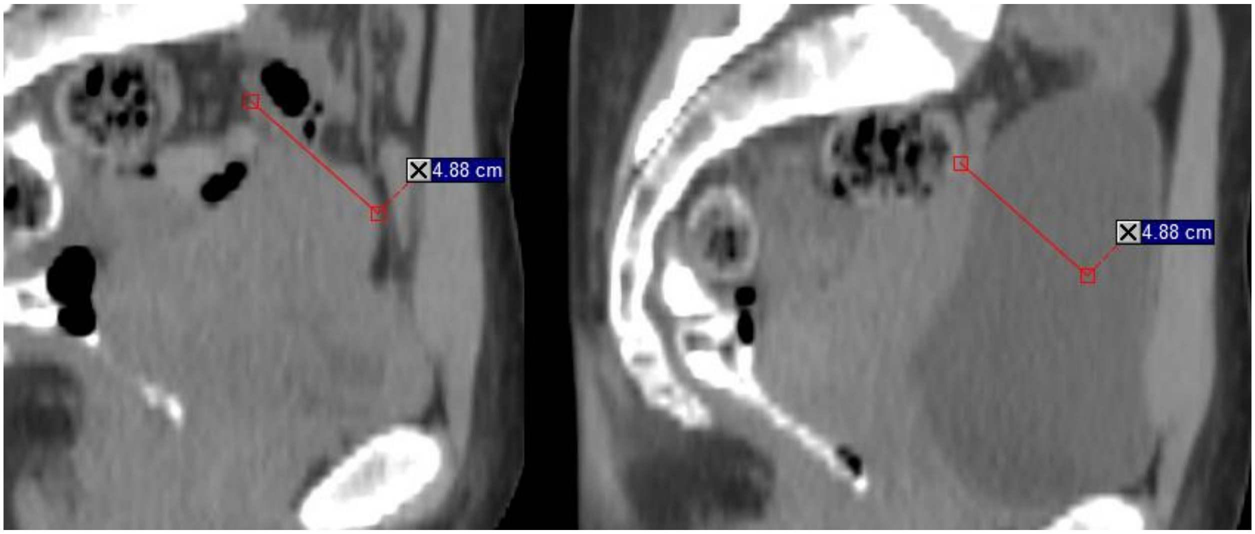


Figure 6. Viable “mover” candidate used for study. Large bladder volume change and mobile uterus is promising for the ART style of treatment.

For the creation of ART plans, a narrower margin full bladder PTV was delineated based on the physician's target contours. Subsequently, an empty bladder PTV was delineated after registering the two original images and aligning them with the physician's PTV coverage. A treatment plan was then devised for the narrower full PTV, the newly delineated empty bladder PTV, and the full Iterative Target Volume (ITV) plan using the empty bladder structure set.

Structure	Type	Volume (%)	Dose (cGy)	Priority
PTV	Upper	0	4750	150
	Upper	2.9	4636	150
	Lower	100	4559	150
	Lower	98.1	4578	150
Bladder	Upper	49	2996	50
Bowelbag	Upper	0	4578	50
	Upper	7.1	4034	150
	Upper	27.9	1182	50
Rectum	Upper	0	4751	70
	Upper	60.6	3465	70
	Upper	80.1	2706	70
Femoral Head R	Upper	7.8	2226	50
	Upper	29.3	1137	50
Femoral Head L	Upper	8.3	2279	50
	Upper	30.3	1433	50

Table 1. List of optimization objective used for treatment planning. This shows the desired limit of dose to a volume of a structure. Priority is the weighting of each constraint to assign it an importance.

Optimization of all plans was conducted using the same metrics as the original plan generated by dosimetry at the onset of the patient’s treatment. In addition to generating these plans to ascertain the gross difference in dose to target and OARs, a single-fraction version of the delivered, the empty bladder, and the full bladder narrower margin plan was developed to assess the true dose per fraction.

These single fraction plans were scaled down from the full treatment plans to match the 180 cGy single fraction dose, enabling a precise analysis of dose per fraction and a comprehensive dose summation. The treatment regimen comprised 25 sessions, exhibiting considerable daily variability. To accurately assess the disparity between expected and delivered doses compared to the ART approach, the dose per day needed to be considered, given the potential for selecting from multiple plans on any given treatment day. To address this, plans were calculated based on CBCTs from each treatment day. While CBCTs are utilized for online adaptive therapy at some facilities and for retrospective analysis at others, there may be slight differences in dose compared to the planning CT due to increased statistical noise, lower resolution, and differing acquisition methods. In a study by Gong H. et al [11], it was determined that variations in correcting a CBCT's Hounsfield unit (HU) density curve resulted in only a 2% difference in dose metrics for the target and negligible discrepancies in OARs and lower dose regions. Nonetheless, challenges arise from using CBCTs, including their reduced scan size compared to full-body scans. While the planning CT encompasses the entire abdomen, portions of the legs, and lower chest, CBCT scans typically capture only a 16 cm long section of the abdomen. As the PTV extends beyond this region to encompass lymph node volumes, not all of the PTV can be accurately contoured on CBCTs. To facilitate direct comparison, a new PTV evaluation structure was delineated on the planning scan, cropped to include only the region visible on CBCTs. This essentially excluded nodal volumes, focusing the analysis on the treatment region where the most movement occurs. Since nodal volumes remain stationary within the body, the analysis remains applicable to the target and facilitates assessment of ART-style treatment. Another issue encountered when using CBCTs to calculate dose is their abutment with air. This aspect necessitates consideration and potential correction during dose calculation to ensure accuracy.

As shown in Figure 7, the PTV abutted air both at the superior and inferior edges of the CBCT, resulting in nearly a 30% dose disparity due to non-buildup conditions. To address this issue, several options were explored.

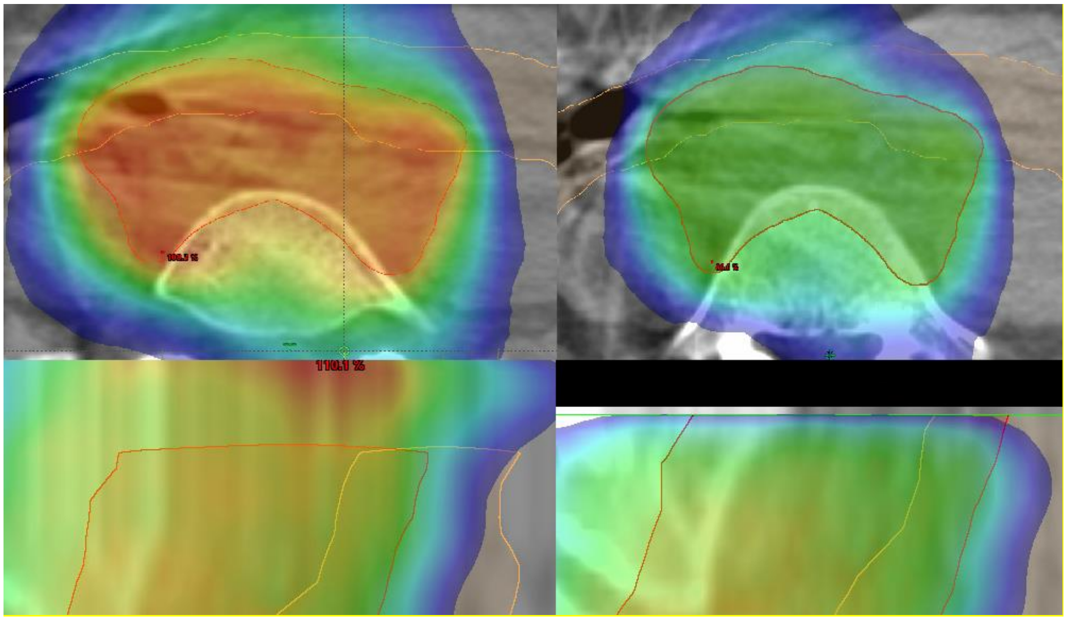


Figure 7. Dose deposition inaccuracy seen from the CT abutting air. Left is the extended scan allowing for lateral scatter. Right is the original cone beam abutting air not allowing for proper buildup

One approach involved creating a water structure around the CBCT to introduce buildup, while another involved extending the CT scan by duplicating existing slices (Figure 8). It was discovered that even with the creation of a water structure, extending the scan was still necessary. Consequently, the decision was made to extend the scans using existing anatomy, which not only proved effective but also preserved essential material properties and anatomical locations within the patient's body. Once the CBCTs were prepared and the PTV, rectum, bladder, and bowel bag were contoured for all 25 fractions, the target contour was examined for each CBCT to determine the most suitable plan. Subsequently, for each treatment fraction, both the "delivered" plan and the selected plan ("empty" or "full") were overlaid onto the CBCT and had the dose calculated to evaluate the dosimetrics for each treatment day. Clinic goals established for the original plan were then assessed using a generated template in the second check software. Doses received by every OAR and the target were recorded and compared. The doses delivered by both the actual treatment and the potential ART plan were then compared to the intended dose of the original plan. Furthermore, these doses were compared to the bladder size for each fraction to identify any correlations between the shift from conventional to adaptive treatment and changes in bladder size affecting dose constraints.

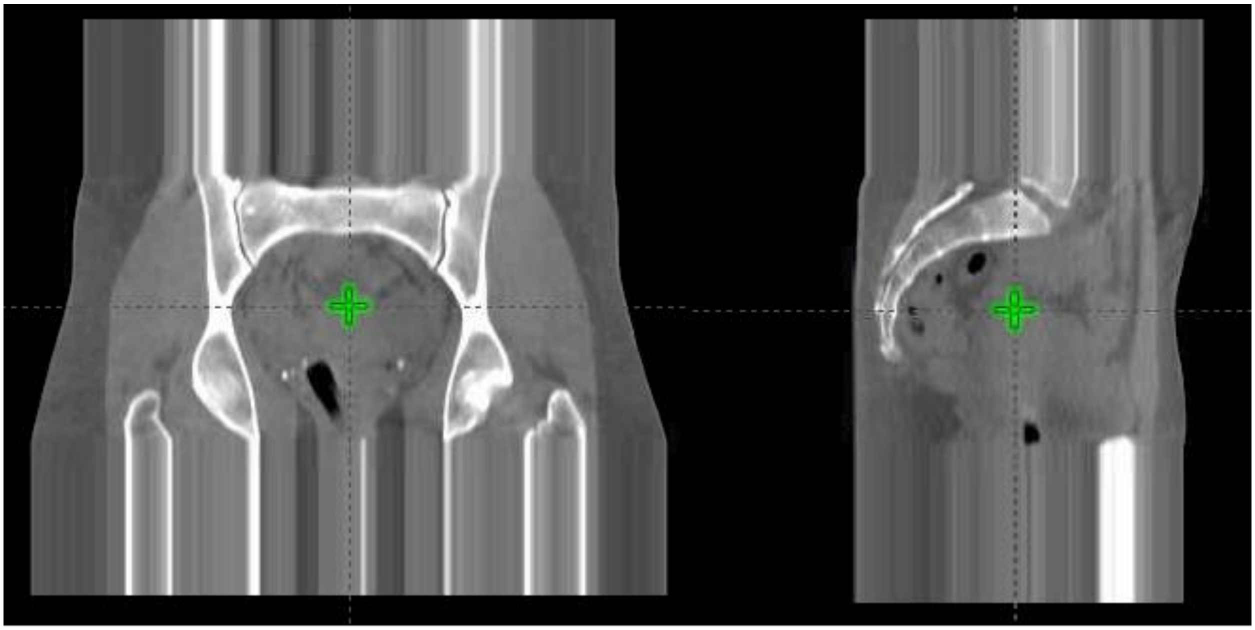
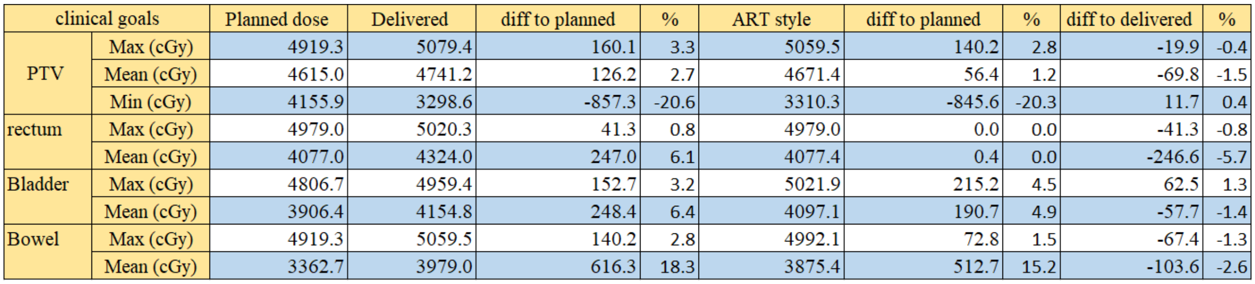


Figure 8. Extended CT used to compensate to air-material interface. Inferior and superior images copied and duplicated for 10 cm in either direction to simulate tissue.

Results

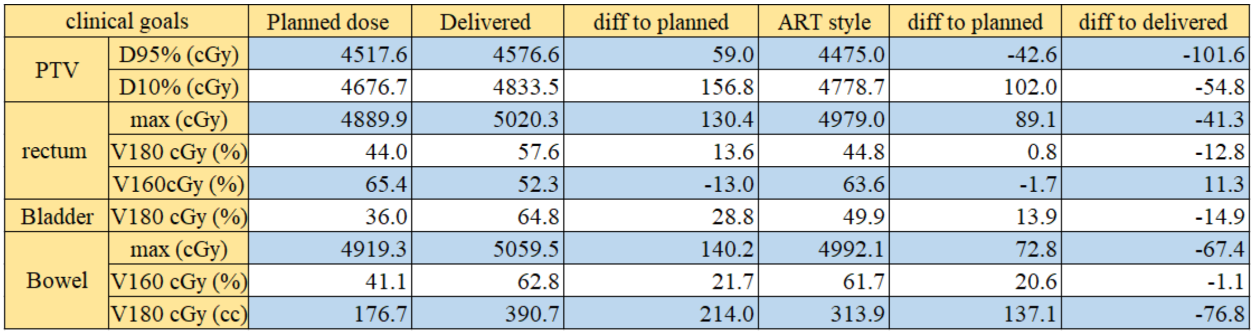
The data was compiled, and both plans were compared to the original treatment plan and each other (Table 2). When compared to the original plan, the results varied depending on the dataset used. Evaluating the mean, maximum, and minimum doses to the PTV revealed very close results, with both the delivered plan and the ART-style test showing a one to three percent change compared to the planned treatment statistics. This trend aligns with the findings of the study by Gong et al. [11], indicating an approximately two percent difference between the treatment site and the planning CT. Furthermore, the dose received by the target remained consistent within a few percent, along with the minimum and maximum doses.



clinical goals		Planned dose	Delivered	diff to planned	%	ART style	diff to planned	%	diff to delivered	%
PTV	Max (cGy)	4919.3	5079.4	160.1	3.3	5059.5	140.2	2.8	-19.9	-0.4
	Mean (cGy)	4615.0	4741.2	126.2	2.7	4671.4	56.4	1.2	-69.8	-1.5
	Min (cGy)	4155.9	3298.6	-857.3	-20.6	3310.3	-845.6	-20.3	11.7	0.4
rectum	Max (cGy)	4979.0	5020.3	41.3	0.8	4979.0	0.0	0.0	-41.3	-0.8
	Mean (cGy)	4077.0	4324.0	247.0	6.1	4077.4	0.4	0.0	-246.6	-5.7
Bladder	Max (cGy)	4806.7	4959.4	152.7	3.2	5021.9	215.2	4.5	62.5	1.3
	Mean (cGy)	3906.4	4154.8	248.4	6.4	4097.1	190.7	4.9	-57.7	-1.4
Bowel	Max (cGy)	4919.3	5059.5	140.2	2.8	4992.1	72.8	1.5	-67.4	-1.3
	Mean (cGy)	3362.7	3979.0	616.3	18.3	3875.4	512.7	15.2	-103.6	-2.6

Table 2. General statistics of plan analysis. Planned dose being original treatment plan. Delivered is the original treatment plan accounting for changes in anatomy on the CBCT's. ART style is the analysis of choosing a plan of the day.

However, an exception was observed in the minimum dose, which can be attributed to the planning CT not accounting for changes in contours for each fraction. The discrepancy between the ART-style and traditional treatment styles becomes more apparent when considering clinical goals rather than standard statistical metrics as seen in Table 3. All structures except the rectum were analyzed, as it was minimally affected by the bladder and primarily influenced the anterior-to-posterior positioning of the PTV, which was covered by the PTV margin. Initially, the dosimetric parameters were compared between the ART-style and the delivered traditional planning style.



clinical goals		Planned dose	Delivered	diff to planned	ART style	diff to planned	diff to delivered
PTV	D95% (cGy)	4517.6	4576.6	59.0	4475.0	-42.6	-101.6
	D10% (cGy)	4676.7	4833.5	156.8	4778.7	102.0	-54.8
rectum	max (cGy)	4889.9	5020.3	130.4	4979.0	89.1	-41.3
	V180 cGy (%)	44.0	57.6	13.6	44.8	0.8	-12.8
	V160cGy (%)	65.4	52.3	-13.0	63.6	-1.7	11.3
Bladder	V180 cGy (%)	36.0	64.8	28.8	49.9	13.9	-14.9
Bowel	max (cGy)	4919.3	5059.5	140.2	4992.1	72.8	-67.4
	V160 cGy (%)	41.1	62.8	21.7	61.7	20.6	-1.1
	V180 cGy (cc)	176.7	390.7	214.0	313.9	137.1	-76.8

Table 3. Statistics for gross difference in treatments using the clinical objectives. Large swings in volumes receiving high dose in the bowel. Bladder had 14.9% less volume receiving the full prescription dose.

Examining the Minimum Dose to 95% of the Planning Target Volume (D95%) graph for both ART and delivered fractions (Figure 9) reveals that, on average, the ART-style plan had a lower dose per fraction. Specifically, 16 out of the 25 fractions fell below the unity line, indicating a reduction in dose compared to the delivered fractions. The remaining fractions either slightly exceeded or closely aligned with the unity line, suggesting minimal to no impact on target coverage. This observation is further supported by the summed fraction data presented in Table 3, where the ART-style plan delivered 42 cGy less than the planned dose and 101.6 cGy less than the delivered plan over the course of 25 fractions. While this discrepancy is measurable, it represents a maximum 2.2 percent difference, which falls within the error margin associated with CBCT calculations. Consequently, the coverage could still be deemed acceptable. Similarly, when examining the unity graph for the bowel bag structure (Figure 10), a similar trend emerges, with one significant outlier observed in fraction 7, particularly concerning the lower dose parameter. In this fraction, an abnormal amount of bowel tissue encroached into the PTV. The graph mirrors that of the PTV unity graph, with the most significant difference in fraction volume receiving 80% of the prescription dose being 15% of the volume.

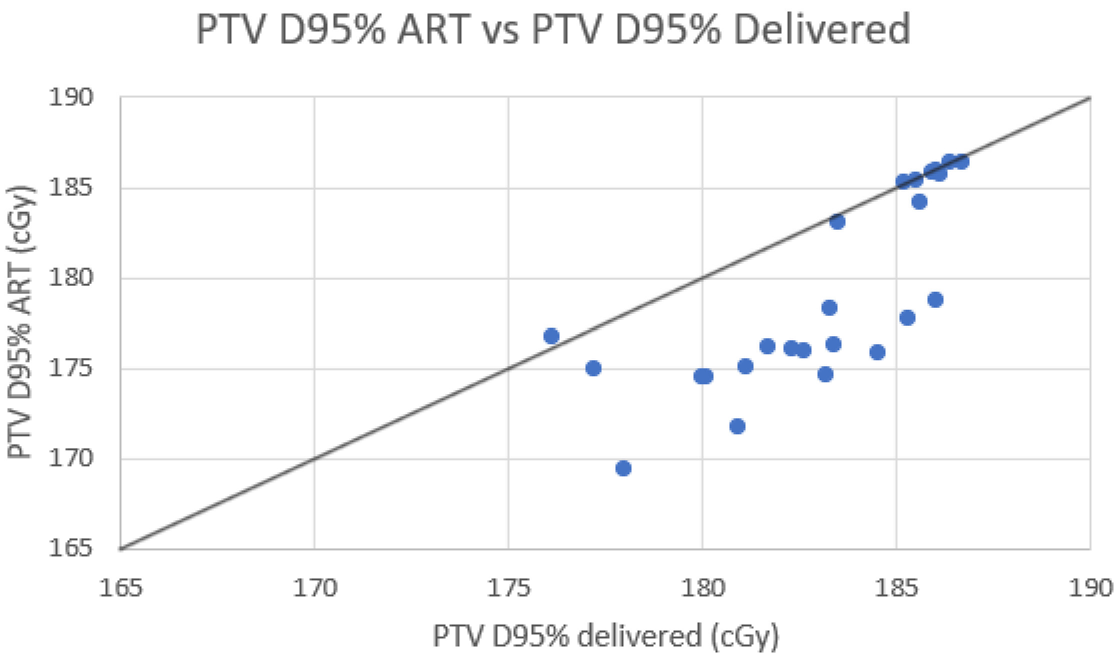


Figure 9. Dose delivered to 95% of the target volume unity graph. Each dot represents one fraction. Points above the line show higher dose seen in ART style. Points below show more dose delivered in the traditional treatment fraction.

All fractions were either on the unity line or below it. Regarding the volume receiving 4000 cGy or higher (V4000 cGy) for the bowel bag, the aggregate averaged percentage volume of V4000 cGy was 62.8% for the delivered plan, while the ART plan showed an average of 61.7%. The planned percentage for the adjusted bowel bag evaluation was 41.8%. Once again, the difference between the delivered plans was relatively small, but what stands out is how both treatment styles deviated from the planned values. Another clinical metric used to assess bowel dose is the volume receiving the full prescription dose (figure 11).

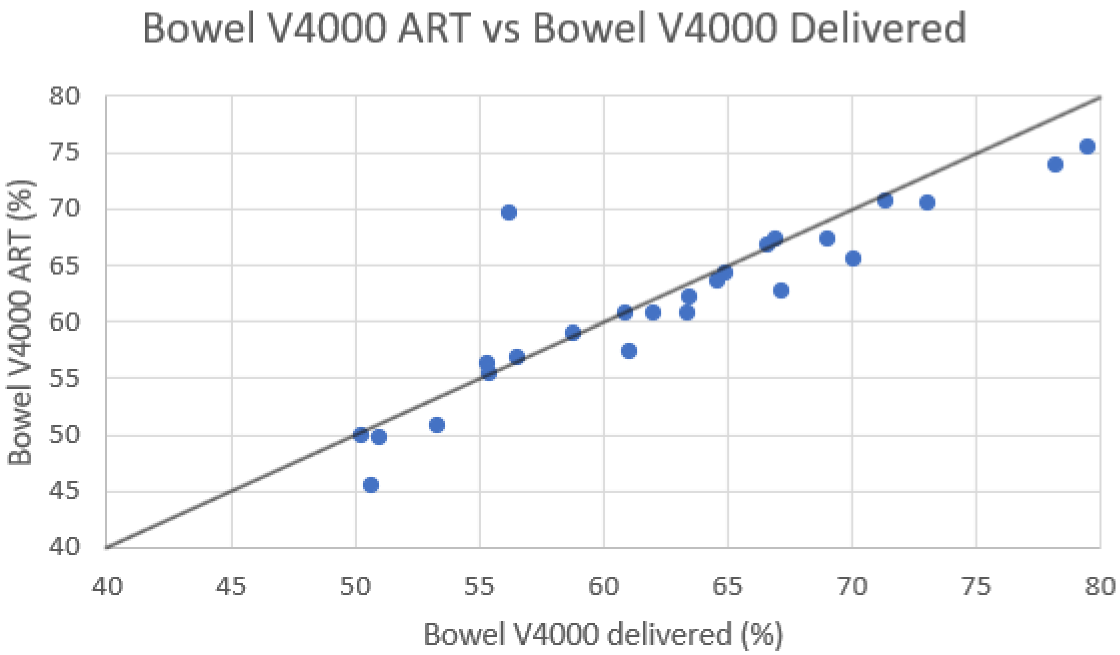


Figure 10. Unity graph for the volume of bowel receiving 80% of the prescription dose. The ART seems to show overall slight advantage with all points either on the line of unity or slightly below, bar one outlier.

In the unity graphs, fractions either fall directly on the unity line or well below it, indicating a significant advantage for the ART-style approach. This trend is consistent when examining the aggregate averages. The planned bowel volume receiving prescription dose was 176.7 cc the delivered plan came in at 390 cc almost doubling the planned volume. The ART dose showed a volume of 313.9 cc which is still higher than the planned dose but 76.8 cc lower than the delivered plan. The bladder fraction doses were the least correlated by far (figure 12) with a seemingly random distribution. When looking at the aggregate average dose to the bladder it was lower with the ART setup most likely due to the tighter margin on the full ART plan as opposed to the ITV style approach.

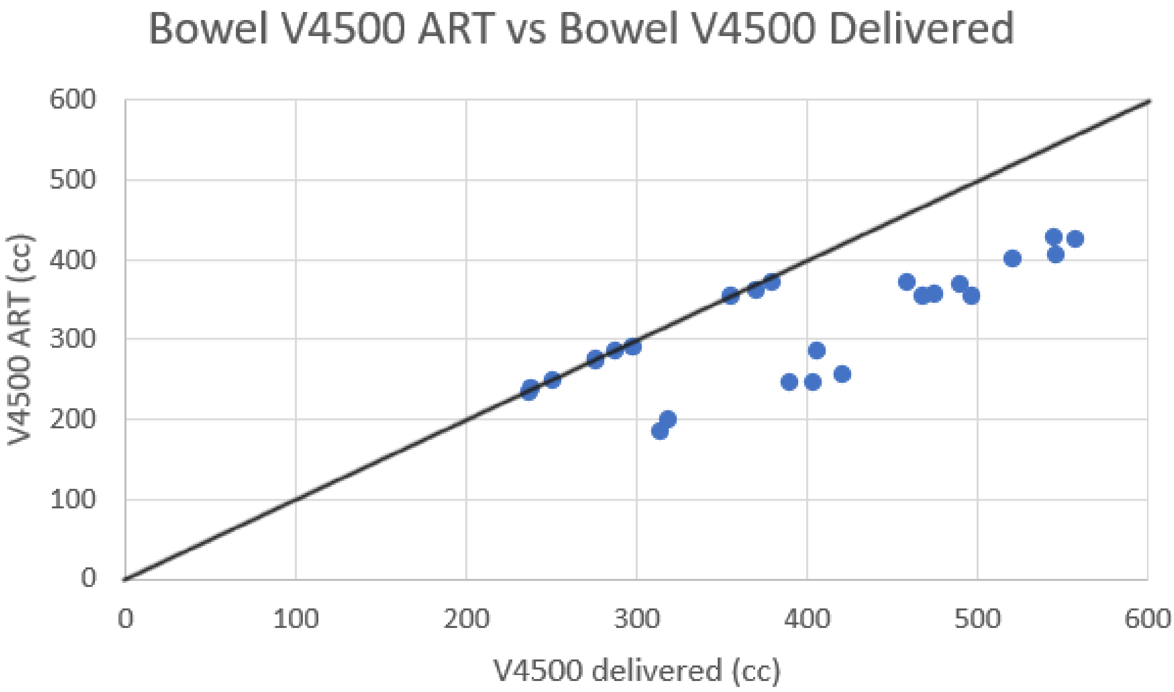


Figure 11. Unity graph of the absolute volume receiving prescription dose. All points are either on unity like showing equal values or below showing the ART style having reduced high dose to the bowel.

After the treatment styles were compared to each other, the relation of OAR doses to bladder fill were explored for both styles. First the bladder dose was considered when comparing to its own volume (figure 13). Surprisingly, the dose to the bladder did not exhibit a clear trend when using the ITV approach; instead, it remained relatively constant, averaging around the 50% volume. In contrast, when analyzing the ART-style approach, the volume of the bladder receiving 4500 cGy (V4500 cGy) decreased as the bladder volume increased, indicating a higher percentage of it was within the treatment field. This trend highlights the impact of the reduced treatment margin on the full bladder ART plan. The difference per fraction between the ART-style and the ITV-style delivered plan was evident in two cases: the higher the bladder fill, and the lower the bladder dose.

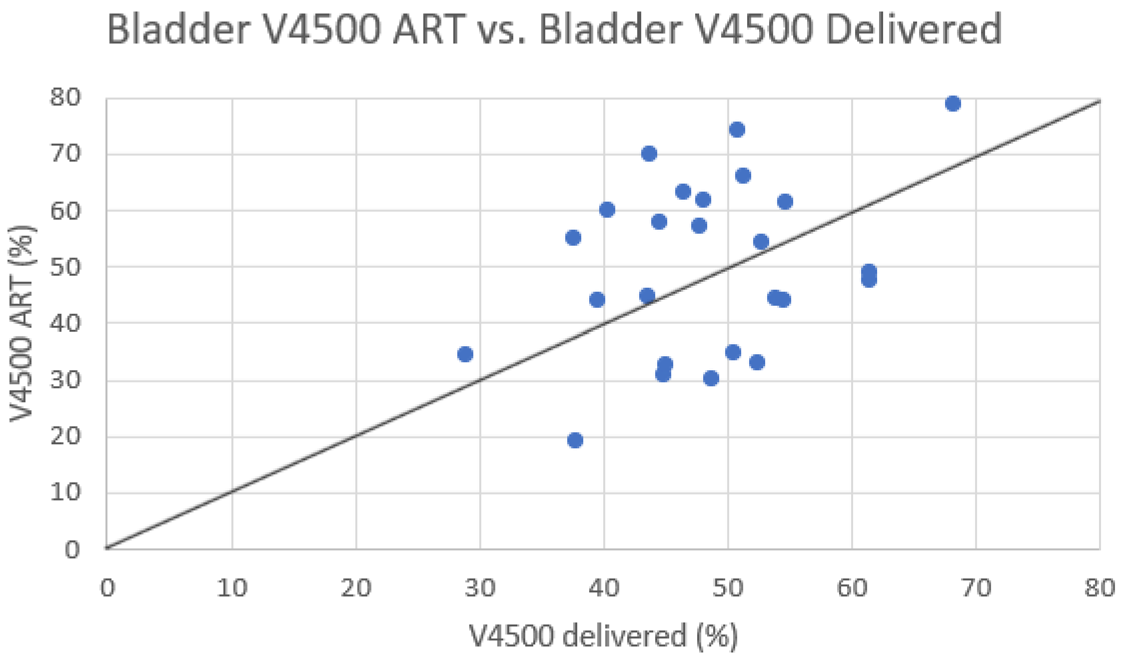


Figure 12. Percent of the bladder receiving prescription dose unity graph. This distribution is the most random of all OARs and being center on the line of unity may hint at no effect of ART style on bladder dose.

This phenomenon is attributed to the tighter conformity of the empty bladder PTV in the ART-style treatment. The separation of the two groups illustrates the distinction between treating in the full bladder case and the empty bladder case. Next, the dose to the PTV was examined in relation to bladder fill in figure 13. The ART-style treatment again revealed a division into two distinct groups. In contrast, the delivered fractions exhibited a more continuous distribution but followed a similar overall trend. This trend displayed an almost L-shaped distribution, wherein bladder volumes below 250 cc resulted in D95% values for each fraction that were erratic, ranging from the planned prescription dose to 10 cGy below it. Under the ART-style treatment, almost every fraction with a bladder volume below 250 cc was under dosed, albeit with a more consistent distribution, while the delivered fractions received almost exactly the planned dose on average. However, when the bladder fill exceeded 250 cc, the doses were nearly identical.

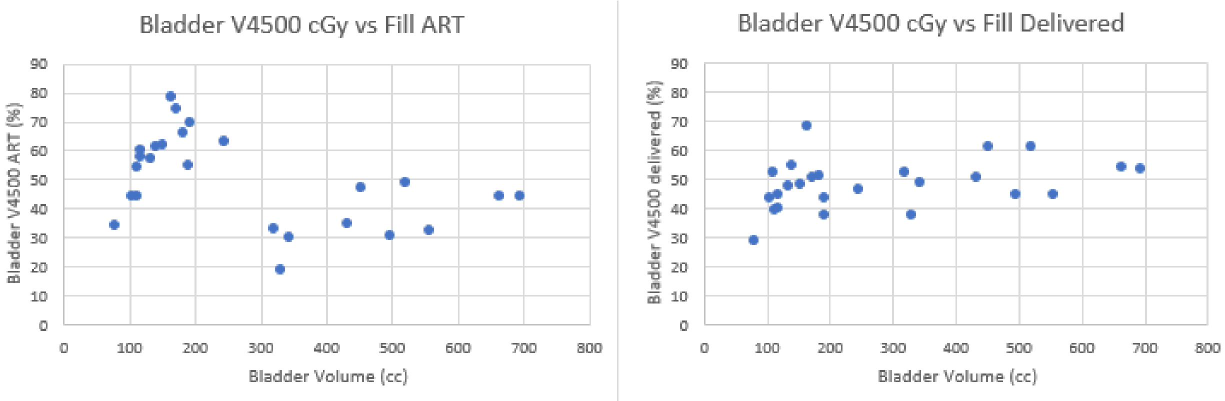


Figure 13. Comparison of bladder volume receiving prescription dose for the ART style (left) and the traditional style of ITV treatment (right).

Finally, the bowel parameters were examined as shown in figure 15. First the 80% parameter was examined, the V4000 cGy. As before when looking at the unity graphs we see the forgiveness of photons for radiation therapy. The graphs for the delivered fractional doses and the ART fractional doses look all but identical when compared to bladder fill, again showing the similarity of the plans since the graphs are almost identical. The other parameter for the bowel that is considered for clinical usage is the volume that receives prescription dose or the V4500 cGy.

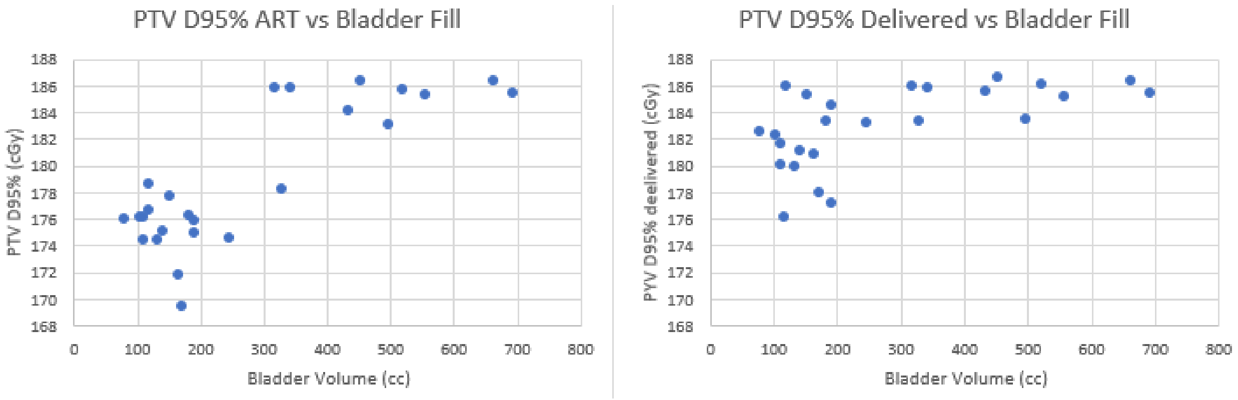
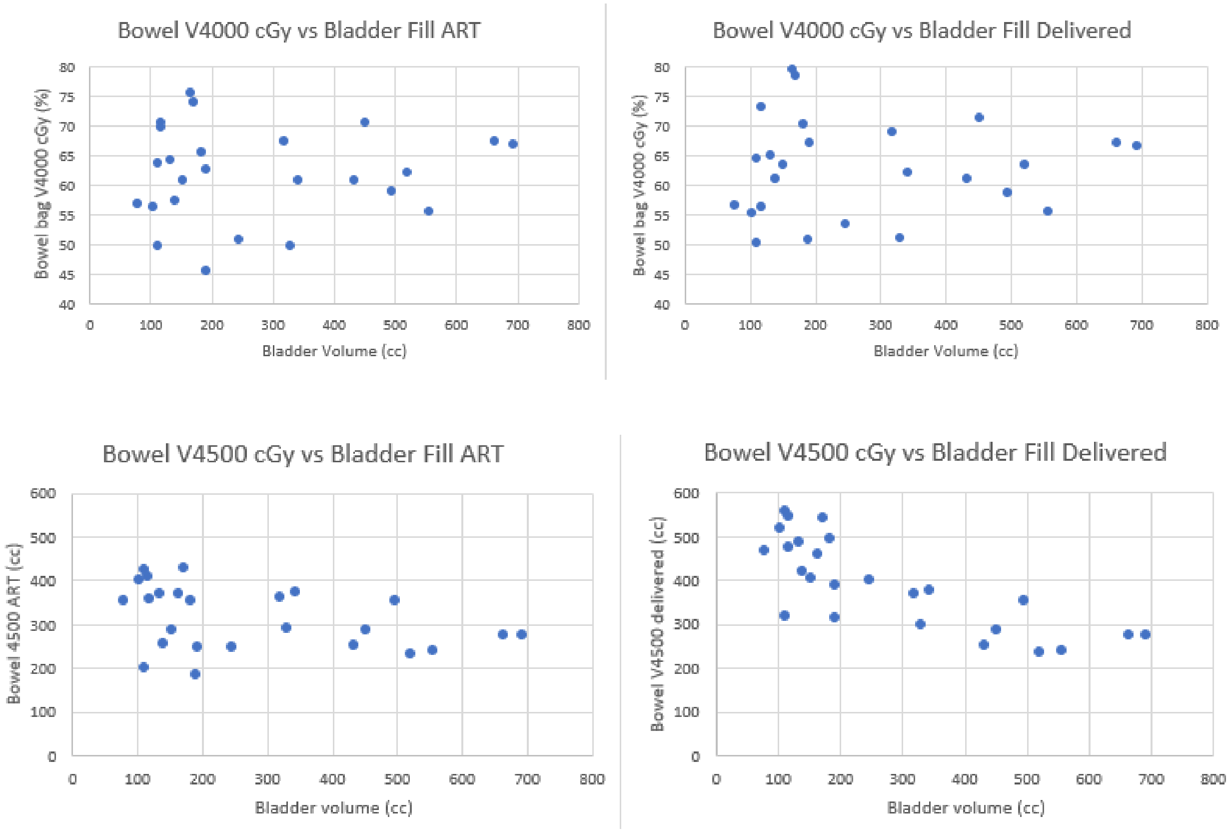


Figure 14. Comparison of the PTV coverage vs bladder fill for ART (left) and traditional approach (right).

When examining the second parameter for bowel, namely the prescription dose constraint, differences between the styles become apparent. Similar to the PTV, once the bladder reaches a fill of 250 cc or greater, the graphs appear almost identical. However, it is in the lower fill region where a distinction emerges. The distribution appears nearly identical in both approaches; however, in this region, the ART-style approach was shifted downward by an average of about 100 cc. This represents a notable difference and could be interpreted as a success for the ART style, as its primary objective is to maintain PTV coverage while reducing bowel dose, particularly in cases like this one.


Bowel V4000 cGy vs Bladder Fill ART

Bowel V4000 cGy vs Bladder Fill Delivered

Bowel V4500 cGy vs Bladder Fill ART

Bowel V4500 cGy vs Bladder Fill Delivered

Figure 15. Bowel doses vs bladder fill. The top two graph showing the 80% volumes being very similar throughout treatment. The bottom graphs showing the prescription dose volumes being slight improved at lower bladder fills.

Discussion

The data from this patient presents an intriguing scenario. The mean doses for nearly all the OARs are very similar, suggesting that both planning styles aim for the same outcome. First, considering the PTV coverage, which is crucial: poor PTV coverage would render this treatment approach unfeasible for the clinic. Fortunately, the gross dose data for the PTV appeared satisfactory. Both the delivered plan and the ART plan were within a few percent of the predicted values from the original radiation plan. However, upon closer inspection of the graphs, the ART plan showed a slightly lower average dose compared to the delivered plan. This contrasts with other research indicating that CBCT data compared to planning CT should typically show consistently higher doses. Moreover, the dose coverage appeared more sporadic with the ART plan, whereas the delivered doses were more predictable. Moving on to the OARs, the bladder seemed to be minimally affected, which aligns with its role as a driving factor for change in soft tissue rather than an affected organ. However, it was observed that the bladder received noticeably more dose at lower bladder fills. Despite this, the gross data revealed that the lower dose received by the bladder when using the full ART plan with a tightened margin more than compensated. Consequently, the bladder had a lower volume receiving prescription dose, even though it experienced a higher maximum dose. Finally, the bowel, which was the primary focus of this approach, also conveniently demonstrated the largest difference between the two planning styles. The forgiving nature of photons was evident in the lower dose metrics, as was the discrepancy between the initially generated plan and the delivered plan on a daily basis. Although the dose constraints for lower doses to the bowel were similar, there were 76cc of bowel that did not receive the full prescription dose compared to the delivered dose. One physician anticipated a minor change in acute and latent effects from this adjustment. Acutely, there would likely be less bloating and possibly reduced nausea. Long-term, there could be a lower likelihood of small bowel obstruction. Another physician concurred but noted that the change would not significantly impact clinical decisions or necessitate a change in the treatment plan. The observed change in bowel dose is not insignificant but does not significantly affect clinical outcomes. When comparing this approach not only to traditional treatment but also to true online adaptive therapy with specialty equipment and adaptive platforms, both the advantages and disadvantages become apparent. Two plans would have been created for this case, effectively doubling the staff workload for this patient. However, this would have been done with the potential effect on low-grade side effects, both acutely and not in the long term. The data also indicate that the effects can effectively be mitigated by treating only when the bladder volume exceeds 250cc. In traditional treatments, the bladder fill and positioning of soft tissue in the abdomen are always assessed before treatment, and adjustments are made as necessary. In this case, the additional time saved at the treatment machine was minimal, as the treatment was only prevented three times throughout the entire course of treatment, resulting in approximately an hour saved in total across all 25 fractions. Moreover, the planning time for a second plan alone exceeds this and is more resource intensive.

Comparing the results observed in this patient with other studies investigating this treatment approach reveals both similarities and differences, influenced by the original treatment style utilized. In the study by Buschmann et al [8], which served as the inspiration for the present work, an increase in target coverage was reported. This is in contrast to the present study in which a marginal decline was observed. However, upon reviewing the data from that paper, a similar trend emerges, with more fractions delivering lower total coverage to the PTV but with more consistent coverage, consistent with the findings of the analyzed patient. Examining the OARs, the Buschmann paper also observed a similar trend, with all the OARs experiencing an equal or lower dose per fraction for the volume constraints used clinically when employing the ART style. The Buschmann study showed a decreased treatment volume with 87cc target shrinkage using the ART style; however, the analyzed patient in the present study exhibited only a 20cc difference on average. This divergence may be attributed to the treatment of paraaortic lymph nodes, which complicates target size reduction in this region. Similarly, in the paper by Bondar et al [12], the intensity-modulated radiation therapy (ITV) style was compared with a two-plan library but with a larger margin on the two plans. Notably, bowel was not included in the analysis, as the paper focused more on proof-of-concept and preparation for clinical implementation. This trend of excluding bowel from analysis was also observed in other studies, such as Nováková et al [13] who examined the ideal number of plans in a plan library for this treatment style. It was found that in cases with greater movement (exceeded 30mm), three plans would be optimal. However, this raises concerns about the increased workload for dosimetry and physics per patient, with marginal reductions in dose to OARs showing no clinically significant benefit. In the retrospective study by Wang et al [10], evaluating various plan-of-the-day approaches, clinics that implemented this approach reported greater benefits. This could be attributed to the flexibility of day-to-day treatments, allowing for minor adjustments more easily on the day of treatment compared to post-treatment simulation. It is worth noting that since the publication of earlier papers like Bondar and Buschmann, there have been improvements in standard treatment techniques. With onboard imaging becoming the norm and newer, more precise treatment machines being adopted worldwide, the need for this treatment style may have diminished before it was thoroughly vetted. Implementing this treatment approach would not only strain clinic resources but also effectively double billing for dosimetry, physics, and physician-based charges, leading to only marginally better treatment outcomes with a reduction in mild grade one side effects, while placing a heavier burden on both the clinic and the patient, excluding the potential rejection from insurance companies.

Conclusions

When examining the plan of the day adaptive therapy for intact uterus patients, it was found that there was a slight improvement in sparing OARs while maintaining comparable target coverage. However, this marginal enhancement in plan quality comes at a significant cost of increased workload for clinic staff. Further refinement of the treatment could be achieved with the introduction of a mid-bladder fill plan, potentially enhancing plan quality but at an even greater expense of clinic workload. Moreover, the fact that only one out of eleven patients was deemed suitable for this approach indicates that, with the current tools available on the market, plan of the day adaptive therapy is neither feasible nor advisable. Instead, emphasis should be placed on patient coaching and bladder fill management, with a potential reduction in margin accompanied by stricter coaching to achieve similar margin benefits with a substantial reduction in clinic workload. While standalone adaptive platforms could be considered for problem cases, their novelty poses challenges, as there is limited data on outcomes or limitations, especially in a dynamic treatment setting like the one in this study. However, specialized adaptive therapy platforms may prove effective for patients who exhibit slightly non-viable movement for this approach but still undergo notable anatomical changes day to day. The main challenge in making this form of radiation therapy truly viable lies in the proper selection of patients, as anatomical changes cannot be predicted accurately, which is precisely what adaptive therapies aim to address. The other patients who were not suitable for this approach demonstrated various forms of anatomical changes, rendering the application of the ART style futile. Even for the theoretically suitable patient, while there were statistical differences in dose metrics, they were not clinically significant. In conclusion, adaptive therapy is still in its early stages and may be considered for specialty machine purchases in the future. However, at present, it cannot be recommended due to its limited applicability and significant resource demands.

Appendix

This section shows the dose volume histograms (DVHs) for each fraction as well as the dose distribution from both the delivered dose and ART test plans. In all DVHs the square points are the delivered plans, and the triangles are the ART plans.

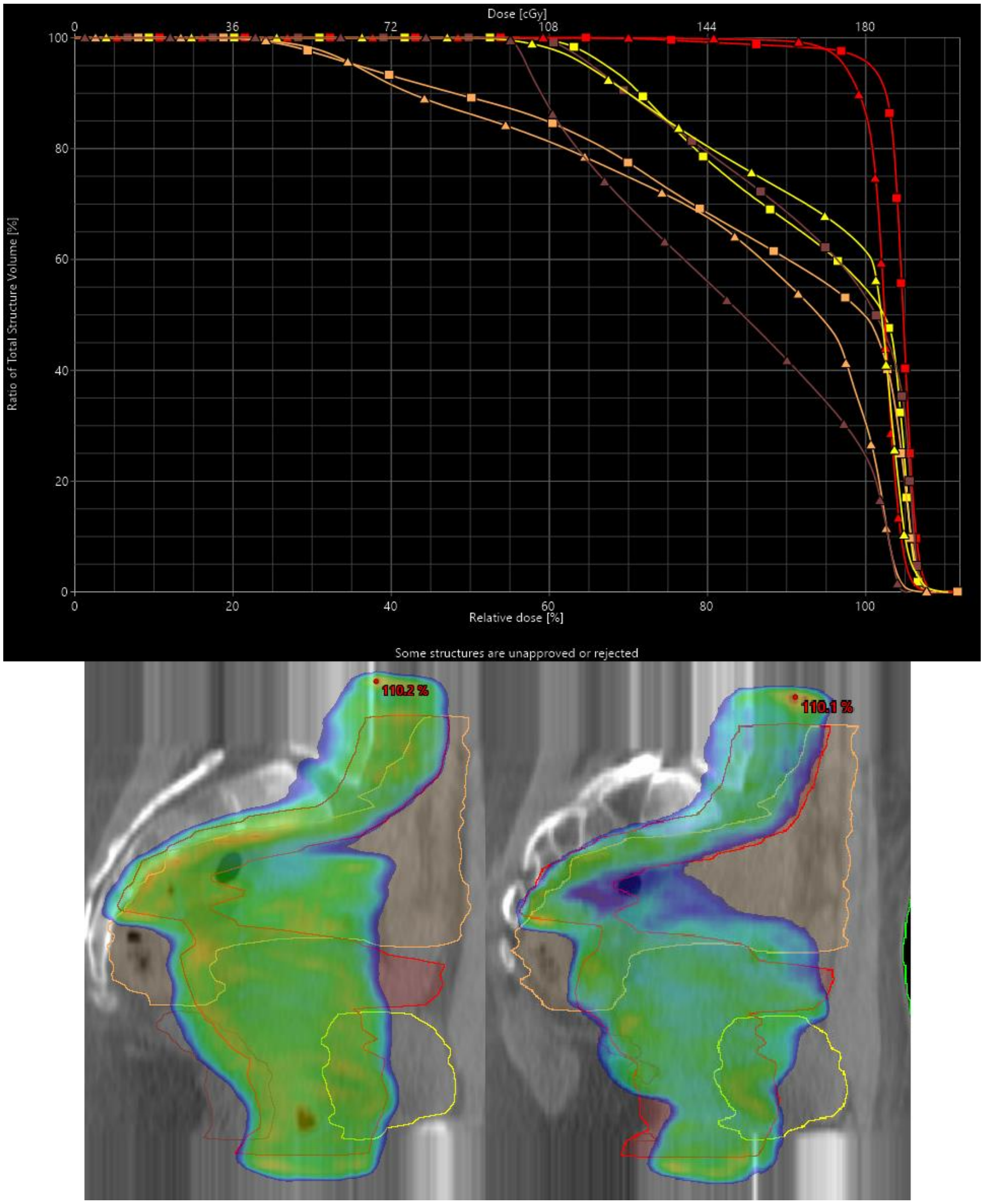


Figure 16. Fraction 1. Empty plan selected.

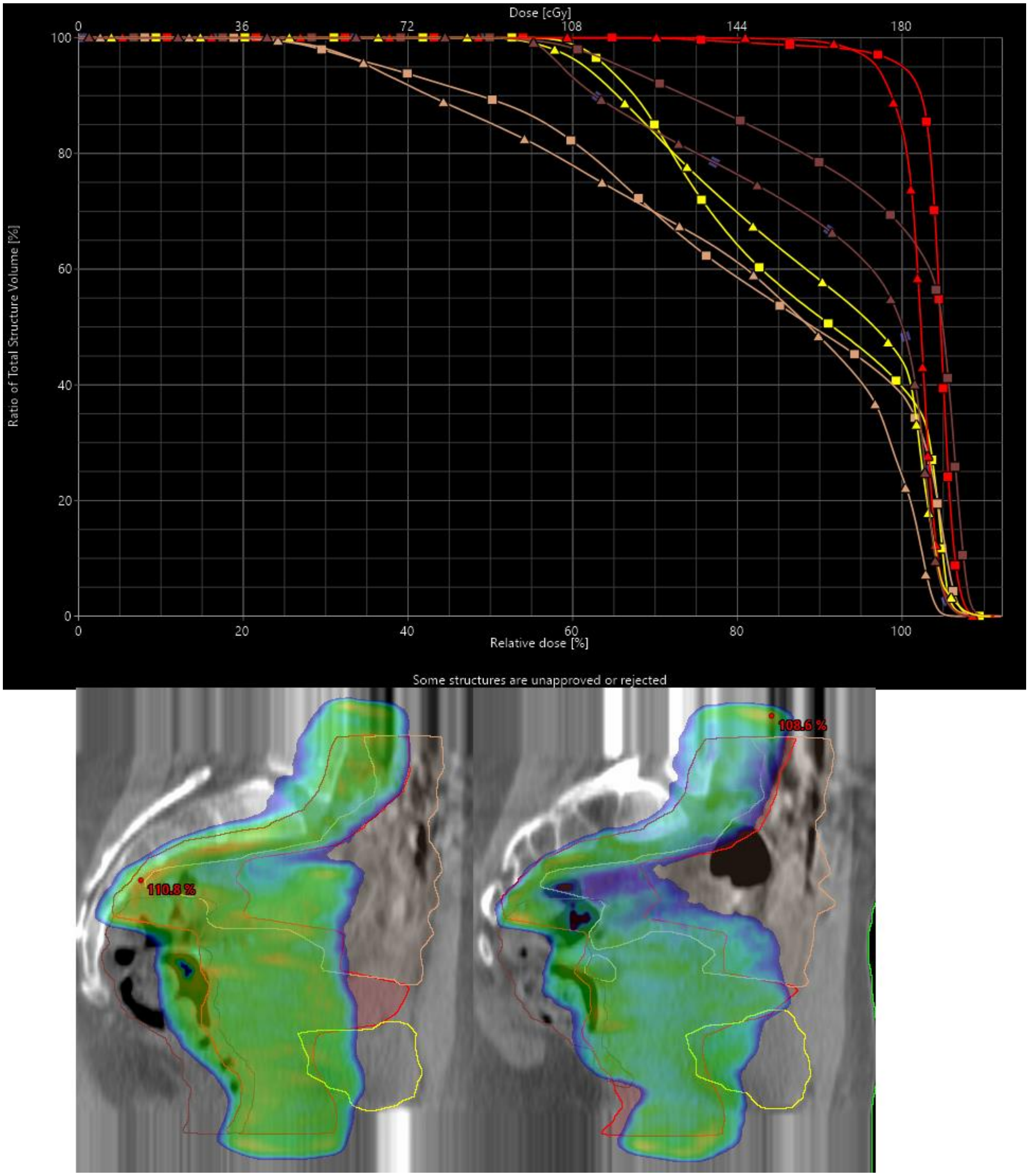


Figure 17. Fraction 2. Empty plan selected

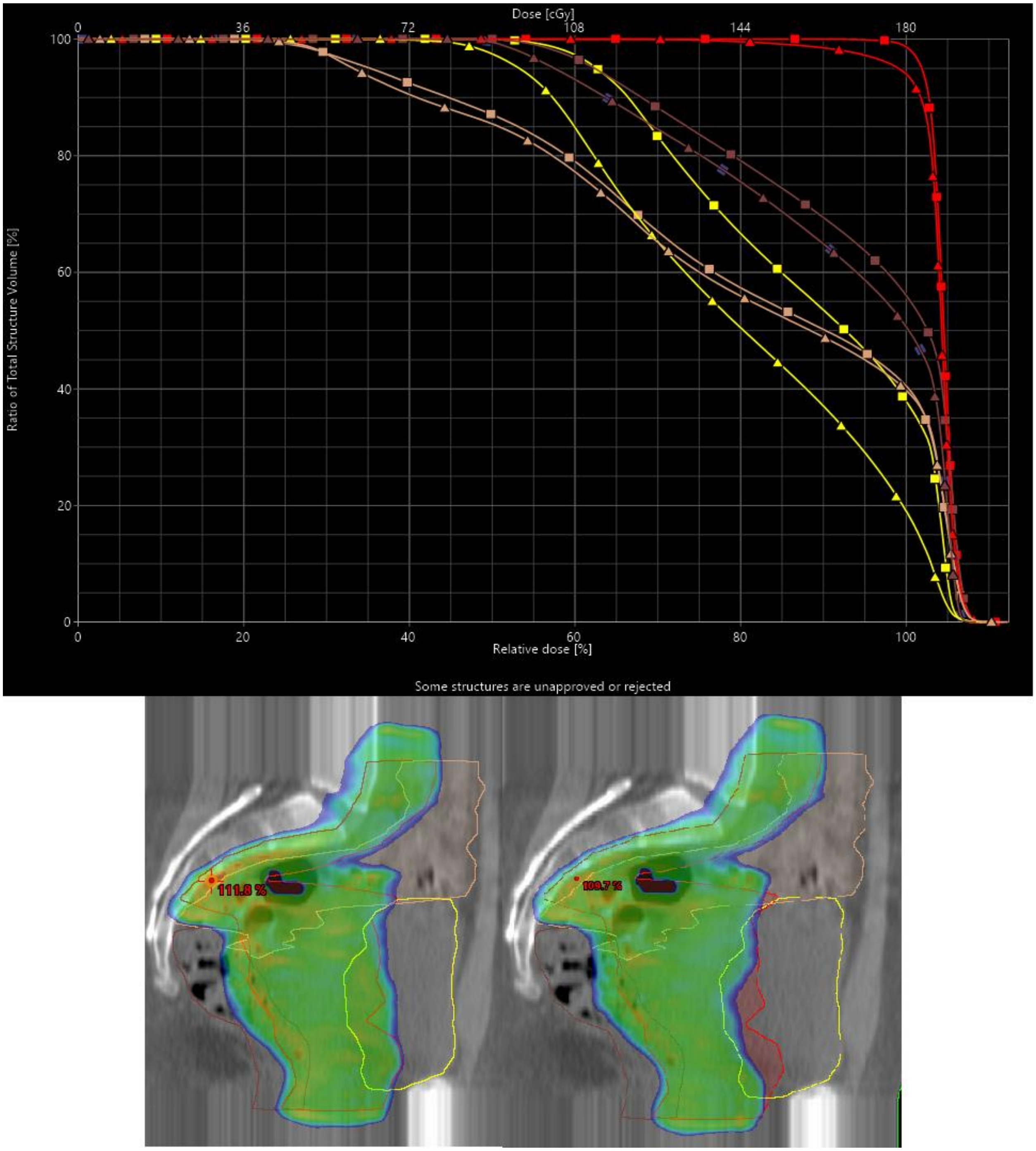


Figure 18. Fraction 3. Full plan selected.

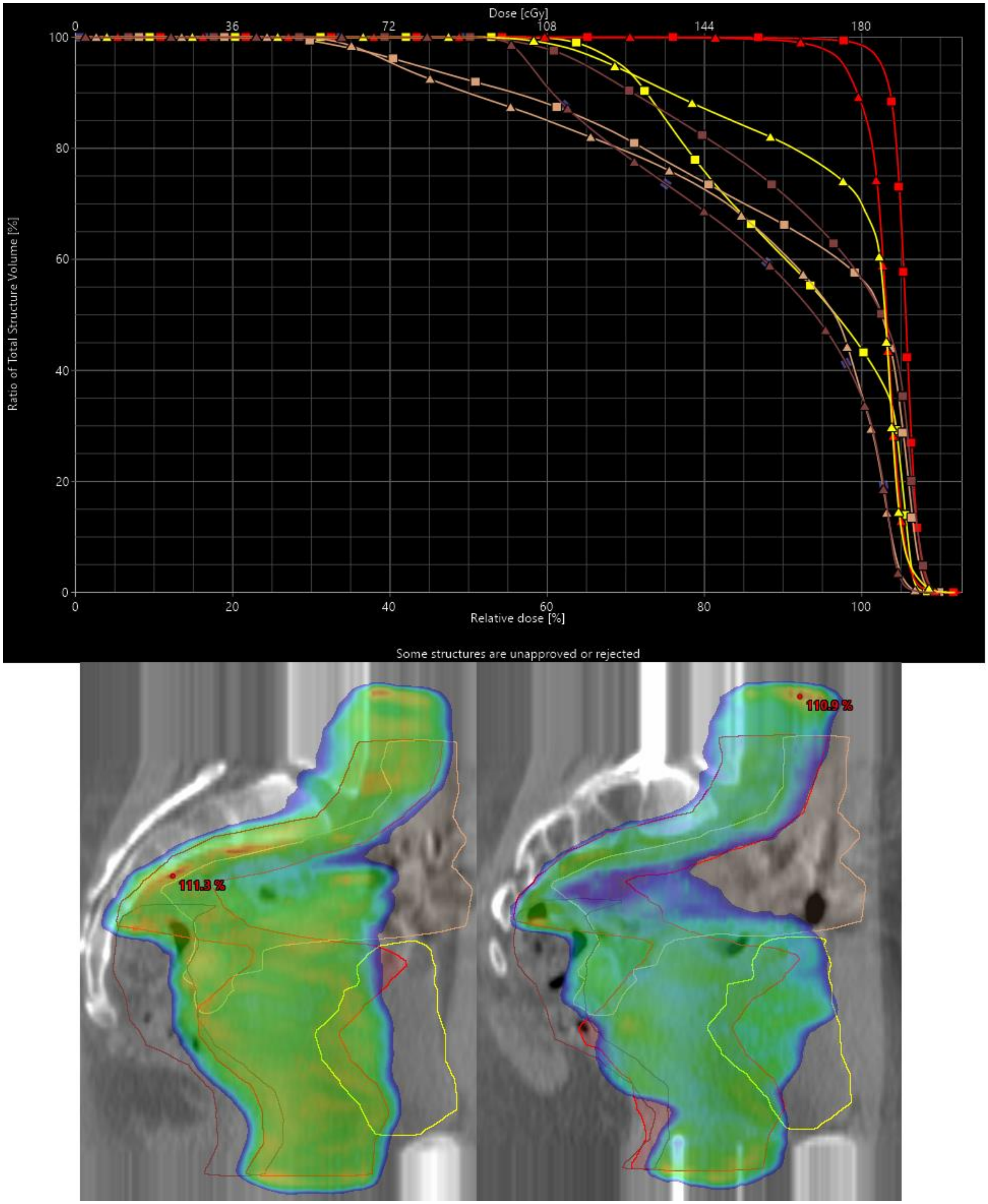


Figure 19. Fraction 4. Empty plan selected.

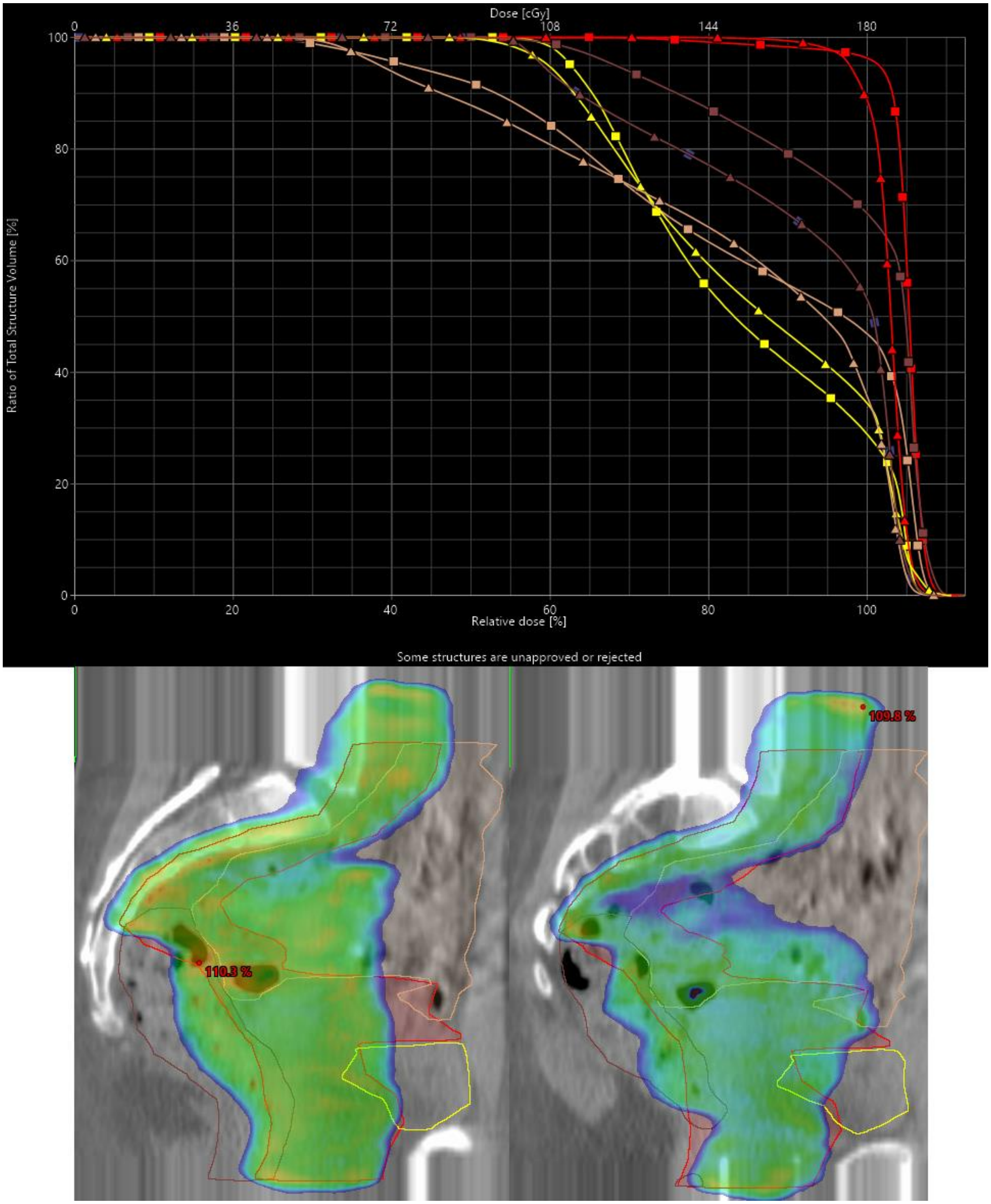


Figure 20. Fraction 5. Empty plan selected.

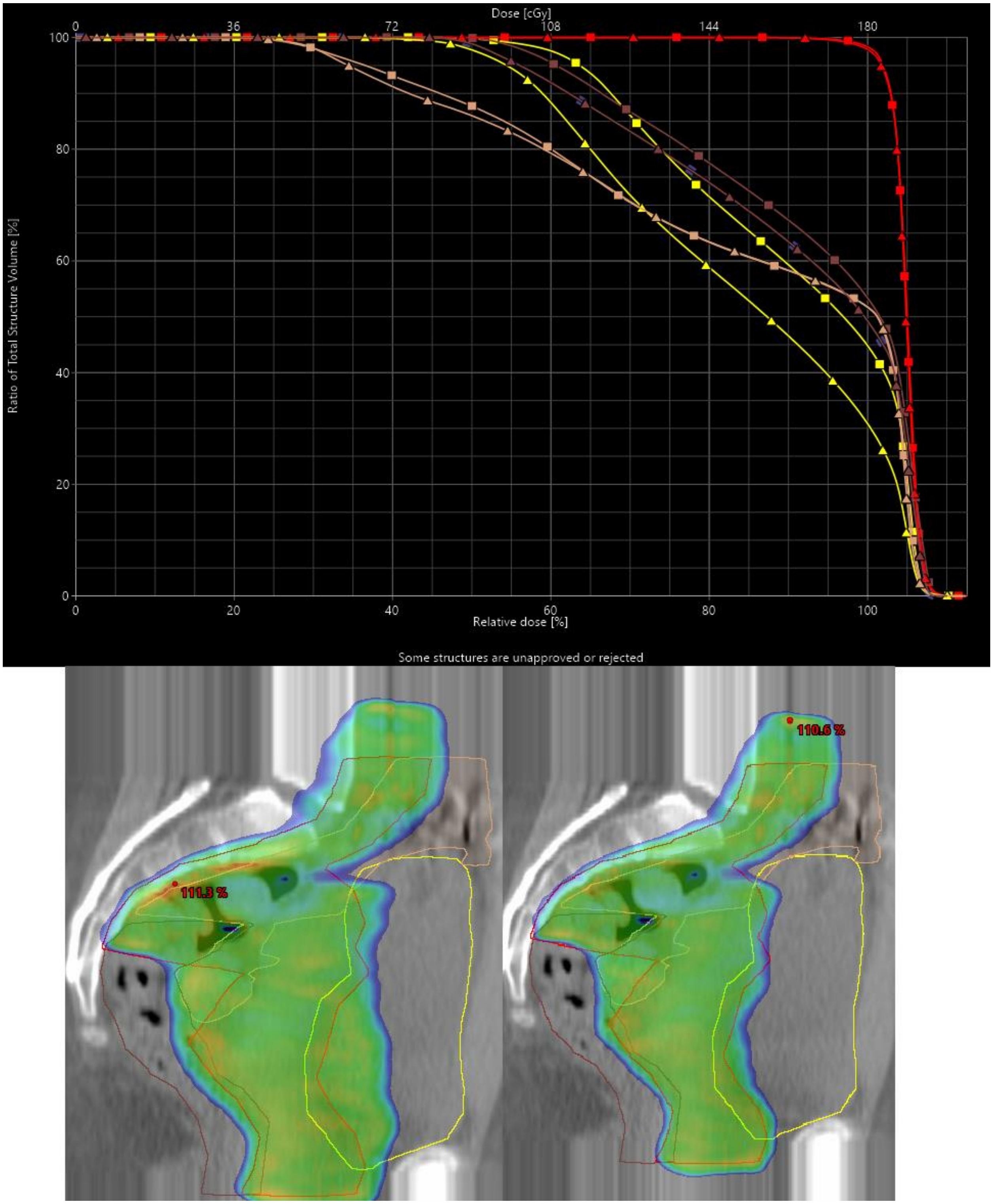


Figure 21. Fraction 6. Full plan selected.

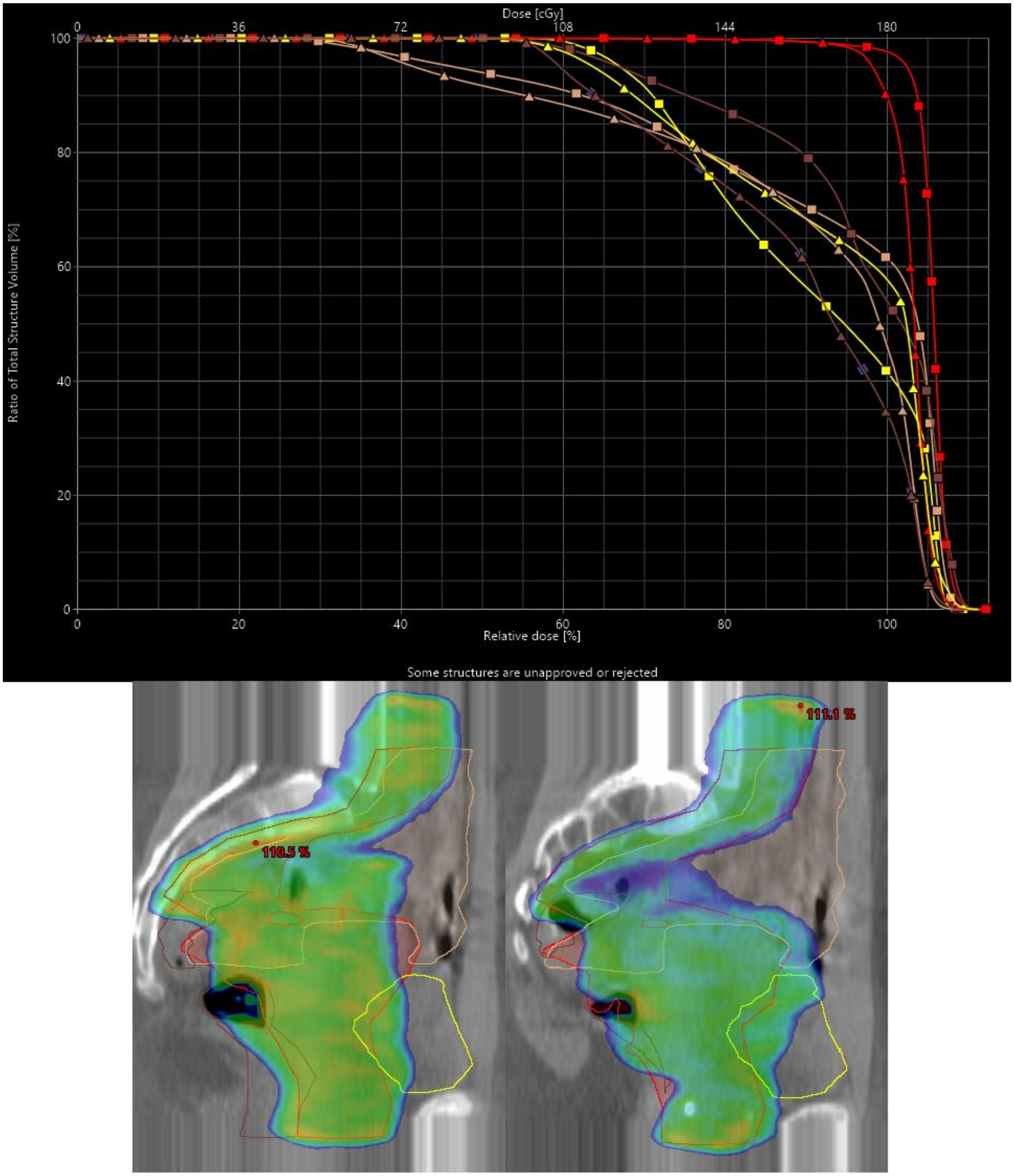


Figure 22. Fraction 7. Empty plan selected.

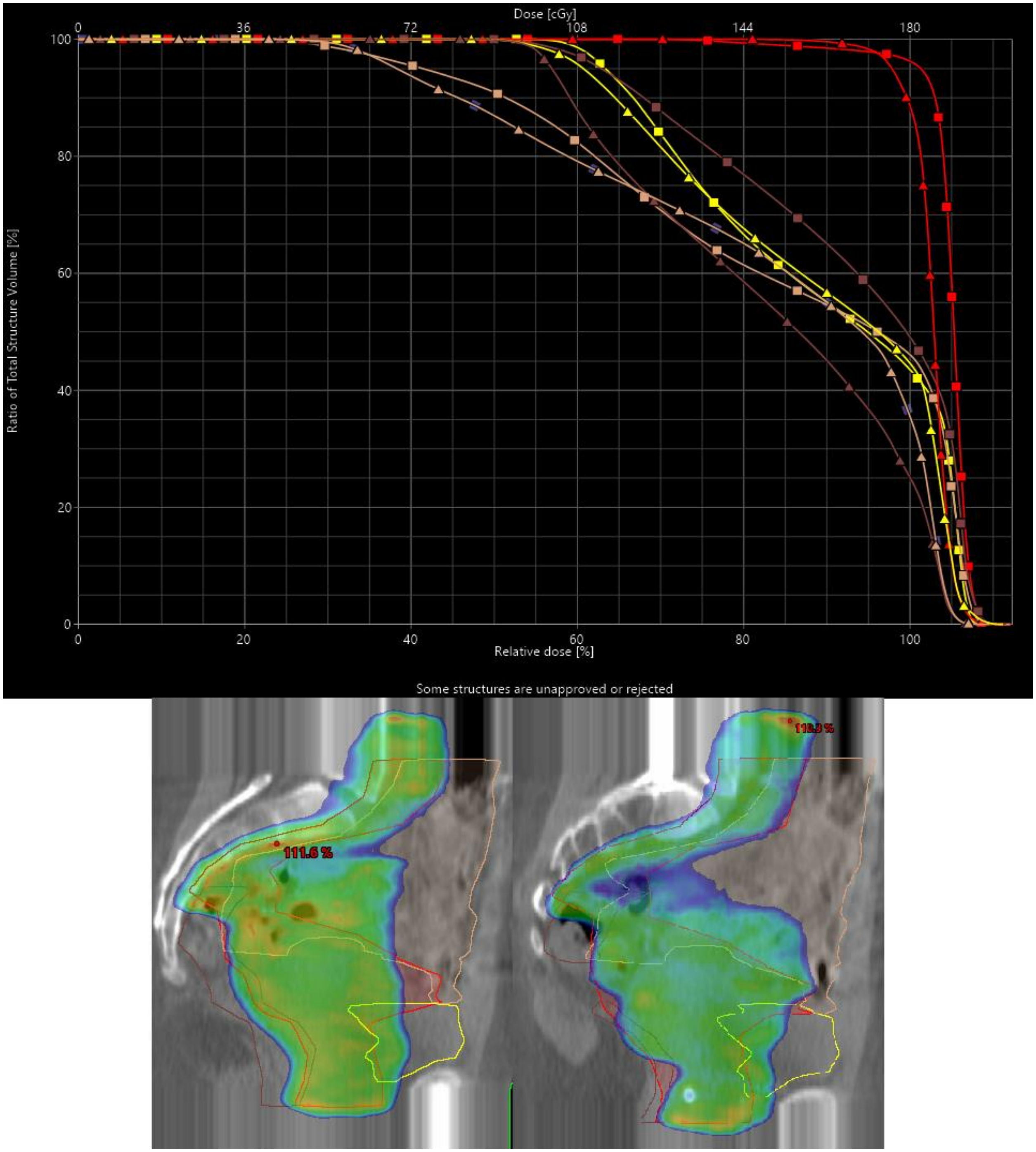


Figure 23. Fraction 8. Empty plan selected.

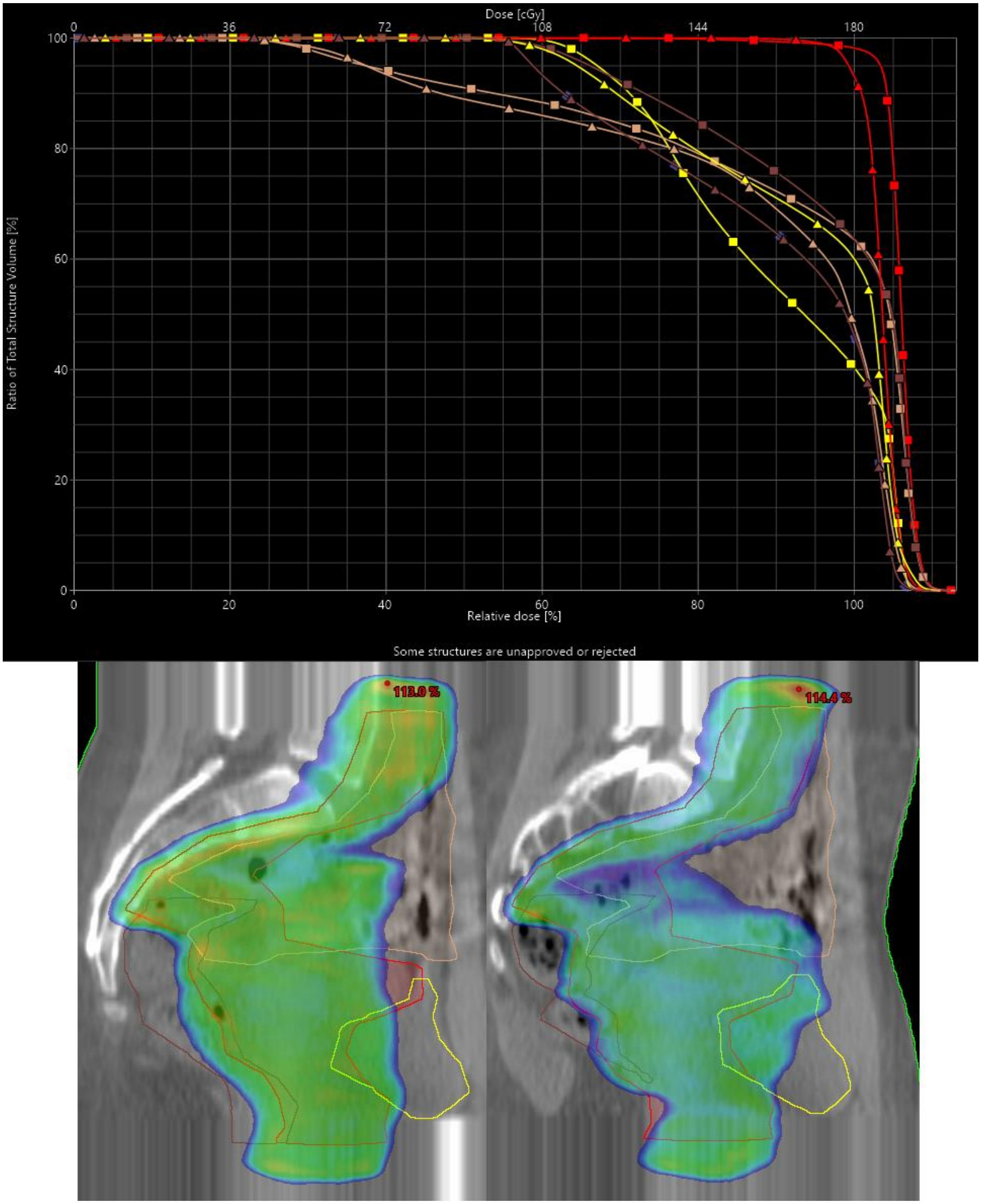


Figure 24. Fraction 9. Empty plan selected.

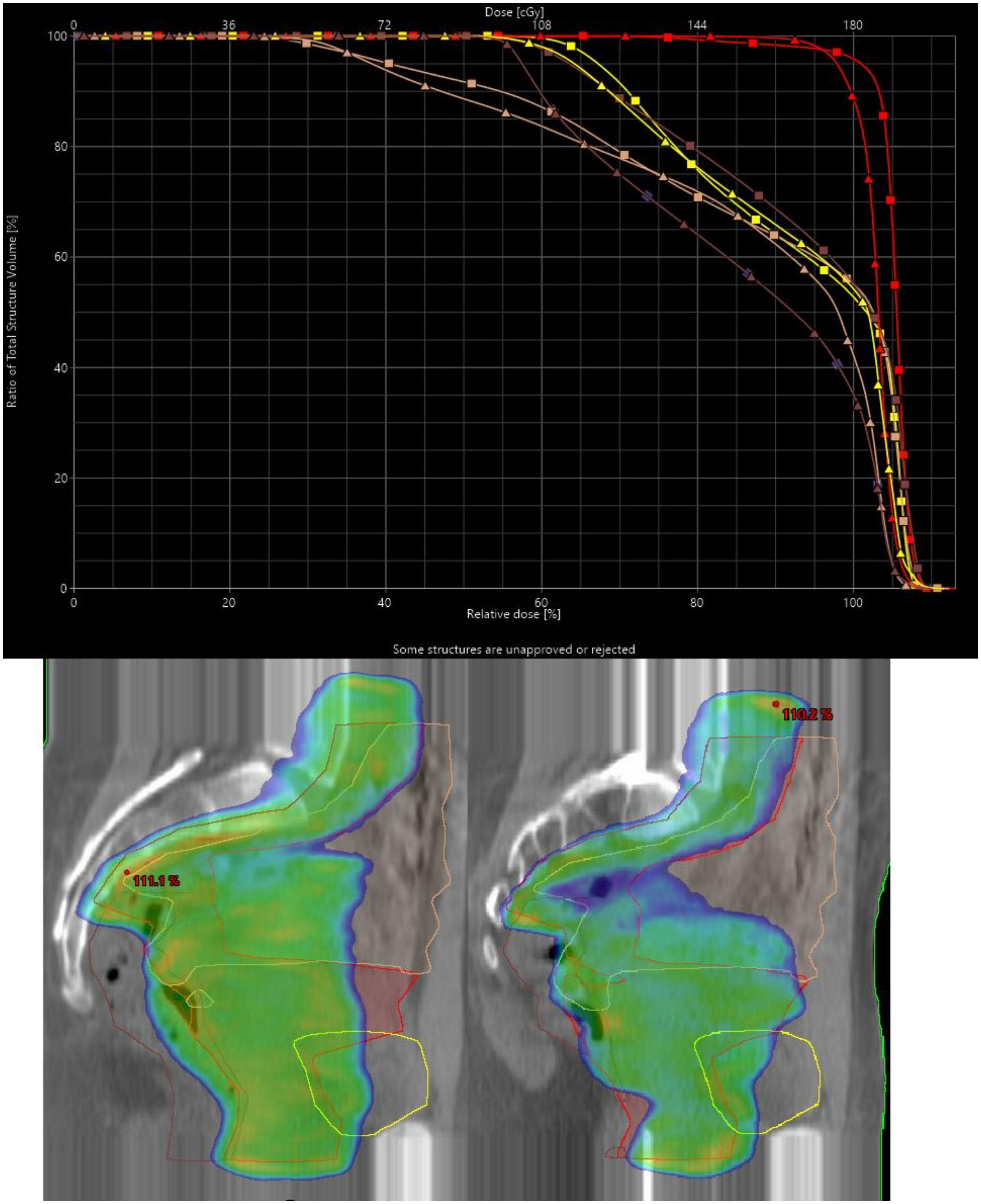


Figure 25. Fraction 10. Empty plan selected.

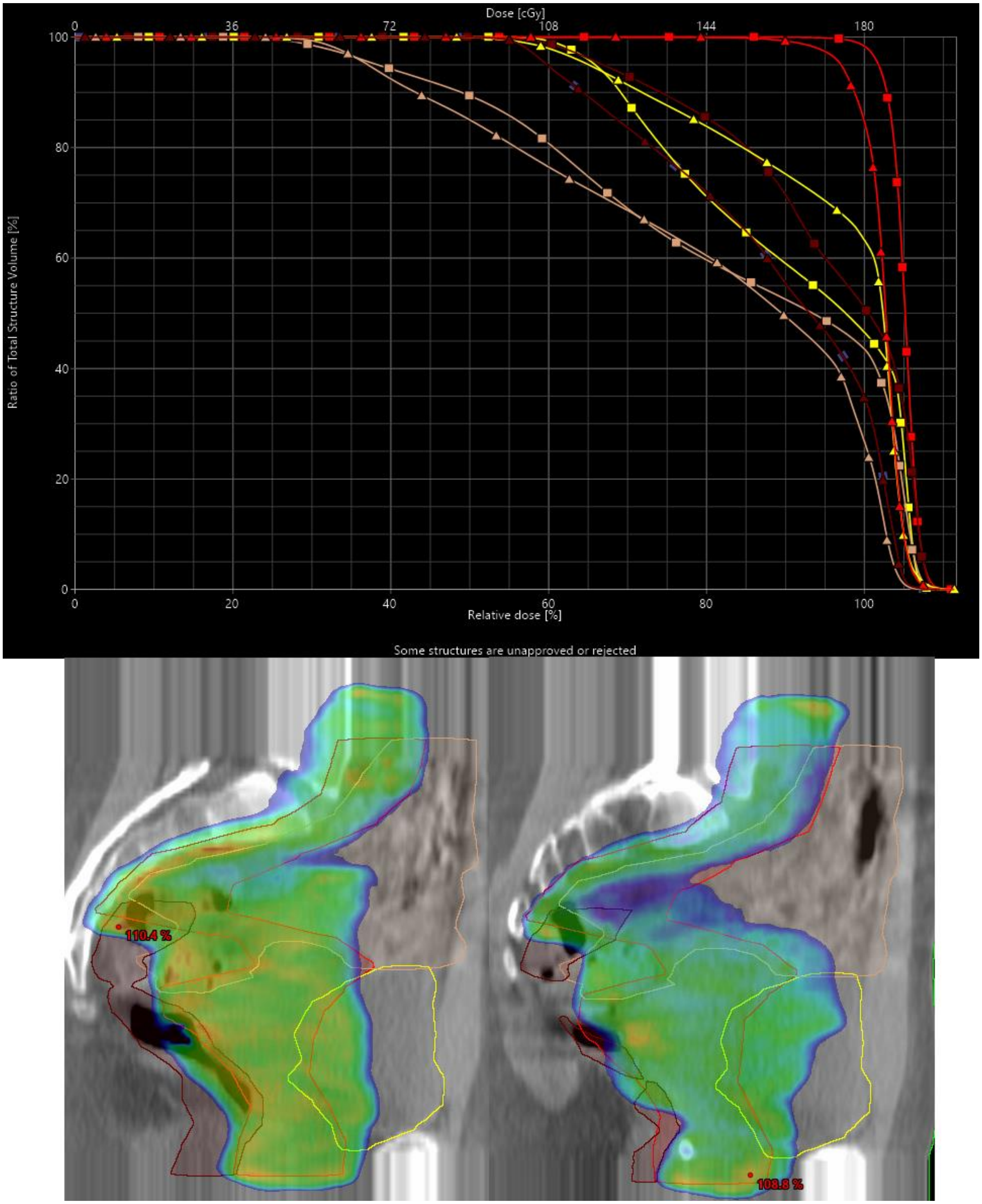


Figure 26. Fraction 11. Empty plan selected.

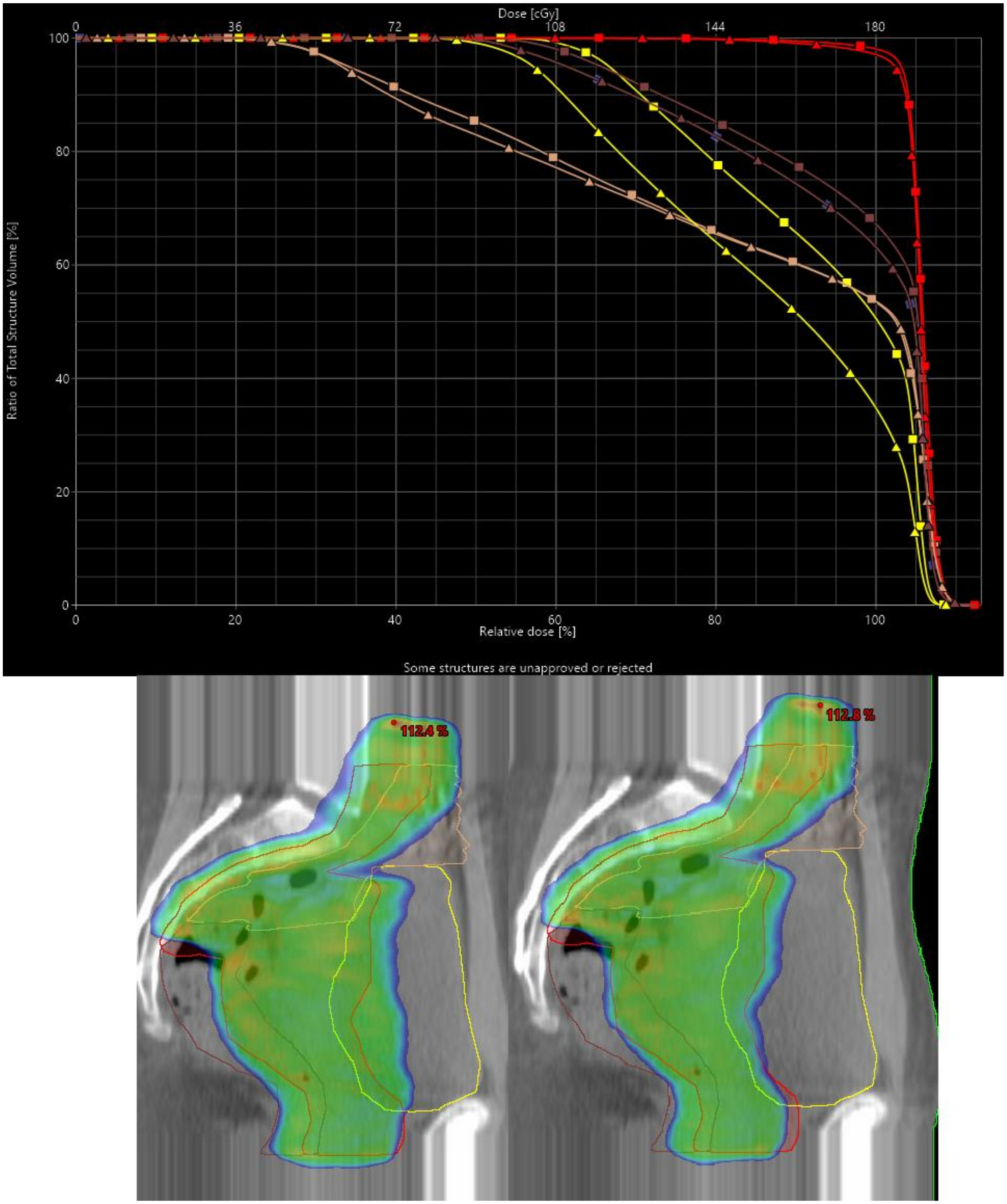


Figure 27. Fraction 12. Full plan selected.

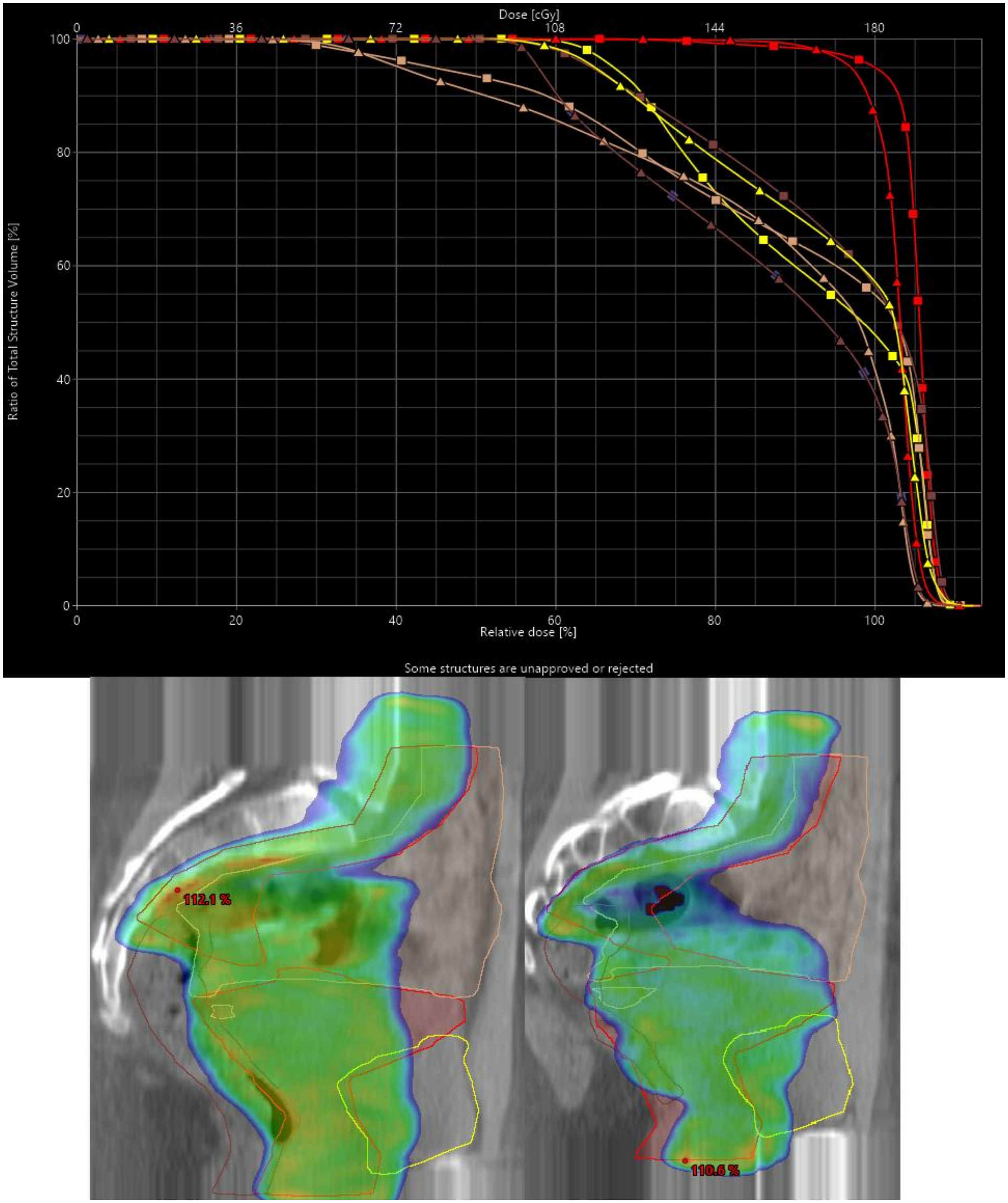


Figure 28. Fraction 13. Empty plan selected.

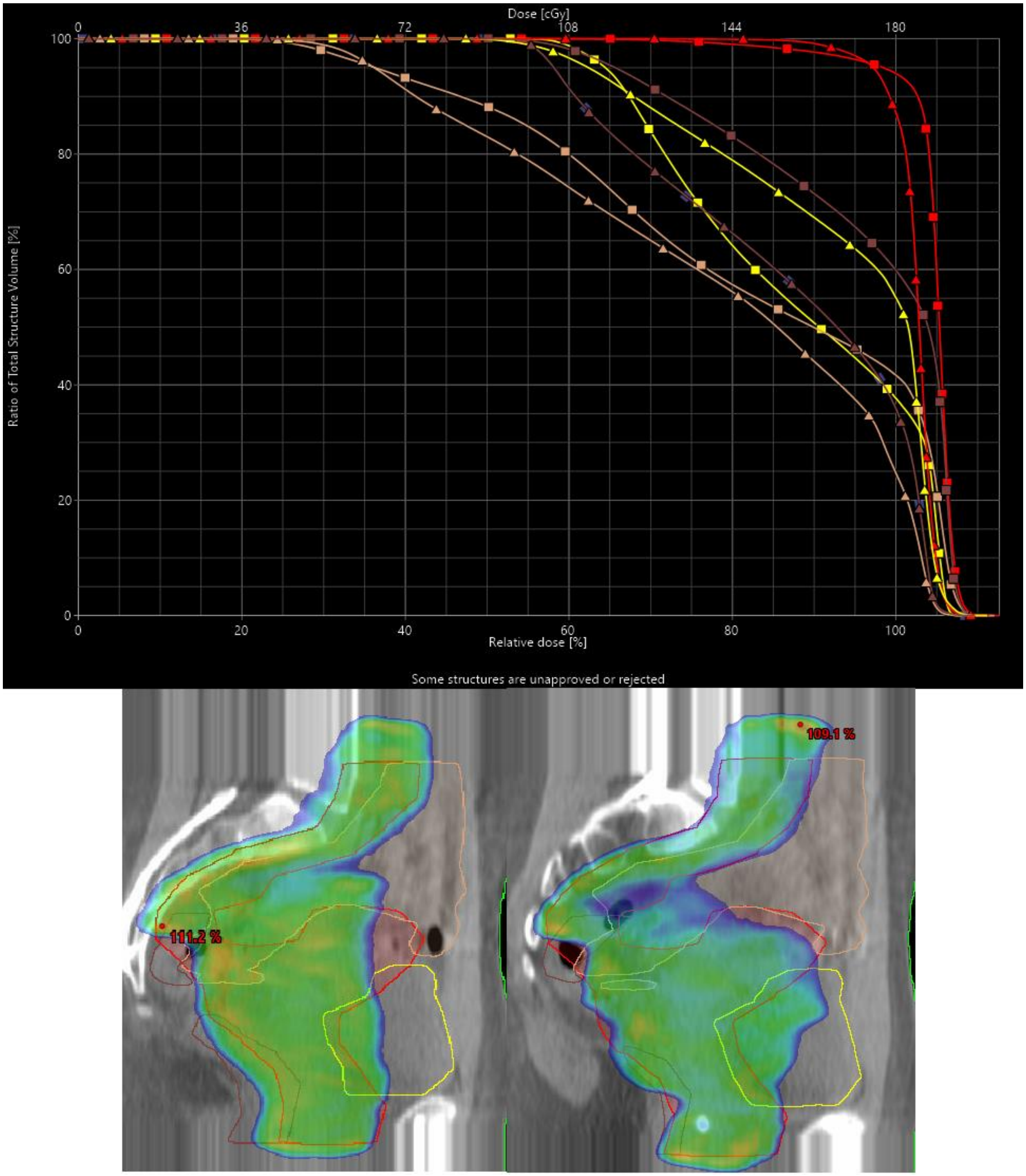


Figure 29. Fraction 14. Empty plan selected.

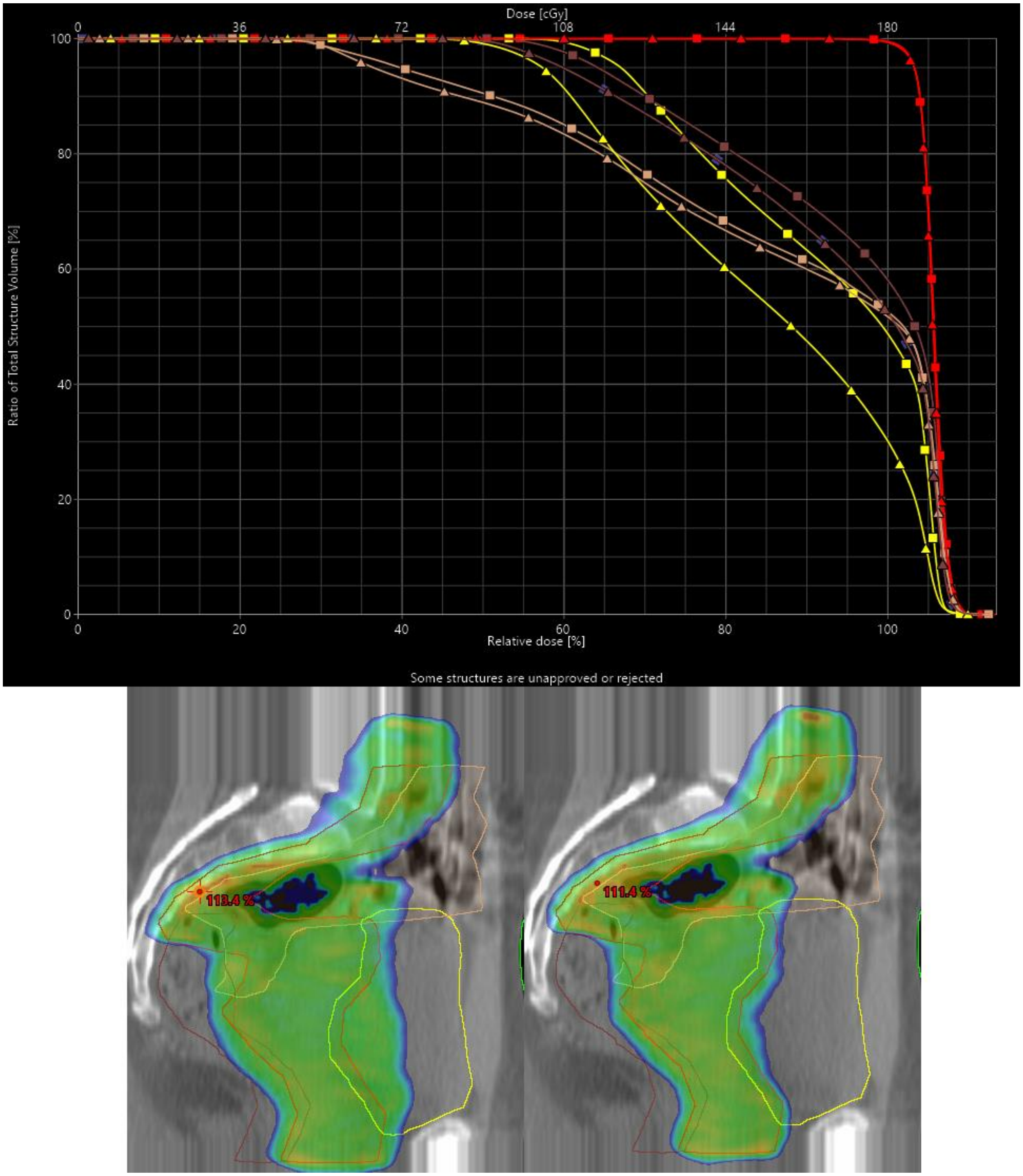


Figure 30. Fraction 15. Full plan selected.

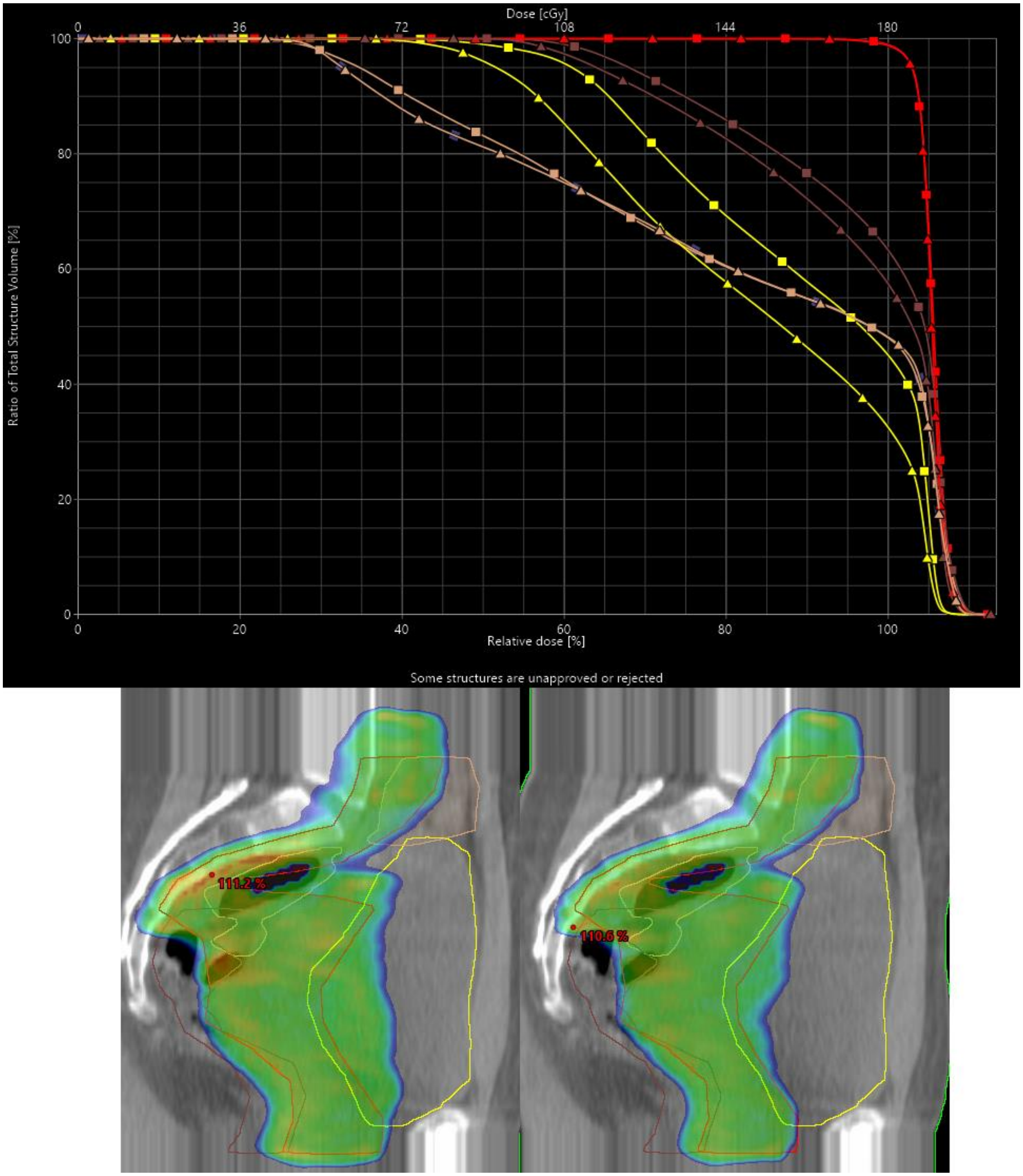


Figure 31. Fraction 16. Full plan selected.

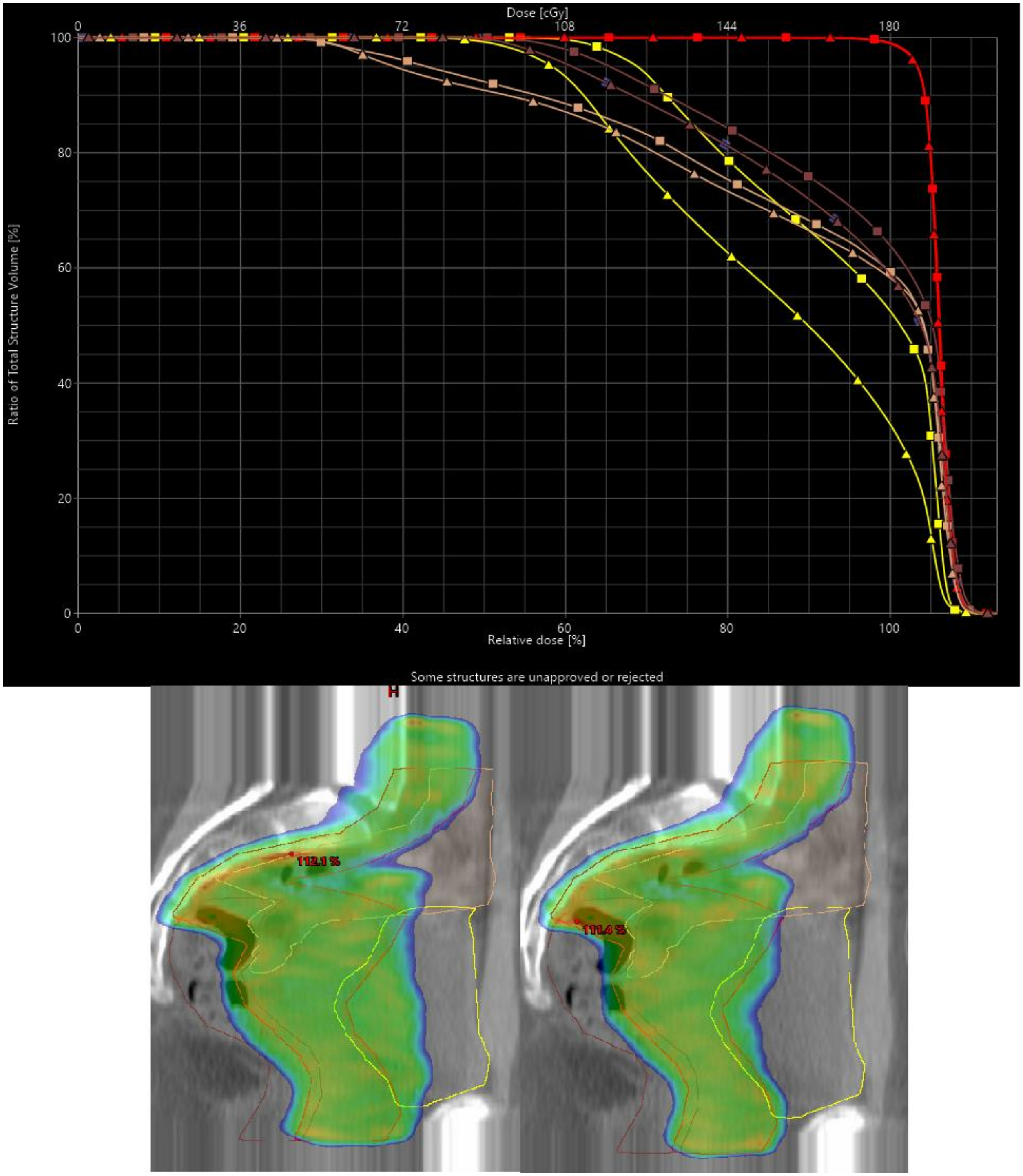


Figure 32. Fraction 17. Full plan selected.

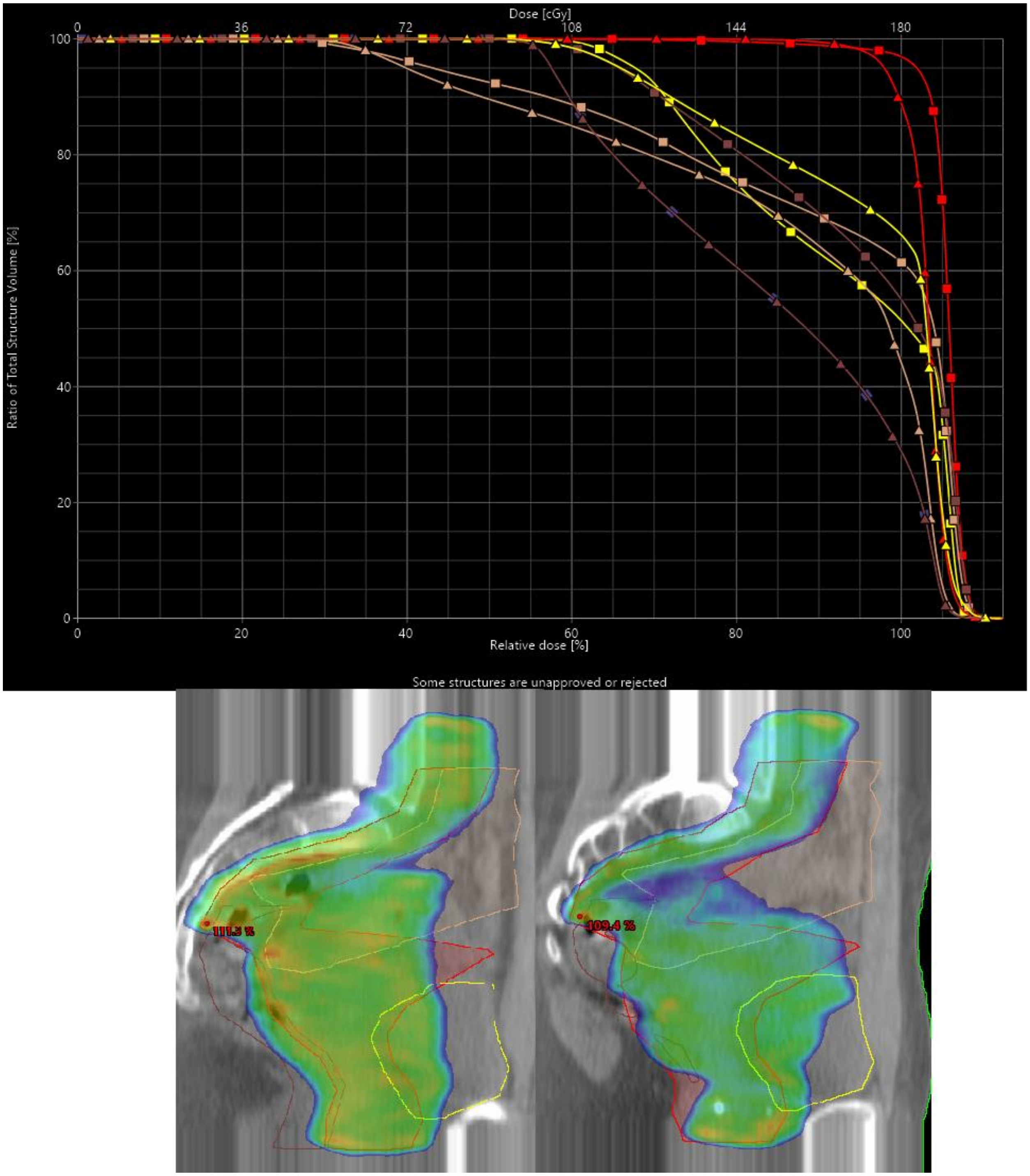


Figure 33. Fraction 18. Empty plan selected.

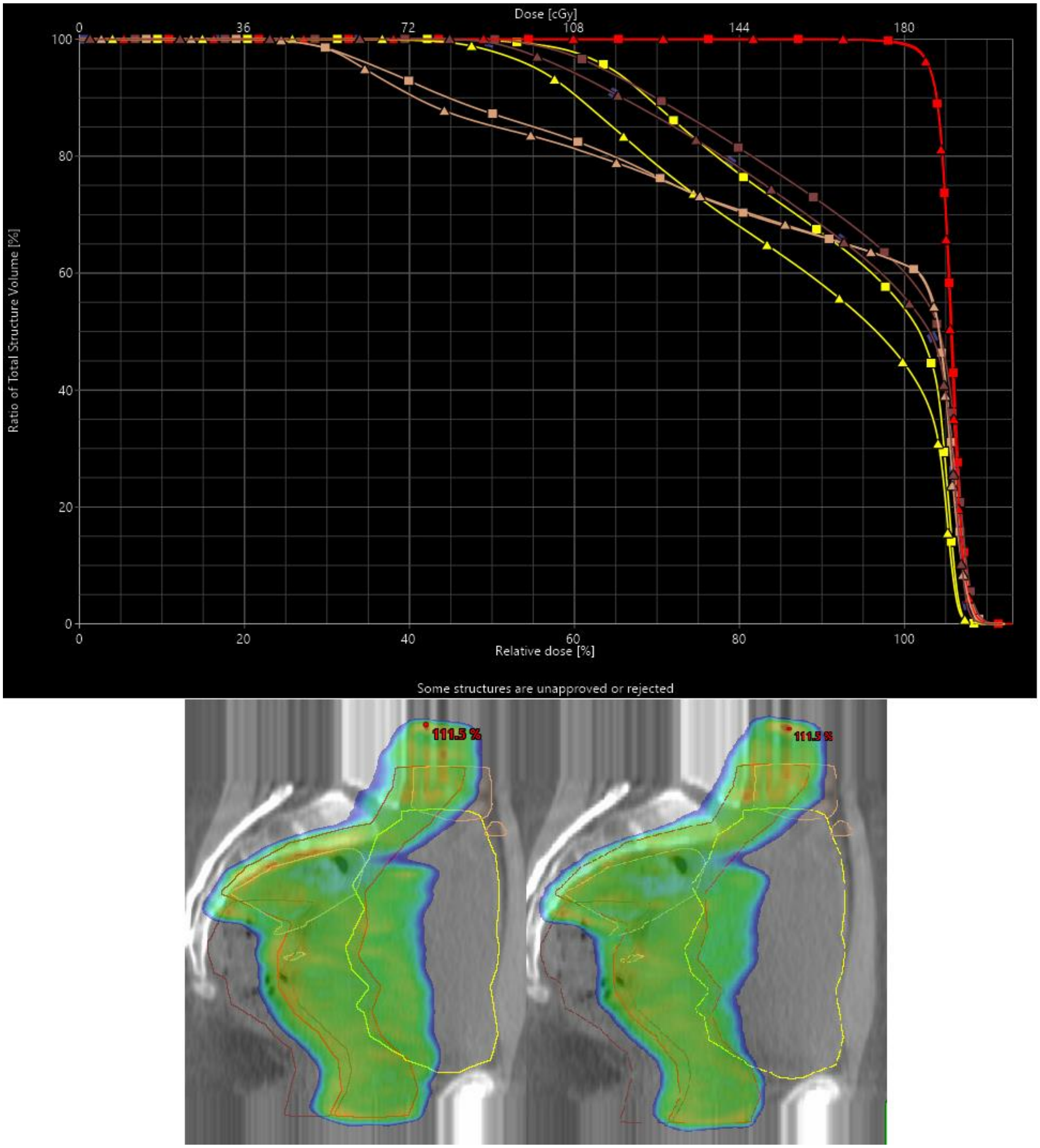


Figure 34. Fraction 19. Full plan selected.

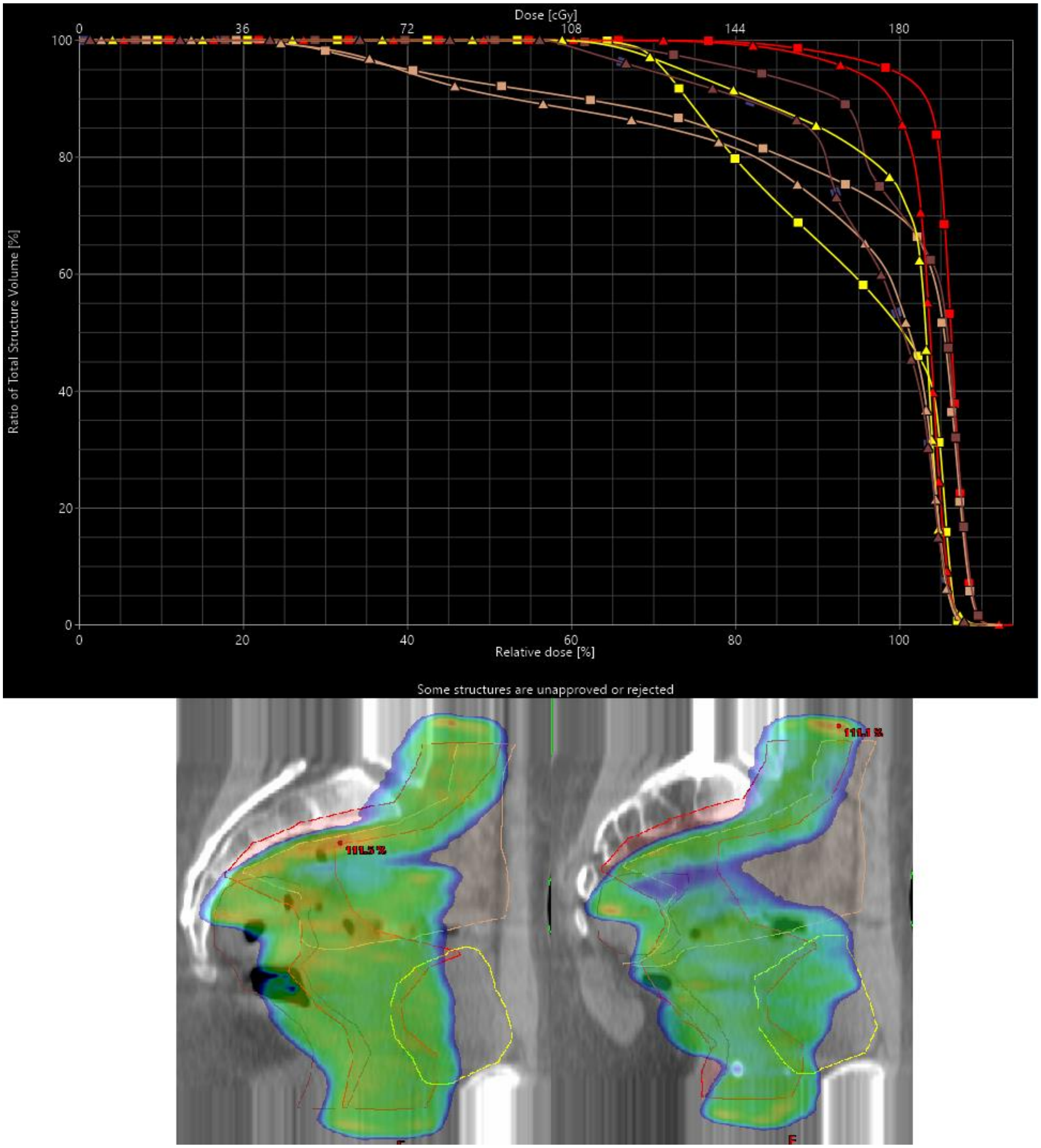


Figure 35. Fraction 20. Empty plan selected.

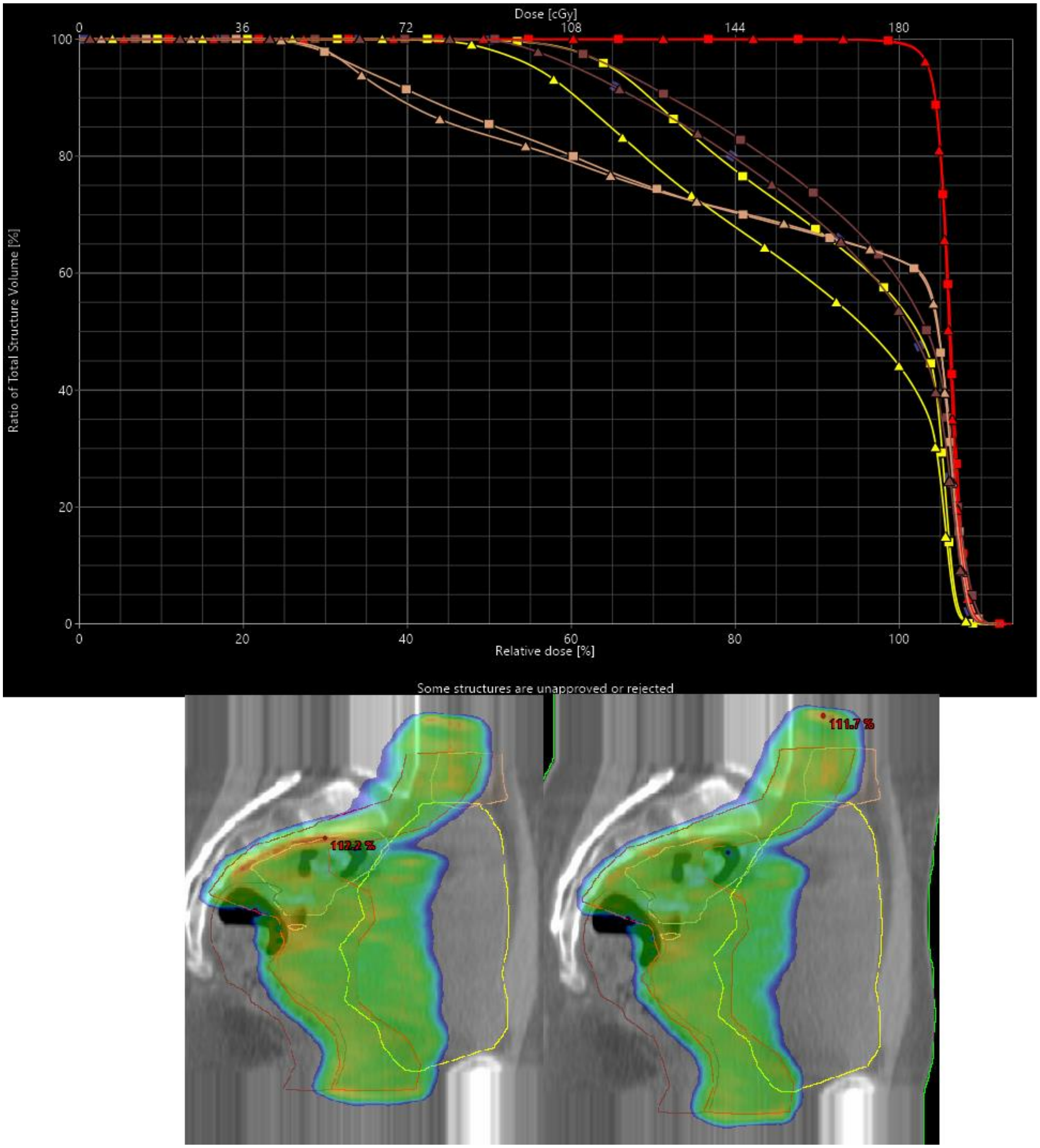


Figure 36. Fraction 21. Full plan selected.

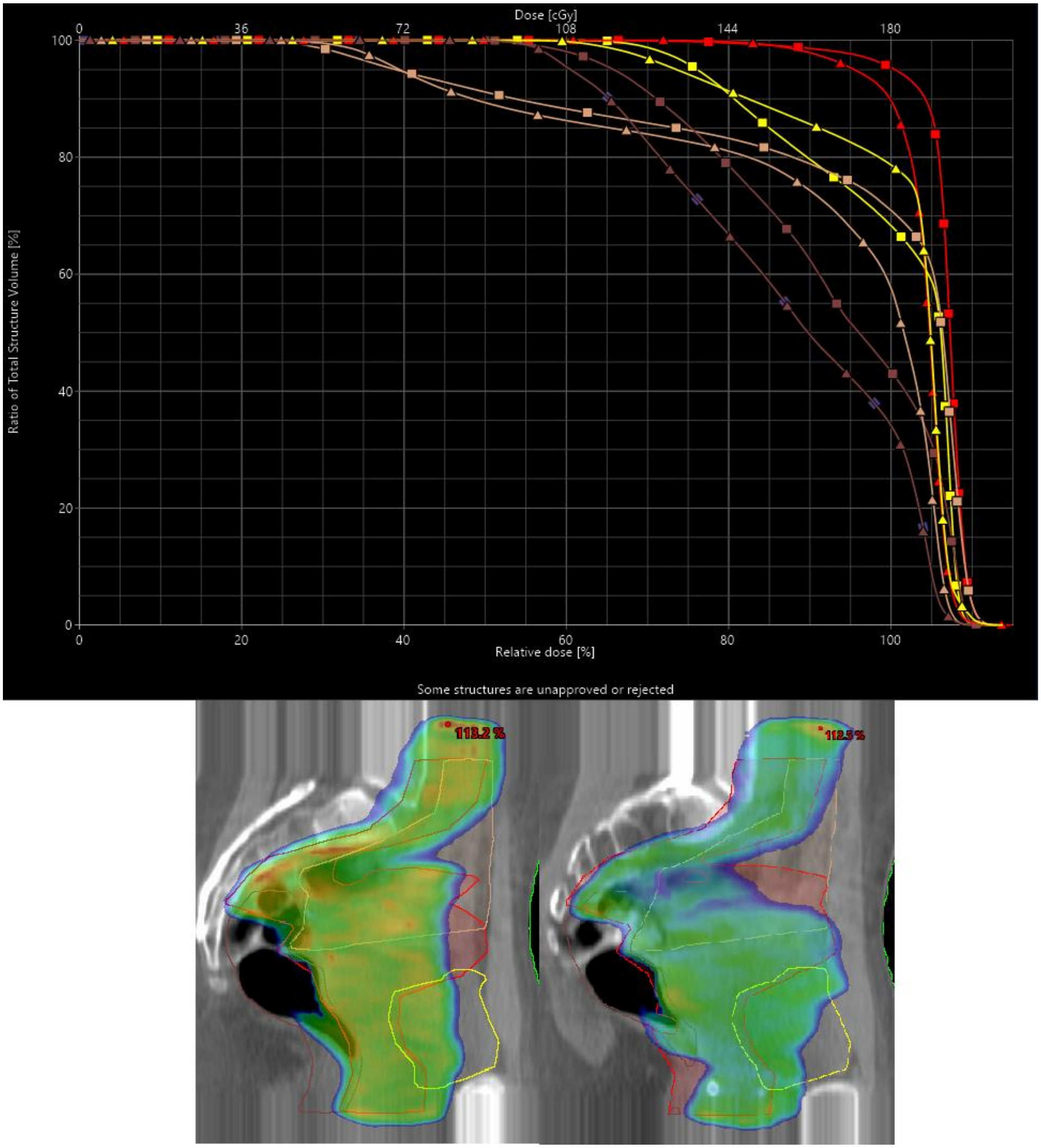


Figure 37. Fraction 22. Empty plan selected.

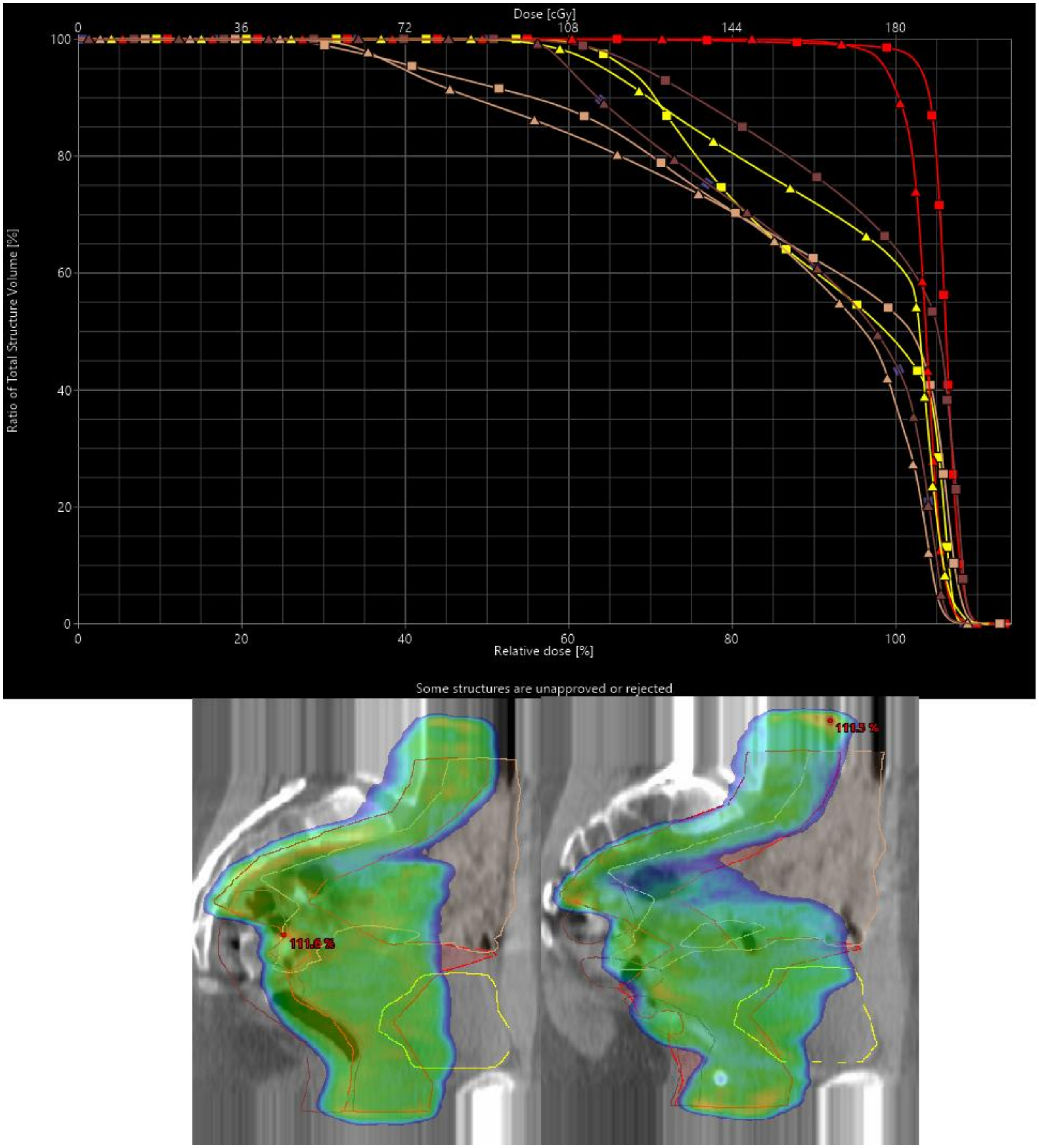


Figure 38. Fraction 23. Empty plan selected.

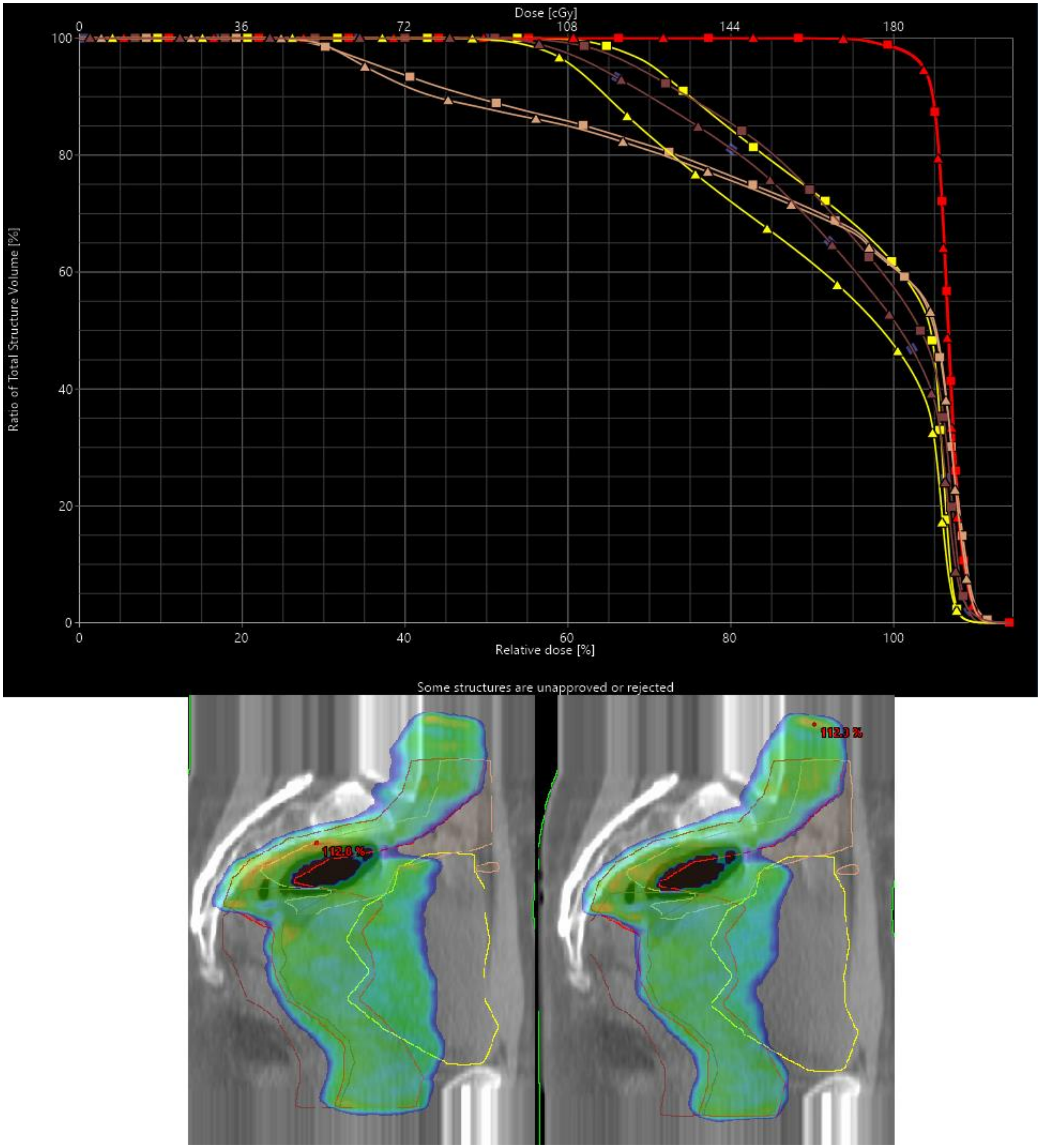


Figure 39. Fraction 24. Full plan selected.

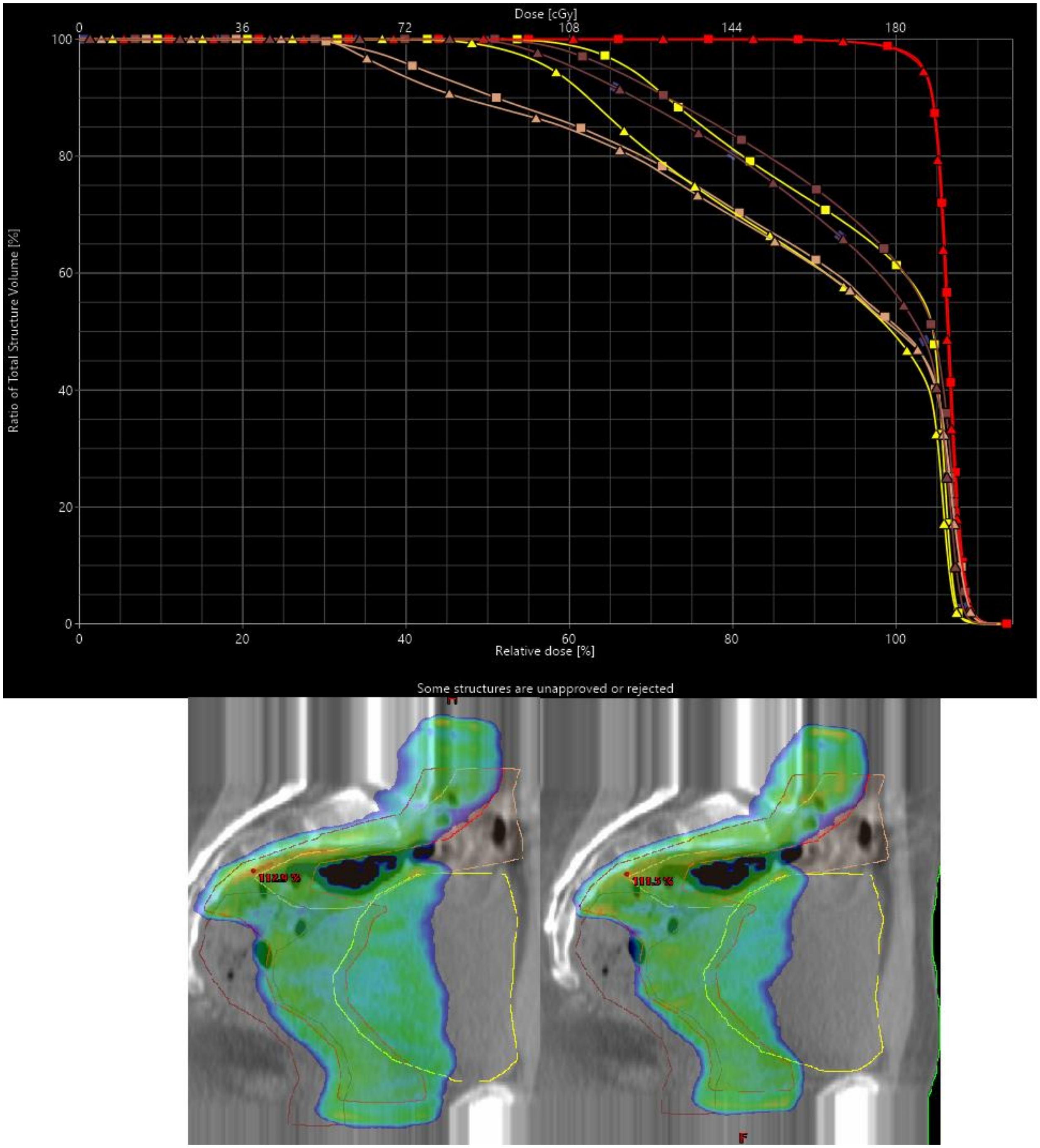


Figure 40. Fraction 25. Full plan selected.

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