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A quantitative investigation at dose to tissue when using physical constraints versus biological based constraints in pancreatic carcinoma patients

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Abstract

Introduction

The purpose of this study was to compare dose to organs at risk as well as PTV coverage. Physical objectives, biological objectives, and a combination of the two were utilized to compare which technique provided the best coverage of the PTV while also preserving the greatest amount of healthy tissue.

Methods

Each randomly selected patient had three separate plans created for them. The first plan used only physical based constraints in the form of upper objectives. The second plan used only biological based constraints in the form of gEUD objectives. The third plan used a combination of both upper and gEUD based objectives.

Results

Results indicate a there was a difference to plan quality when using both uppers and gEUD based objectives. In regard to organs at risk, a physical upper constraint of 0% of the organ volume receiving a maximum dose, as well as a gEUD constraint with an alpha value of 1 provided the most optimal plans. A low priority value on the gEUD (60-70) in conjunction with the upper value provided a gentle, yet effective way to control dose to nearby organs at risk without resulting in suboptimal dose to planning target volume.

Conclusion

A combination of upper values and gEUD objectives provided lowest dose to organs at risk while maintaining a desired dose to PTV coverage. For further success, it was recommended that the organs at risk be cropped out of the PTV in order do provide the lowest dose as reasonably achievable in that organ, while not influencing coverage of the PTV itself.

Introduction

In the year 2021, the American Cancer Society estimates that 60,430 new cases of pancreatic cancer will be diagnosed[1]. Out of these newly diagnosed patients, the predicted deaths from this malignancy are projected to be nearly 48,220 representing an unfavorable prognosis[1]. Pancreatic cancer accounts for 2-3% of all cancers in the United States today[1]. It occurs more frequently in men than women with the average age ranging from 50-80 years old[2].

Risk Factors

Certain risk factors attributable to pancreatic carcinoma include cigarette smoking which is thought to cause 20% of cases[2]. Other risk factors include exposure to chemicals, chronic pancreatitis, certain types of familial breast cancer, colorectal cancer as well as family history of pancreatitis[2]. Diets rich in fat, red and processed meats, lack of physical activity as well as obesity have also been found to increase the risk of this diagnosis[2]. Those with type 2 diabetes are at a higher risk for pancreatic cancer as well[1].

Anatomy

The pancreas lies across the upper abdomen and posterior to the stomach at the vertebral levels of L1-L2[3]. It is divided into three areas including the head, body and tail[2]. The head resides in the C shaped loop of the duodenum which is the first segment of the small bowel[2]. The body of the pancreas sits posterior to the stomach while the tail hugs the hilum of the spleen[2].

Treatment Information

Surgery is the optimal treatment for pancreatic cancer[2]. Although at presentation most tumors are unresectable due to local invasion of critical structures such as the small bowel, stomach and colon leaving radiation therapy as a viable option[2]. If surgery is possible, the Whipple procedure is the most commonly performed[2].

Radiation in conjunction with chemotherapy is the main stay of treatment for patients who present with locally advanced, unresectable tumors[2]. High doses of radiation to the tumor bed and target volume may contribute to an increase in survival rates and local control of the disease[2].

One technique used to deliver adequate dose to the PTV is conformal 3D treatment planning often called 3DCT[2]. This is a traditional approach in which dose conformality around the target volume is achieved by the use of a combination of static beams (4-6) which enter at unique angles[2].

A technique gaining popularity is intensity modulated radiation therapy (IMRT) or volumetric arc therapy (VMAT). In this technique, the beam intensity and field shape is modulated with the use of multileaf collimators (MLC's) [2]. These MLCs act as individual leaves that shape the field helping deliver dose to the PTV and spare the surrounding OARs of unnecessary dose. The advantage of IMRT/VMAT over 3DCRT is a reduction in dose to nearby OARs such as the kidneys, bowel and liver and a more conformal dose distribution surrounding the PTV through the use of optimization techniques.

Optimization

When using an IMRT/VMAT planning technique, optimization is required to modulate dose to tissue. The goal is to achieve a high likelihood of local tumor control termed tumor control probability (TCP), as well as a decreased risk of normal tissue complication often referred to as NTCP[6]. Objectives are utilized in the optimization of treatment planning to specify acceptable dose to various anatomical structures. These objectives can be used in many different combinations to obtain a treatment plan with optimal dose to the planning target volume as well as the nearby organs at risk. Reduced dose to organs at risk decreases the likelihood of later complications in functionality of the structure.

Physical Optimization

Physical optimization is DVH based in which dose constraints are outlined with the tolerance doses defined by QUANTEC. With the use of functions termed uppers and lowers, the treatment planner can set maximum and minimum dose constraints to the PTV and OARs. For example, an upper constraint tells the TPS the 0% of the GTV can receive no more than 105% of the total dose. A lower constraint tells the TPS that 100% of the PTV must receive at least 95%100% of the total treatment dose. Mean dose to the structure is an additional parameter that may be set in the optimizer. A priority value is also utilized to tell the optimizer how hard to work on a given objective set by the treatment planner.

Biological Optimization

Biological optimization differs from physical optimization in that gEUD parameters are utilized in place of upper constraints. The Varian Eclipse treatment planning software (TPS) database describes the gEUD as “the uniform dose distribution that gives a biological effect

equivalent to that of a given heterogeneous dose distribution" [7]. This technique aims to provide the same type of tumor response achieved by physical constraints, while at the same time attempting to lower the dose that healthy tissue receives from ionizing radiation.

Literature Review

A comparable study was performed by Dirscherl et al. regarding physical versus biologic optimization in prostate cancer planning[8]. Plans were compared using physical dose volume objectives on one plan and only biologic based constraints on the other[8]. Beam angles, number of beams as well as dose all remained the same[8]. Results show a "small and negative value" resulted in a plan with inhomogeneity of dose as well as hot and cold spots withing the TV[8]. Sparing of OARs proved more favorable with use of gEUD although dose to the PTV decreased[8]. The study proved bladder and rectum sparing greatly depend on the α value used.

Sakthivel et al. also compared this technique in 10 treatment plans in the case of hypopharyngeal tumors[9]. All parameters were kept the same besides optimization techniques and values[9]. The results show comparable plan quality regarding dose to the PTV although the biological based optimization plan revealed greater OAR sparing for serial structures (in this case the brainstem and spinal cord) [9]. The physical based optimization plan showed better OAR sparing for parallel structures such as the parotid glands[9]. The overall treatment time was also more favorable in the biological based optimization plan[9]. Although, the research proved further investigation into the variety of α values available is needed to obtain greater understanding of how to secure the greatest amount of OAR sparing[9].

D Mihailidis et al. investigated which plan proved superior in regard to head and neck planning as well as chest wall treatment plans when using gEUD versus DVH based

constraints[10]. 10 plans were compared, and the results showed the gEUD based plans allow for an increase of dose sparing to OARs while the PTV coverage remained optimal[10]. The ipsilateral lung V20 was reduced from 22% to 18% for the gEUD plan[10]. This shows a 1.2% improvement for dose to lung volume. Dose to all OARs decreased, even below the constraint recommendation[10].

Dogan similarly compared head and neck plans using Pinnacle. Physical DVH based objectives were used as well as gEUD based objectives[11]. The gEUD based plan resulted in reduced spinal cord dose by 55%, 14% reduction in brainstem dose as well as a 35% reduction in parotid gland dose[11]. Dogan utilized various α values (1, 5, 10) and in doing so noticed an increase in monitor units (MU) by 12%, 19%, and 21% [11].

Fogliata et al. analyzed the performance and effectiveness of gEUD parameters in OAR sparing in the photon optimizer (PO) of the Varian Eclipse TPS[12]. The treatment plans included head and neck, prostate, rectum and one parotid carcinoma plan[12]. The OARs were placed at variable distances (4mm, 1 cm, 2 cm) and cropped (0mm, 2mm, 4mm) from the target and evaluated[12]. The α value was varied from 1-40 to assess the effectiveness of said variable[12]. The findings revealed a reduction in OAR dose when the OAR was within 1-2 cm distance from the TV along with an increase in α values[12]. The ideal α value was dependent upon the distance from the target as well as seriality of the OAR[12]. The α parameters in the conjunction with OAR sparing needs to be investigated further[12].

Purpose of Study

While research has been performed comparing biologic and physical based optimization strategies, there has yet to be a quantitative study on how varying α values (1 and

40) within the biologic optimization compares to physical based DVH optimization. This research aims to provide a quantitative investigation into the PTV coverage as well as dose at various volumes when using physical versus biological optimization strategies with a variation in α parameters. A question that remains unanswered is does a physical or biological based optimization strategy provide a more favorable quality plan in regard to PTV coverage and OAR dose in pancreatic treatment plans. A hypothesis that may be assumed from prior research is that the use of gEUD will provide a more favorable dose to critical structures than physical based objectives.

Methods and Materials

Patient Selection

This was a retrospective study of 15 male and female patients previously treated for locally advanced pancreatic carcinoma. These patients were treated using a volumetric modulated arc therapy (VMAT) technique at the Memorial Sloan Kettering Cancer Center. The patients were chosen at random using the Cancer Imaging Archive (TCIA) which de-identified patient information and hosts cancer imaging data online.

The researcher submitted a research determination form to the Office of Research Compliance & Integrity. It was determined that the project did not meet the definition of human subjects due to the fact that no private or identifiable information had been utilized. Therefore, it did not meet the federal definition of human subjects and subsequently IRB oversight was not needed.

Simulation

A common technique was utilized to simulate the patient in the supine position with the arms above the head with the help of a wing board. This ensured the arms were out of the treatment field and the wing board aided in reproducibility of the positioning. Oral contrast may be used to better visualize the duodenum while intravenous contrast can help better delineate the target volume4. Breathing motion can influence the positioning of the pancreas. To account for this the use of 4-dimensional computed tomography (4DCT) was implemented. Tumor and organ motion was visualized on a computer during simulation utilizing this technique. For this study, each patient had one treatment planning CT and two CBCT scans. They were acquired using a deep inspiration breath hold (DIBH) which was then verified by using an external respiratory monitoring device. The planning CT was obtained with a diagnostic quality scanner in helical mode with iodinated contrast.

Planning

A volume of interest (VOI) was drawn on the planning CT and a margin of 1cm was added. This VOI or target volume (TV) includes the gross tumor volume (GTV) which can be described as the gross palpable disease that can be visualized on diagnostic imaging, as well as any lymph nodes suspected of involvement[4]. Also included is the clinical target volume (CTV) which is the GTV in addition to a 1-2 cm margin to account for any possible microscopic disease spread[4]. Further, a planning target volume (PTV) margin is included to account for any uncertainties in patient set up error or patient movement during treatment[4]. This margin can be anywhere from .5 mm if 4DCT is utilized up to 1 cm[4]. The organs at risk (OARs) were delineated by the same physician for continuity purposes including the stomach and small bowel.

The additional OARs were contoured by the same planner, again, for continuities sake. These OARs included large bowel, lungs and kidneys and were reviewed by the researcher.

Each patient was planned utilizing a 2-arc VMAT technique with 6MV beam energy. The full arcs rotated from 181-179 degrees around the patient. The collimator was rotated to encompass the shape of the VOI also termed planning target volume (PTV). A complimentary collimator angle was used for the 2nd arc. Jaw tracking was utilized for each plan. The multileaf collimator (MLC) was fitted to the PTV with a .5cm margin. The PTV was given a dose of 4500 cGy broken down to 180cGy daily in 25 fractions. Each plan was created using the Varian Eclipse Treatment Planning Software with the Photon Optimizer version 15.6.05 and the Anisotropic Analytical Algorithm for all calculations. After all initial setup fields and gantry angles were established, the plan was then copied and pasted to duplicate the exact same parameters for a true comparison.

Three plans were created for each patient. The first plan utilized physical constraints with only upper objectives. The second plan used only biological gEUD constraints with alpha values of 1 and 40. The third plan used a combination of physical and biological constraints.

The physical plan utilized constraints based on certain points on the dose volume histogram (DVH). A lower constraint defined the minimum dose the structure should receive while an upper constraint defined maximum dose the structure can receive. The physical plan had a lower constraint on the PTV of 100% of the structure receiving 4500 cGy with a priority of 125. The upper constraint had 0% of the PTV receiving 105% dose being 4725 cGy with a priority of 125. Two upper constraints were then added to all applicable OARs. The upper constraints were defined at a volume of 0% and 50% of the structure to limit unnecessary dose.

Two upper gEUDs were utilized for the biological plan. The upper gEUD defines the maximum equivalent uniform dose value that a structure (target structure or OAR) may receive[7]. A value of critical importance is referred to as the α value. This value represents the specific area on the DVH the optimizer will focus on regarding dose limits. The α value ranges from -40 to 40[7]. Negative α values will work on the low dose section on the DVH while positive values will focus on the high dose area[7]. The gEUD uppers were given to all applicable OARs. The alpha values used were 1 (aiming to control the mean dose) and 40 (aiming to control max dose). GEUD objectives prove to be very powerful and have a large impact on the dose an organ receives.

The third plan used a combination of the previous two techniques. The optimization values for the PTV remained the same, while the values for the OARs were changed. The OARs had an upper constraint with 0% of the structure receiving no more than the prescription dose if the OAR was located inside the PTV. If the OAR was not inside the PTV the constraint was set to limit the dose as low as reasonably achievable. An upper gEUD with an alpha value of 1 was used to control the mean dose to the structure.

After calculation was completed, the plans were then normalized so that 100% of the dose covered 95% of the structure. This was done to ensure the coverage intended was identical between all 3 treatment planning techniques. The dose volume histogram (DVH) was utilized in evaluating dose to critical structures. There are strict constraints that must be adhered to during the treatment planning process. These constraints limit the amount of dose a structure can receive to decrease the likelihood of long-term complications. The following constraints are summarized by Quantitative Analyses of Normal Tissue Effects in the Clinic (QUANTEC) and Emami et al:

Tolerance of Normal Tissue to Therapeutic Irradiation: for the bilateral whole kidneys a mean dose of less than 1500-1800 cGy to decrease likelihood of renal dysfunction[5]. Specific points on the dose volume histogram (DVH), which provides a plot of target volumes and cumulative dose the structures receive, are of key importance as well[2]. The volume receiving 12 Gy must be less than 55% (V12 <55). Further, V20 <32%, V23 <30%, V28 <20%[5]. The Stomach has a constraint of D100 <45 to avoid ulceration and must receive a max dose of less than 4500 cGy[5]. The liver must receive a mean dose of less than 3000-3200 cGy to decrease the likelihood of classic radiation induced liver disease[5]. The small bowel individual loops V15<120cc, entire potential space within peritoneal cavity V45 <195cc, V50 <5%, with a max dose of less than 5000 cGy to reduce acute toxicity[5]. The spinal cord max dose is 4500 cGy to decrease likelihood of myelopathy[5].

Data Analysis

Statistical analysis was performed by the Grand Valley State University statistic counseling center using the IBM SPSS program, version 24. A one way repeated measures ANOVA test was used for the initial testing. If the results proved to be significant, a post hoc statistical analysis was then performed. A t-test was used to evaluate the difference between three dependent means in the form of matched pairs with an effect size of 0.8. The matched paired t-test is used when the data from three groups can be shown in pairs. Before and after observations can be made on the same subjects. The effect size is the magnitude of the difference between groups. The assumptions that must be met to use this test require the dependent variable must be continuous, the observations must be independent of each other, the dependent variable must be normally distributed and should not contain any outliers.

Results

This studies research aimed to provide a look at dose to multiple structures. PTV coverage as well as dose to nearby organs at risk were evaluated when using physical, biological, and a combination of both optimization techniques. The plan resulting in the greatest amount of PTV coverage as well as lowest dose to critical organs was of particular interest to the researcher. The results are indicated below.

PTV

The PTV minimum, maximum, and global dose max were evaluated for all 3 plans. The minimum ($F(2.0, 28.0) = 10.9041$, $p = 0.0003$), maximum ($F(2.0, 28.0) = 17.95$, $p = <0.0001$), and global dose max ($F(2.0, 28.0) = 16.6472$, $p = <0.0001$) all proved to be statistically significant.

Mauchly's test indicated sphericity assumed for the minimum, $\chi^2(2.0) = 2.728$, $p = 0.2556$. A post hoc analysis was preformed using a paired sample t-test. The results proved the physical plan had greater minimum coverage to the PTV (90%) compared to the biological (87%) and duo plan (85%). See table 2.

Mauchly's test indicated sphericity assumed for the maximum, $\chi^2(2.0) = 5.2447$, $p = 0.0726$. Post hoc analysis revealed the max dose was greatest with the biological plan (108%) compared to the physical plan (106%) and duo plan (107%).

Mauchly's test indicated sphericity assumed for the global dose max, $\chi^2(2.0) = 4.7592$, $p = 0.0926$. Post hoc analysis revealed the physical plan had the lowest dose max to tissue (106%) compared to the biological plan (108%) and duo plan (107%).

Spinal Cord

The V45 was evaluated for the spinal cord between the 3 plans. Mauchly's test indicated the assumption of sphericity had been met, $\chi^2(2.0) = 1.2253$, $p = 0.5419$. The results proved a statistical difference between the 3 plans, $F(2.0, 28.0) = 7.935$, $p = 0.0019$. A paired sample ttest was used to conduct a post hoc analysis of the results. Results showed the biological plan was lower than both the physical ($t(14) = 2.4$, $p = 0.0309$) and duo ($t(14) = -4.3334$, $p = 0.0007$). The physical plan was also lower than the duo ($t(14) = -1.2061$, $p = 0.2478$). The V45 physical mean was 2877 cGy, the duo was 2976 cGy, with the lowest mean being the biological at 2642 cGy.

Large Bowel

The mean and max were both evaluated for the large bowel. For the mean Mauchly's test indicated that the assumption of sphericity had been met, $\chi^2(2.0) = 0.618$, $p = 0.7342$. The results show that there was a significant effect of which plan was used on the mean dose to the large bowel, $F(2.0, 28.0) = 13.5452$, $p = 0.0001$. Therefore, the paired samples t-test was used to conduct post hoc tests to see which of the three plans differ. The results show that duo was significantly lower than both physical ($t(14) = 4.9121$, $p = 0.0002$) and biological ($t(14) = 2.2256$, $p = 0.043$), and biological is also significantly lower than physical($t(14) = 3.2342$, $p = 0.006$). The mean dose for the physical plan was 1503 cGy, 1414 cGy for the biological, and 1342 cGy for the duo.

The max also proved to be statistically significant, $p = 0.014$. Mauchly's test indicated that the assumption of sphericity had been met, $\chi^2(2.0) = 2.756$, $p = 0.2521$. Results indicated there was a significant effect of which plan was used on the max dose of the large bowel, $F(2.0, 28.0) = 4.9937$, $p = 0.014$. A paired samples t-test was used to conduct a post hoc test to evaluate

the differences. The max with the biological plan was less than both the physical ($t(14) = 2.5961$, $p = 0.0211$) and duo ($t(14) = -2.2279$, $p = 0.0428$). The duo was also less than the physical ($t(14) = 1.1534$, $p = 0.2681$). The mean dose for the physical plan was 4177 cGy, 4125 cGy for the duo plan, and the lowest dose being 4005 cGy for the biological plan.

Small Bowel

The mean and max were evaluated for the small bowel. For the mean results Mauchly's test indicated the assumption of sphericity had been met, $\chi^2(2.0) = 2.1462$, $p = 0.342$. The results showed that there was a significant effect of which plan was used on the small bowel, $F(2.0, 28.0) = 15.6388$, $p = <0.0001$. Therefore, the paired samples t-test was used to conduct post hoc analysis to see which plan differed. The results show that the duo plan was significantly lower than both the physical ($t(14) = 4.6556$, $p = 0.0004$) and biological ($t(14) = 2.0457$, $p = 0.0601$). The biological results were also lower than the physical ($t(14) = 4.0169$, $p = 0.0013$). The mean dose for the physical plan was 1930 cGy, 1813 cGy for the biological, and the lowest being 1755 cGy for the duo plan. No statistical significance was shown between any of the plans for the max, $p=0.423$. See table 3.

Kidneys

The V18 and mean constraints were evaluated, as well as the maximum dose received were all evaluated for the right and left kidneys. The right kidney showed no statistical significance for the V18 ($p=0.4765$) or mean ($p=0.422$). The max dose proved to be statistically significant, $F(2.0, 28.0) = 8.2192$, $p = 0.0016$. Mauchly's test indicated assumed sphericity, $\chi^2(2.0) = 4.5199$, $p = 0.1044$. Post hoc analysis showed the biological plan was significantly lower than both the physical ($t(14) = 2.9765$, $p = 0.01$) and duo ($t(14) = -3.3464$, $p = 0.0048$).

The duo plan was also less than the physical (t(14) = 0.1432, p = 0.8881). The mean dose for the max measure of the right kidney was 3503 cGy for the physical plan, 3422 cGy for the biological, and the lowest dose at 3193 cGy for the biological plan. Results showed that the V18 and mean results were also insignificant for the left kidneys as well (p=0.3314, p=0.3698). The max dose proved to be statistically significant, F(1.4104, 19.7463) = 3.9933, p = 0.0474. Mauchly's test indicated a violation of sphericity assumption, $\chi^2(2.0) = 7.0365$, p = 0.0297 so the Greenhouse- Geisser Correction factor was used, Epsilon 0.7052, F(1.4104, 19.7463) = 3.9933, p = 0.0474. A post hoc analysis was performed which showed the biological plan was significantly lower than both the physical plan (t(14) = 2.3062, p = 0.0369) and the duo plan (t(14) = -1.7097, p = 0.1094). The duo plan was also lower than the physical (t(14) = 1.4982, p = 0.1563). The mean dose for the max measure was 3517 cGy for the physical plan, 3422 cGy for the duo, and the lowest dose at 3229 cGy for the biological plan. See table 4.

Liver

The V30 and mean constraints were both evaluated for each plan, as well as the maximum dose received. The V30 and max proved to be statistically insignificant (p=0.207, p=0.4949). The mean dose proved to be statistically significant, F(2.0, 28.0) = 20.211, p = <0.0001. Mauchly's test indicated sphericity assumed, $\chi^2(2.0) = 0.194$, p = 0.9076. Post hoc analysis revealed the duo plan was lower than both the physical (t(14) = 6.0407, p = <0.0001) and biological (t(14) = 1.8108, p = 0.0917). The mean dose to the physical plan was 1248 cGy, 1197 cGy for the biological, and the lowest dose of 1178 cGy for the duo plan. See table 5.

Stomach

The V45, mean dose and max dose were all compared for the stomach. Results indicate no statistical significance for either the V45 or max dose (p=0.7254, p=0.4949). The mean dose did prove to be statistically significant, $F(2.0, 28.0) = 11.0276$, $p = 0.0003$. Mauchly's test indicated sphericity assumed ($\chi^2(2.0) = 5.5738$, $p = 0.0616$). A post hoc analysis was performed using a paired sample t-test. Results show the duo plan was lower than both the physical ($t(14) = 3.8081$, $p = 0.0019$) and the biological plan ($t(14) = 2.5189$, $p = 0.0246$). The biological plan was also lower than the physical plan ($t(14) = 3.1129$, $p = 0.0076$). The mean dose for the physical plan was 2538 cGy, 2483 cGy for the biological, and 2421 cGy for the duo plan. See table 6.

Discussion

The goal of this study was to compare dose to organs at risk while using different optimization techniques. For good measure, PTV coverage was also assessed. Physical objectives, biological objectives, and a combination of the two were utilized to compare which technique provided the best coverage of the PTV while also preserving the greatest amount of healthy tissue.

Minimum coverage to the PTV was best achieved using the physical planning technique. See figure 1. Although, while this was optimal for PTV coverage the physical planning technique also yielded the greatest dose to nearby organs at risk. The physical plans also provided the lowest max dose and global max dose between all 3 planning techniques. See table 1. The importance of PTV coverage is of utmost concern due to the recurrent nature of cancer when microscopic disease remains left behind. If a plan achieves both acceptable PTV coverage and lowest dose to nearby organs at risk, the plan may be considered optimal.

While the use of gEUD objectives proved to be influential in lowering dose to the OARs as prior research had suggested[8], the homogeneity of the dose distribution as well as PTV coverage was compromised. This may be due to the inherent power of the gEUD and the indiscriminate nature of working on the mean of the isodose lines. Using only gEUDs to achieve low dose to OARs created an inconsistent dose distribution as well as lack of overall plan quality. This was an important finding to conclude due to the fact that while using only gEUD objectives in the aim of sparing dose to OARs and healthy tissue was achieved, and is an important goal of radiation therapy, it is equally as important to provide sufficient dose to kill to the tumor volume to decrease risk of recurrence. So, while the lowered dose to each structure was preferable, the conformality of dose was not.

Limitations and Future Research

Multiple limitations to this study were observed. Had the organs at risk been cropped out of the PTV structure there may have been better dose control to OARs as well as a decrease in the influence it had on PTV coverage and conformality. An attempt at lowering dose to a structure located inside the PTV will inherently decrease coverage. Also, as time progressed the planner acquired new techniques that may have impacted plan quality due to more experience with planning. Furthermore, lack of investigation into the conformality index of each plan may skewed the results.

A continuation of research would prove to be beneficial in regards to the conformality index between the 3 plans. Also, further investigation into alpha values other than 1 and 40 should be conducted while used in conjunction with physical based upper values in the

optimizer. Lastly, examination of a variation in treatment volumes used for the physical constraints could prove to be impactful.

Conclusion

Overall, the plans that utilized both physical and biological constraints provided the lowest dose to organs at risk as well as best conformality. While PTV coverage was not the highest with the duo plan, it was still deemed acceptable in conjunction with other plan parameters such as OAR dose as well as dose homogeneity. A physical upper constraint of 0% of the organ volume receiving a maximum dose, as well as a gEUD constraint with an alpha value of 1 provided the most optimal plans in pancreatic cancer treatment planning. A low priority value on the gEUD (60-70) in conjunction with the upper value provided a gentle yet effective way to control dose to nearby organs at risk without resulting in an unacceptable variation in dose to planning target volume.

Generally, the research was found to be in accordance with the previous findings related to dose variations. The results were in agreement with the Apinorasethkul study[12,] being that a combination of uppers and a gEUD would provide a higher quality plan than using gEUDs alone. It also verified the inherent power of the gEUD that the work of D Mihailidis et al suggested[10], although unlike the Mihailidis study the minimum dose to PTV did not remain optimal. This may have been due to the proximity of the organs at risk to the planning target volume. It also may be due to the fact that the organs at risk were not cropped out of the target volume.

Table 1. Dose Statistics for PTV

Structure	Measure	Mauchly	Plan	Mean	SE	Epsilon	F_test
PTV	Min	$\chi^2(2.0) = 2.728$, $p = 0.2556$	Physical	90.18	1.3168	Sphericity assumed	$F(2.0, 28.0) = 10.9041$, $p = 0.0003$
			Biological	86.56	1.4857		
			Duo	85.54	1.7505		
	Max	$\chi^2(2.0) = 5.2447$, $p = 0.0726$	Physical	106.38	0.2606	Sphericity assumed	$F(2.0, 28.0) = 17.95$, $p = <0.0001$
			Biological	108.3933	0.3653		
			Duo	107.6933	0.1626		
	Global Max	$\chi^2(2.0) = 4.7592$, $p = 0.0926$	Physical	106.3867	0.2613	Sphericity assumed	$F(2.0, 28.0) = 16.6472$, $p = <0.0001$
			Biological	108.2933	0.3492		
			Duo	107.6933	0.1626		

Table 2. T-Test Post Hoc Analysis For PTV

Structure	Measure	Comparison	Mean_Diff	SE_Diff	T_Test
PTV	Min	Physical - Biological	3.62	0.8022	$t(14) = 4.5125$, $p = 0.0005$
		Physical - Duo	4.64	1.0846	$t(14) = 4.2782$, $p = 0.0008$
		Biological - Duo	1.02	1.2049	$t(14) = 0.8465$, $p = 0.4115$
	Max	Physical - Biological	-2.0133	0.4	$t(14) = -5.0335$, $p = 0.0002$
		Physical - Duo	-1.3133	0.2246	$t(14) = -5.8464$, $p = 0.0001$
		Biological - Duo	0.7	0.3725	$t(14) = 1.8792$, $p = 0.0812$
	Global Max	Physical - Biological	-1.9067	0.3919	$t(14) = -4.8655$, $p = 0.0002$
		Physical - Duo	-1.3067	0.2273	$t(14) = -5.7487$, $p = 0.0001$
		Biological - Duo	0.6	0.3706	$t(14) = 1.6191$, $p = 0.1277$

Table 3. Dose Statistics for Small Bowel Max

Structure	Measure	Mauchly	Plan	Mean	SE	Epsilon	F_test
Small Bowel	Max	$\chi^2(2.0) = 4.8329$, $p = 0.0892$	Physical	4608.3333	51.905	Sphericity assumed	$F(2.0, 28.0) = 0.8873$, $p = 0.423$
			Biological	4581.6	88.2157		
			Duo	4632.1333	72.3338		

Figure 1. PTV Bar Chart

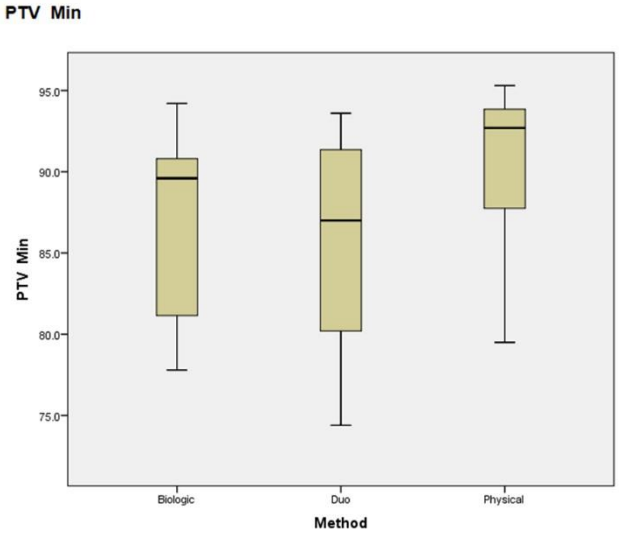

Table 4. Dose Statistics for Kidneys V18, Mean, Max

Structure	Measure	Mauchly	Plan	Mean	SE	Epsilon	F_test
Right Kidney	V18	$\chi^2(2.0) = 0.0143$, p = 0.9929	Physical	29.324	5.6852	Sphericity assumed	F(2.0, 28.0) = 0.7613, p = 0.4765
			Biological	26.7033	6.4601		
			Duo	25.39	6.0669		
	Mean	$\chi^2(2.0) = 2.7614$, p = 0.2514	Physical	1345.3333	138.2356	Sphericity assumed	F(2.0, 28.0) = 0.8899, p = 0.422
			Biological	1280.5333	162.9567		
			Duo	1267.4	163.6647		
	Max	$\chi^2(2.0) = 4.5199$, p = 0.1044	Physical	3503.2	258.4088	Sphericity assumed	F(2.0, 28.0) = 8.2192, p = 0.0016
			Biological	3193.8667	283.9441		
			Duo	3494.4	250.747		
Left Kidney	V18	$\chi^2(2.0) = 110.06$, p = 0.0	Physical	335.3953	311.531	Greenhouse-Geisser Correction (0.5001)	F(1.0001, 14.0015) = 1.0124, p = 0.3314
			Biological	18.8333	6.1532		
			Duo	22.308	6.5123		
	Mean	$\chi^2(2.0) = 1.3042$, p = 0.521	Physical	1222.3333	156.9226	Sphericity assumed	F(2.0, 28.0) = 1.031, p = 0.3698
			Biological	1133.1333	155.2448		
			Duo	1157.2	175.6181		
	Max	$\chi^2(2.0) = 7.0365$, p = 0.0297	Physical	3517.4	315.1009	Greenhouse-Geisser Correction (0.7052)	F(1.4104, 19.7463) = 3.9933, p = 0.0474
			Biological	3229.3333	323.019		
			Duo	3422.5333	338.1329		

Table 5. Dose Statistics for Liver V30, Mean, Max

Measure	Mauchly	Plan	Mean	SE	Epsilon	F_test
V30	$\chi^2(2.0) = 1.1507$, p = 0.5625	Physical	8.6313	2.0698	Sphericity assumed	F(2.0, 28.0) = 1.6671, p = 0.207
		Biological	8.4653	2.0509		
		Duo	8.38	1.991		
Mean	$\chi^2(2.0) = 0.194$, p = 0.9076	Physical	1248.4667	156.9931	Sphericity assumed	F(2.0, 28.0) = 20.211, p = 0.0
		Biological	1197.6	159.846		
		Duo	1178.2	156.4864		
Max	$\chi^2(2.0) = 15.4663$, p = 0.0004	Physical	4491.6	145.1038	Greenhouse-Geisser Correction (0.5897)	F(1.1795, 16.5124) = 1.9264, p = 0.1839
		Biological	4426.4	191.8417		
		Duo	4513	142.6306		

Table 6. Dose Statistics for Stomach

Structure	Measure	Mauchly	Plan	Mean	SE	Epsilon	F_test
Stomach	V45	$\chi^2(2.0) = 6.8308$, p = 0.0329	Physical	23.2567	6.4575	Greenhouse-Geisser Correction (0.7099)	F(1.4197, 19.8763) = 0.2235, p = 0.7254
			Biological	23.5853	6.4191		
			Duo	23.6087	6.568		
	Max	$\chi^2(2.0) = 12.8639$, p = 0.0016	Physical	4667.4667	44.2522	Greenhouse-Geisser Correction (0.6142)	F(1.2283, 17.1964) = 0.5694, p = 0.4949
			Biological	4668.0667	80.0443		
			Duo	4698.1333	49.1653		

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