



Forward Planning SBRT for Borderline-Resectable Pancreatic Cancer

On the frontier of survival

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Highlights

- Overview of pancreas cancer
- Definition of borderline resectable
- Treatment options
- Treatment techniques
- SBRT

Thank you. For this presentation I am going to tell the story of the development of a modified technique – developed at the H. Lee Moffitt Cancer Center – to deal with cancer of the pancreas.

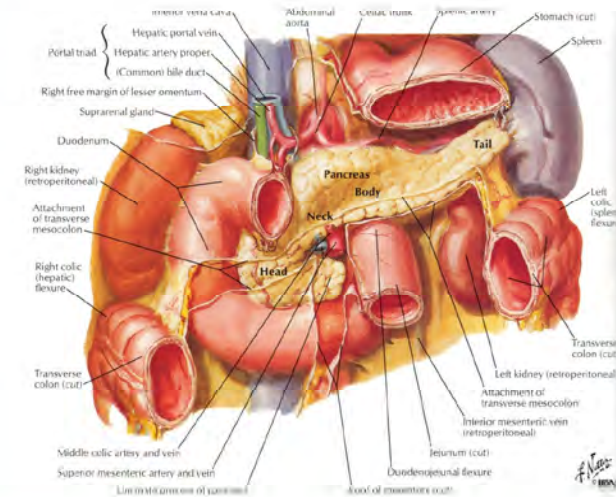
First I'm going to describe the pancreas, and talk briefly about pancreas cancer.

Next I shall touch on what it means to be borderline resectable, and why this is so important.

I'll move on to the treatment options that are used and I'll describe the treatment techniques that are employed to combat this disease. I shall then describe in more detail the stereotactic body radiation therapy technique currently being employed at Moffitt Cancer Center.

But first we should begin with a discussion of the pancreas and its function.

The Pancreas



The pancreas consists of four parts: the head, located here next to the duodenum, the neck, the body, and the tail, located beneath the stomach.

Several important blood vessels are the superior mesenteric artery and vein. Furthermore, there are several nearby critical organs including the duodenum, both the left and right kidney, the liver, the spinal cord, the small bowel, and the stomach.

Please note the location of these blood vessels and the nearby critical organs as they will be important in determining resectability and in guiding radiation therapy.

Knowing the location of the pancreas is important. However, we should also learn what the function of the pancreas is.



What does the pancreas do?

- Hormone production (endocrine)
 - Insulin – decrease glucose
 - Glucagon – increase glucose
 - Somatostatin – regulate insulin/glucagon production
- Digestion (exocrine)
 - Break down protein, carbohydrates, and fat
 - Neutralize acid from stomach

The pancreas is a dual-function organ that provides both endocrine and exocrine services.

It has islet cells throughout that produce insulin – which down-regulates blood sugar concentration, glucagon – which up-regulates blood sugar concentration, and somatostatin – which regulates the production of insulin and glucagon.

For exocrine purposes the pancreas produces pancreatic juices that help break down our food. The pancreas also produces juices that neutralize the acid from the stomach, in preparation for the transit of our food through the small bowel.

The pancreas can suffer from diabetes, pancreatitis, and cancer. But the worst of these is cancer, and cancer shall have its day.



Pancreas Cancer

- 9th most common cancer in U.S.
- 4th most common cause of cancer death in U.S.
- ~38,000 new diagnoses per year
- Most present at advanced stage
- 15 – 20% resectable at diagnosis
- R0 resection offers chance for cure

Pancreas cancer is the 9th most common cancer in the U.S. Although it may lag behind in incidence it makes up for this in lethality. In the U.S. it is the 4th leading cause of cancer mortality.

It is found primarily in Western countries with 38,000 new diagnoses per year in the U.S.

Known risks include tobacco use, high animal fat diet, exposure to benzene and gasoline, age, gender, and obesity.

Hence, at diagnosis few (approximately one-fifth) present with resectable disease. Surgery with negative margins – i.e. no disease present in the margins of the removed tissue – is called an R0 resection. A complete surgical removal with no microscopic disease at the edges of the excised portion of the pancreas offers the best chance for a cure.

How does pancreatic cancer present itself?



Pancreas Cancer

- Most present at advanced stage
- Clinical presentation
 - Jaundice
 - Weight loss
 - Diabetes
 - Abdominal pain
 - Pruritus (itchy sensation)
 - Steatorrhea (excess fat in stool)

Most pancreatic cancers present at an advanced stage because the early-stage symptoms are either below the level of a nuisance, or not present.

Advanced stage symptoms include; jaundice, weight loss, diabetes, abdominal pain, an itchy sensation, and excess fat in the stool.

These symptoms are by no means specific, and in some cases, such as in weight loss, can be construed as desirable, and in other cases, such as abdominal pain, can be attributed to other more prosaic explanations, like a piece of underdone potato. And are, therefore, miss-interpreted as no cause for concern.

The concern, however, is grave...



Pancreas Cancer

- Prognosis is grim
 - Long-term survival for all patients 3 – 4%, 5 yr
 - If have surgery 5 yr survival to 20%
 - “systemic disease”
- Median survival
 - After resection: 12 – 26 months
 - Locally advanced: 9 – 13 months
 - Metastatic: 3 – 6 months

The prognosis is grim.

As stated earlier, more than 80% present at an advanced or metastatic stage of disease. Long term survival, beyond 5 years, is a dismal 3 – 4%.

Median survival is the amount of time that passes between initial diagnosis, and the survival of 50% of the initial number of patients. These numbers are grim. However, they do serve to demonstrate one important conclusion: that the best chance for survival is a resection.

After resection the median survival is 12 – 26 months.

For locally advanced disease the time drops to 9 – 13 months, and for metastatic disease the survival time is 3 – 6 months.

Most patients do not present with ideal cancer. Most are locally advanced. So, one important goal of therapy is to determine which patients can yield the greatest benefit from treatment, so that we may spare the ones who will gain little from needless, time-consuming, ineffective, and costly procedures.

Before we continue we shall make a pit-stop for some definitions.



Definitions

- Resectable
- Locally advanced – non-resectable
- Borderline resectable
- Resection classification

What is a resectable pancreatic tumor?

How is this distinguished from a non-resectable tumor?

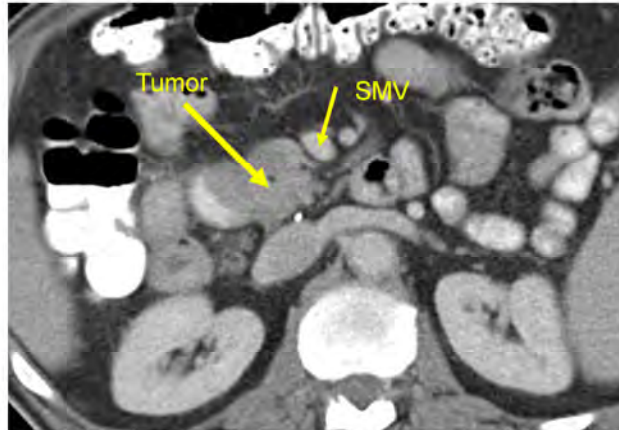
And then, across the U.S. there is a developing definition of a gray region between resectable and non-resectable. The borderline resectable tumor. What is the definition of borderline resectable pancreatic cancer?

How is a resection classified?

These are the definitions we shall cover in the next 4 slides.

(Most patients do not present with ideal cancer. Most are locally advanced. No screening. No need to subject the patient to needless procedures.)

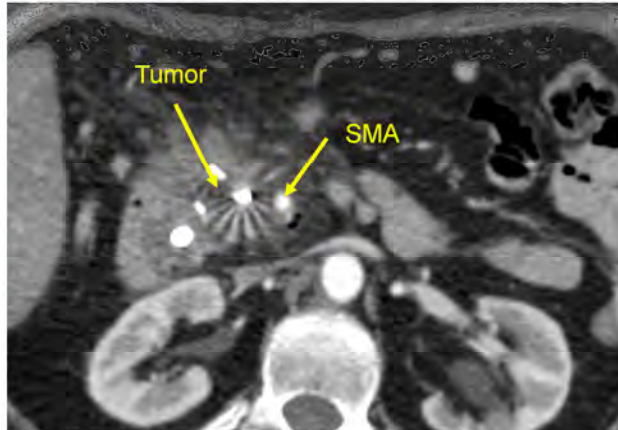
Resectable



This is a CT image of a tumor of the pancreas. Here is the tumor, and this arrow indicates the superior mesenteric vein. Let me draw your attention to this thin layer which clearly separates the tumor from the SMV. This image defines a resectable pancreatic cancer because there is no involvement of the surrounding vasculature.

Resectable pancreatic cancer is distinguished from non-resectable cancer, as illustrated in the next slide.

Locally advanced/unresectable



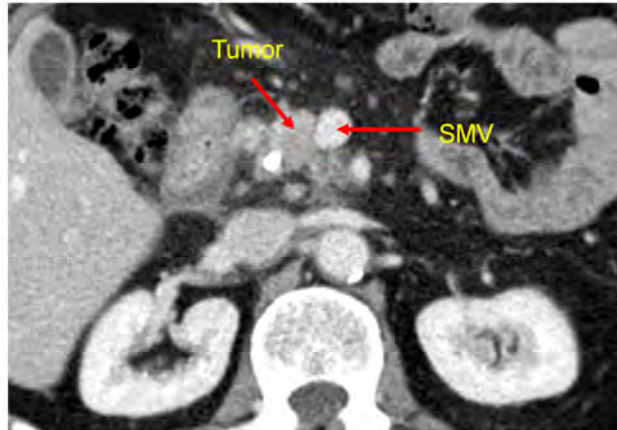
S.E. Hoffe, *Personal communication*

Here is another CT image of a locally advanced or unresectable tumor. There are several things that need to be described in this image. This is the tumor, and this area of white contrast is the contrast-agent enhanced superior mesenteric artery. Because the SMA is completely surrounded by the tumor this case is classified as unresectable.

Also visible in this image is a stent, deployed to open the biliary-tract and prevent obstruction, and several fiducial markers.

You can also see the kidneys, the cord, part of the small bowel, and part of the liver. The situation is not completely black-and-white. There is an emerging gray-area.

Borderline-resectable



Again we have a CT image showing the kidneys, liver, small bowel, cord, and the tumor. Right next to this tumor is the SMV. Although the vessel is not completely encased by the tumor, the thin layer of tissue that separated the tumor from the vessel in the first image is absent. This image defines borderline-resectable cancer.



Borderline Resectable Definition

1. $\leq 180^\circ$ circumferential tumor abutment of portal vein (PV), superior mesenteric vein (SMV), or superior mesenteric artery (SMA)
2. Short segment (1.5 cm) encasement of PV or SMV amenable to partial resection and reconstruction
3. Gastroduodenal artery encasement to origin of hepatic artery

A more precise definition of borderline-resectable follows. When a patient with pancreas cancer meets a surgeon, it is very important to see how much of the tumor is adjacent to the blood vessel. As you can see in point #1 if there is less than 180° of encasement of the portal vein, superior mesenteric vein, or the superior mesenteric artery we call that borderline. That means there is a good chance we can get a negative margin if we treat the patient first with neoadjuvant therapy.

There is less than 1.5 cm of encasement of the PV or SMV that is amenable to resection and reconstruction, or

There is gastroduodenal artery encasement to the origin of the hepatic artery, then the tumor is borderline resectable.

Many different strategies have been tested to shift this sub-set of patients from this gray region into the area of resectability.

Once a resection is performed – if warranted – how is the success of the resection graded?



Margin definitions

- Negative margins
 - R0
- Microscopically positive margins
 - R1
- Grossly positive margins
 - R2

Once a tumor is removed, it is examined grossly and microscopically to determine its resection classification.

If there is no sign of the tumor at the margins of the tissue then this is called an R0 resection.

Even though there may be no obvious signs of tumor at the margin, there may still be tumor cells present. This type of resection is referred to as R1: microscopically positive margins.

And, as you may have already guessed, if the margins are obviously tumor, or grossly positive, this is an R2 resection.

So, what is the goal of treatment?



Goal of treatment

- Complete surgical removal of the tumor
- With no cancer at the edges of the specimen

This most desirable outcome is an R0 resection. In the frame of the borderline-resectable patients, an R0 resection is the goal of all the therapies, and represents the best chance at long-term survival.

If the patient presents with a resectable tumor the next step is surgery.

A patient presenting with a locally advanced tumor will be given palliative care.

In the case of a borderline-resectable tumor, neoadjuvant therapy is employed to create the conditions for a successful resection.

I will discuss briefly the neoadjuvant therapies that have been tested, and I will present the therapy we are currently employing.



What are possible tactics?

- Combination chemotherapy and radiation
 - What drugs?
 - What radiation techniques?
 - Chemotherapy first followed by chemotherapy and radiation
 - Chemotherapy first followed by radiation alone

To transform a borderline tumor into a resectable tumor there are several tools at our disposal.


There is chemotherapy using drugs like gemcitabine.

There is radiation therapy, which provides many possible treatment schedules, and doses, and techniques such as 3D-conformal, and IMRT.

We can also combine chemotherapy with radiation therapy in several ways.

We can deliver chemotherapy and chemoradiation, or we can provide chemotherapy first and then follow it with radiation therapy.

But which combination should we choose? Which combination works the best?



Pilepich	40-46 Gy	No chemo	12% R0
Evans	50.4Gy	5FU	50% R0
Jessup	45Gy	5FU	12% R0
Hoffman	50.4Gy	5FU/MMC	32% R0
Snady	54Gy	5FU/MMC/strepto.	28% R0
Crane	30-33Gy	Gem	9% R0
Wilkowski	45-50Gy	Gem/CDDP	29% R0
Safran	50.4Gy	Gem/paclitaxel	30% R0
Fogelman	45Gy	Induction GTX, gem concurrent	57% R0
Crane	50.4Gy	Gem/bevac.	8% R0

As you may have guessed, the answer to this question is not yet clear, and a host of different combinations have been tested.

This table lists some of those combinations, along with the percentage of patients who, at the conclusion of treatment had a successful resection.

Our approach is again a combination of chemotherapy and radiation therapy, which is not new. The new component is the use of stereotactic body radiation therapy.



Evolution of our approach

- Begin with GTX
 - Gemcitabine (IV infusion)
 - Taxotere (IV infusion)
 - Xeloda (oral)
- Chemo given over 9 week course
- Now doing SBRT for 5 days

Chemotherapy is given first for 9 weeks. A cocktail of three chemotherapeutic agents: Gemcitabine, Taxotere, and Xeloda are given. The Gemcitabine and Taxotere are given by infusion, while the Xeloda is taken orally.

This is followed by a five fraction course of stereotatic body radiation therapy. The purpose of the short course of radiation therapy is to ensure that the patient receives the entire treatment.

The origin of stereotatic radiation therapy is in the head. To hit small legions in the brain with narrow beams requires a high degree of positional accuracy.

In the body the goal is the same: to hit a same volume with a large daily dose.



Re-evaluation 3-4 weeks after

- Restaging PET and CT of the pancreas
- Tumor board presentation to see if lesion has shrunk away from blood vessel enough for surgeon to attempt operation

But before I get to that once the combined treatment is delivered a restaging PET and CT of the pancreas is acquired 3 – 4 weeks later.

If at this point the tumor is judged to have responded then a resection is attempted.



SBRT delivery

- Tumor localization
 - Find tumor location accurately for each fraction.
 - Goal is to identify a GTV borderline (that portion next to abutting blood vessel) vs. entire GTV
- Patient simulation
 - Modified simulation for SBRT
- SBRT planning
 - Craft a set of beam angles and portals that deliver the treatment & the boost simultaneously – Dose painting

As in SRT in SBRT a high degree of accuracy in target localization is necessary. This requires several components.

First the tumor location must be determined and carefully marked. This makes it easy to find the tumor accurately for each fraction.

Next the patient is simulated to give anatomical information. The simulation is modified from ordinary simulation because of the special needs of SBRT. It is a 4D-CT, where the CT data is sorted into the phases of the breathing cycle. The exhale phase is used for planning.

Finally, the planning for SBRT is crucial to produce a treatment plan that is tailored to the patient's tumor.

Prior to Simulation

- Patient undergoes implantation of fiducial markers
 - Done via Endoscopic ultrasound (EUS)
 - Place 3-4 coiled wire gold fiducials into the tumor itself
 - Fiducial markers will be useful for target delineation and for daily image guided gated delivery

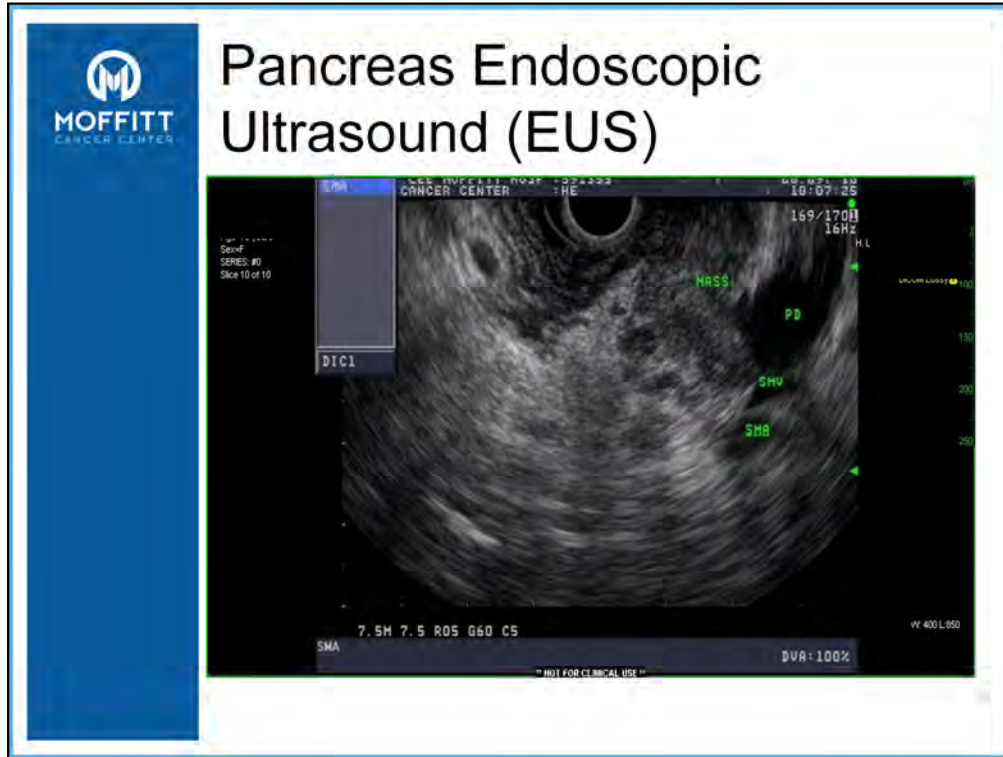


As I mentioned, the location of the tumor must be known.

Prior to simulation, under endoscopic ultrasound guidance, between 3 to 4 gold wire markers are implanted into the tumor.

These markers are visible both in CT, where they will assist in target delineation, and under set-up imaging, where they will assist in daily patient positioning.

The fiducial markers are extremely important, without which SBRT would be impossible. We have noted shifts as large as 2 cm on daily set-up. Without the fiducials we would be unable to correct for these shifts.



Here is an endoscopic ultrasound image of a pancreas tumor. As mentioned earlier the ultrasound is used to guide the placement of the fiducial markers. It may also be used to stage the tumor.

Fiducial markers



These are the fiducial markers. They are thin wires of gold. Gold is a good x-ray attenuator, and show up well on fluoroscopy and radiography.



At simulation

- Full length custom cradle immobilization
- Arms up overhead
- Simulate on empty stomach
- Oral gastrograffin at least 30 mins prior to simulation
- IV contrast with time delay to capture venous phase.... Scan 60 seconds after injection

At simulation the patient is further immobilized using a custom cradle that is shaped to the patient's body.

The patient's arms are overhead, and in preparation for simulation the patients are asked to fast.

Oral and IV contrast agents are used. The IV contrast agent is timed so that when the scan is taken the contrast agent provides contrast to the veins.



Motion analysis: how much does the pancreas move

- Superior to inferior range
 - ~ 1 cm
- Medial to lateral
 - ~ 1 cm
- Ant – Post
 - ~ 1 cm

Extent of motion as well as direction of motion. Literature shows we should check motion. Have study showing motion.

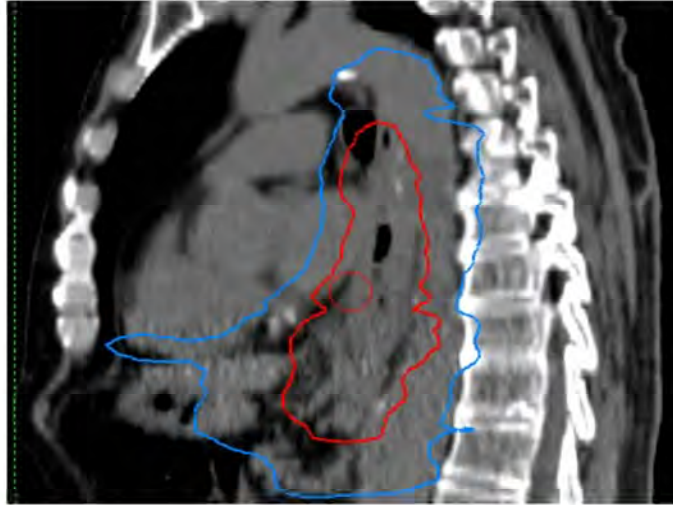
The motion of the pancreas throughout the breathing cycle is a major concern, and it must be managed, otherwise there is no reason to use a stereotatic technique.



Evaluate the motion

- 4D CT
- Evaluate the phases of maximum exhale
- Usually 40-60%
- If 50% is maximal exhale, this will be primary dataset
- Fuse the 40 and 60 and the free breathing to it

Example of motion

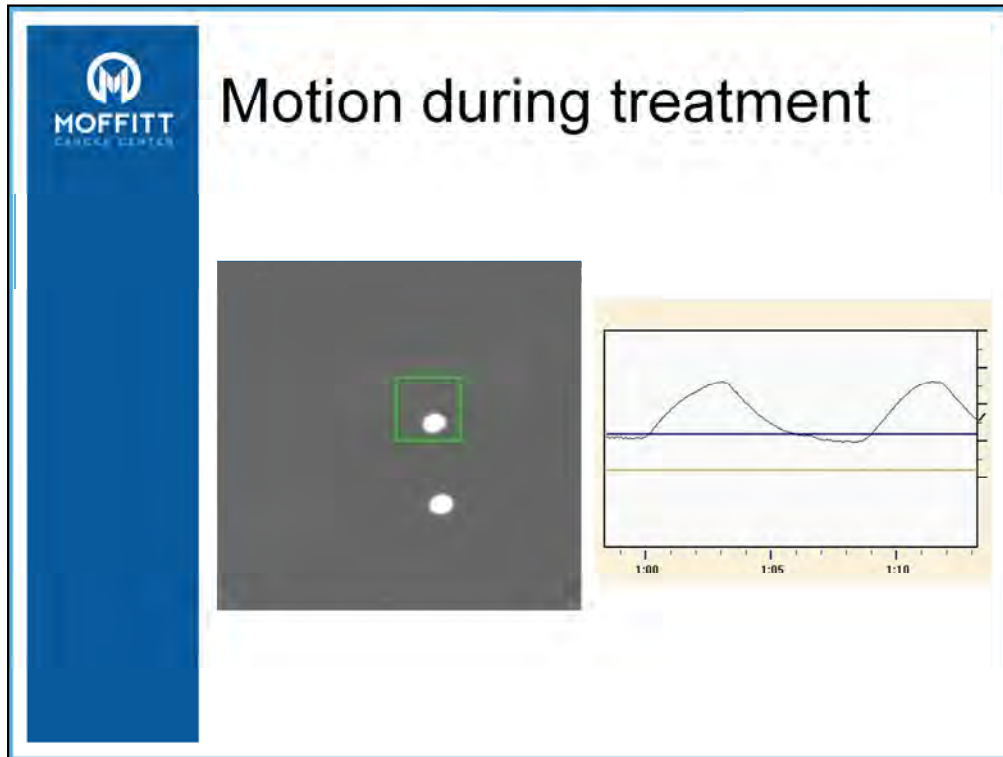


And there is a great deal of motion to manage, as shown by this movie loop of the abdomen.

The motion in planning is managed by using 4D-CT to simulate the patient, and using the exhale CT for planning. Later on, another strategy is required to manage patient motion during treatment.



During treatment, an infrared reflector is placed on the patient's surface in a reproducible manner. An infrared camera is used to track the reflector, providing a surrogate for motion due to breathing.

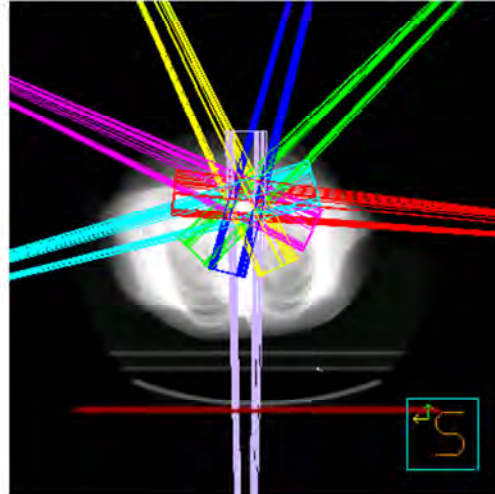


Using the breathing trace provided by the infrared tracking system a gating window is set such that treatment is allowed to proceed provided the breathing trace is within the bounds of the gating window.

The gating window is set to the exhale phase of the breathing cycle, with a duty cycle of approximately 30%.



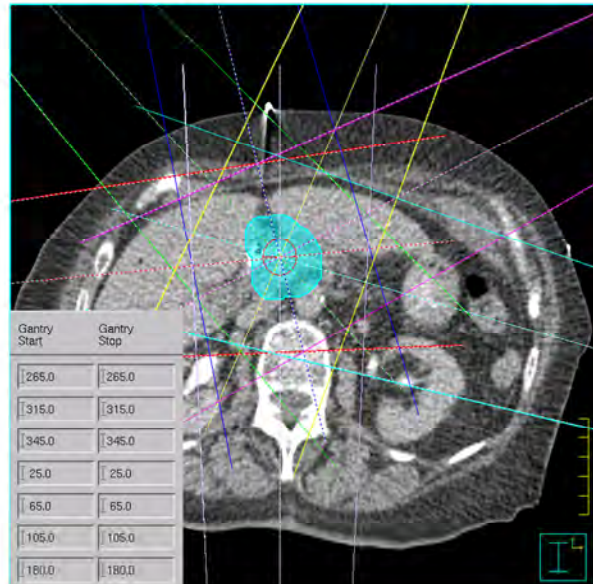
SBRT planning



With the 4D-CT data set in hand, we are ready to begin SBRT planning.

Our planning will be forward planning. We do not need IMRT since it isn't necessary to produce a homogeneous distribution of dose, but rather to produce a distribution with hot spots. It is as if a regular treatment and a boost were combined into a single treatment and delivered simultaneously.

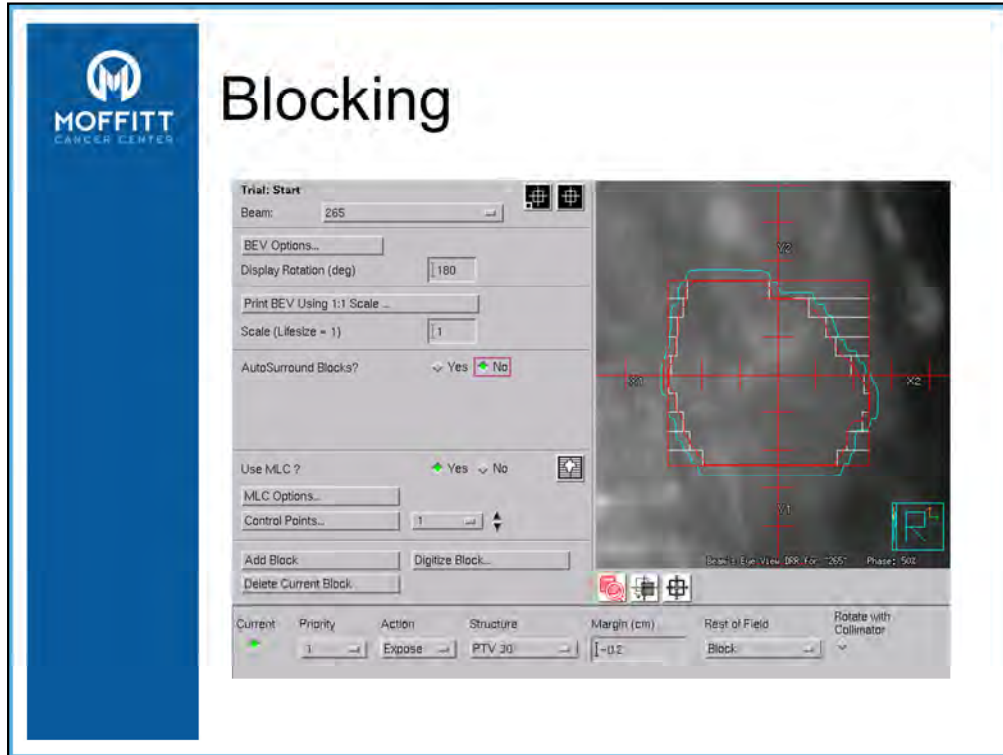
Beam angle selection



We typically use a 7 beam technique. Most of the beams are located to the anterior of the patient. The beam angles are usually chosen to avoid the nearby critical organs.

You may have noticed that the 105 beam passes through the left kidney. This beam angle may not seem optimal. Of course it may be changed to suit the patient, but from experience we have learned that this angle usually works once the collimators have been conformed to the tumor.

We may also adjust the beam energy to decrease dose to the NCO, but we begin planning using the highest energy available, namely 15 MV.



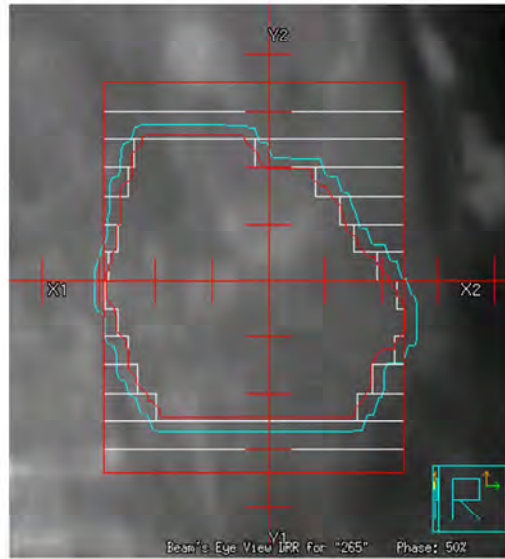
Once the beam angles have been chosen, the next step is to set the field size, and to choose the position of the MLC leaves.

As a preliminary step in setting the collimators the low dose PTV, seen here as the light blue outline, is used with a negative 2 mm margin.

It has been our experience that a -2 mm margin produces an isodose line that closely matches the PTV contour.

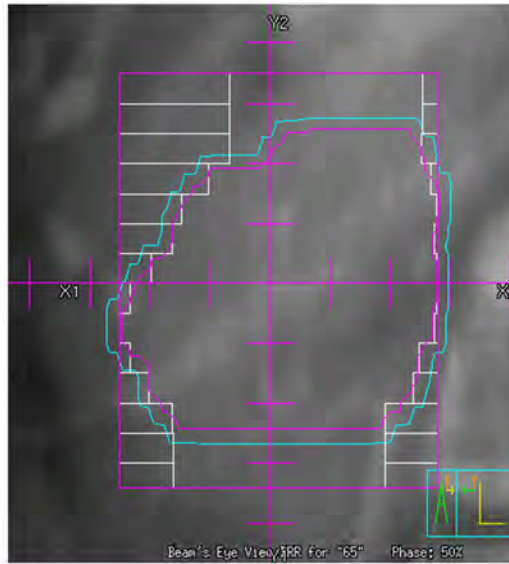
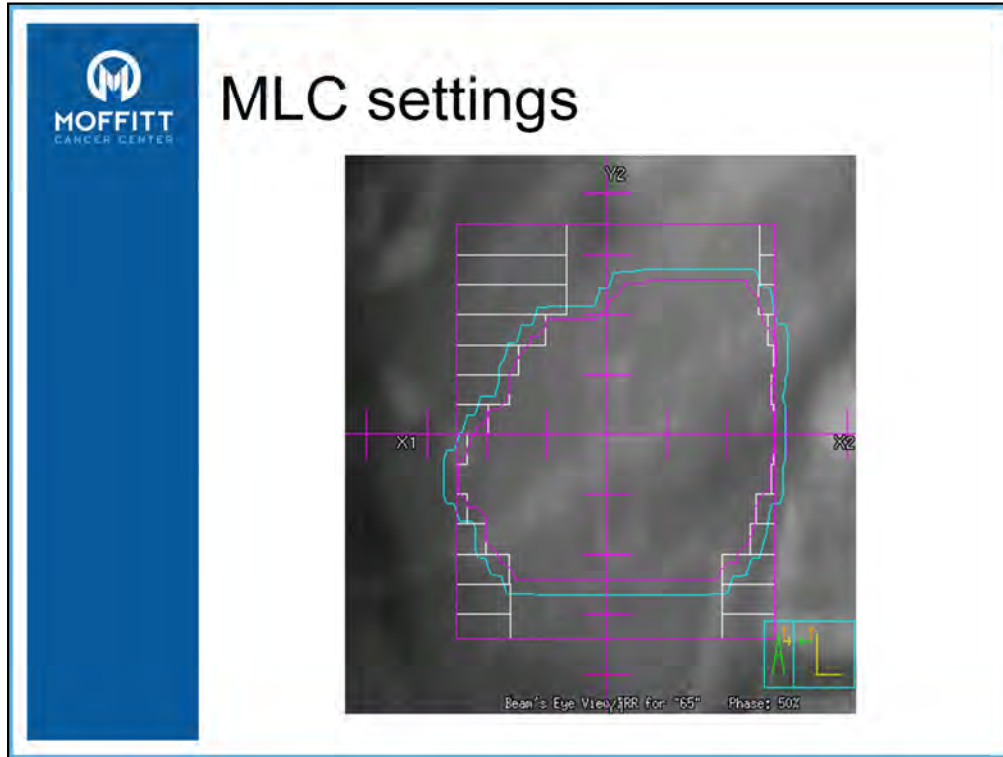
However, this is not the case at the superior and inferior edges of the contour.

Jaw setting



To deal with the superior and inferior edges of the PTV the Y-jaws are opened by 1 cm in both directions.

This of course does not open the MLC leaves.

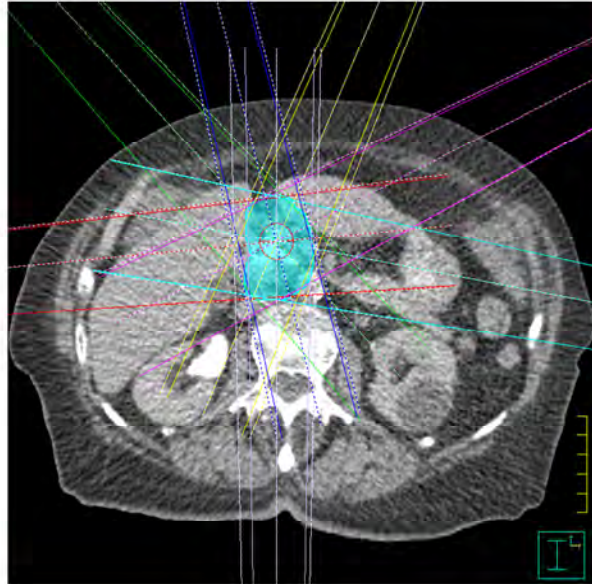


The leaves at the superior and inferior edges of the field are opened and aligned with the edges of the leaves adjacent to them.

It has been our experience that a better dose distribution is produced when leaves that lie over portions of the PTV that run parallel to the leaves are opened further, as indicated in this example.

Here we have a shelf, and the corresponding leaf is opened further.

Off kidneys



With the field size and MLC leaf positions set we can now go back and indeed see that we are off the left kidney.

At this point we are ready to set the prescription and compute the preliminary dose.



Prescription

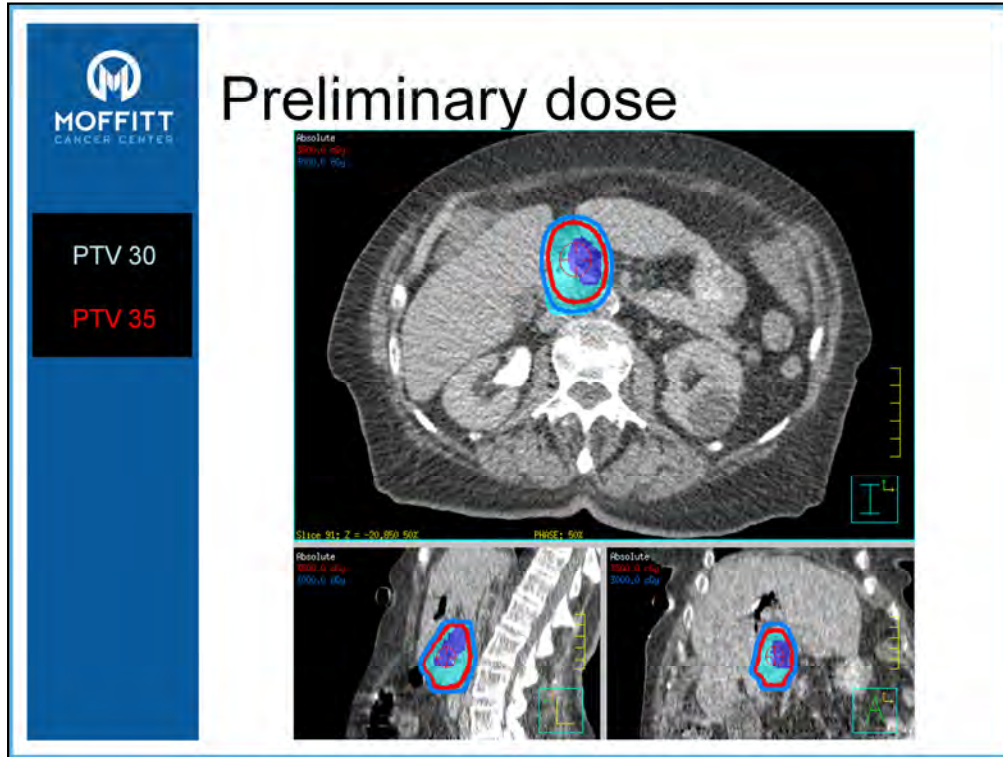
- Multi-level prescription
- Prescribe to lowest dose level
- Prescribe to 85% isodose
 - Will adjust later
- Typically 5 fractions
- Start with 15 MV
 - Adjust lower if needed
- Equally weight all beams
 - Will adjust later
- Compute

The plan is a combination of treatment and boost, so the prescription is a multi-dose prescription.

To deal with this the prescription is set to the lowest dose level. For example if we had a 30 and a 35 Gy prescription the input prescription would be set to 30 Gy, and prescribed initially to the 85% isodose line. However, this is not set in stone, and may be adjusted later to produce a more satisfying dose distribution.

There are usually 5 fractions. At least initially the beam weights are all equal, but this can be adjusted later as desired.

With all this set a preliminary dose is computed.



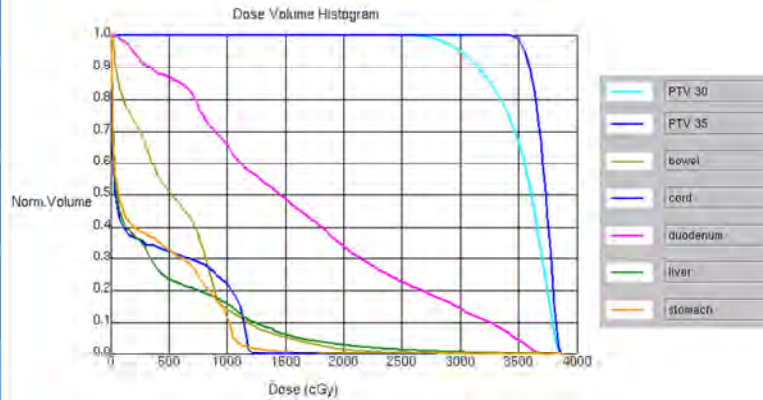
Here is the axial, sagittal, and coronal view of the preliminary dose distribution.

The light blue and dark blue areas are the PTV low dose and PTV high dose respectively. In this case the low PTV dose is 30 Gy and the high PTV dose is 35 Gy.

As you can see the light blue isodose line – the 30 Gy isodose – conforms closely to the PTV30.

There also already is a hot spot within the PTV, and the goal of the next step is to shift that hot spot towards a more appropriate location, towards the PTV35.

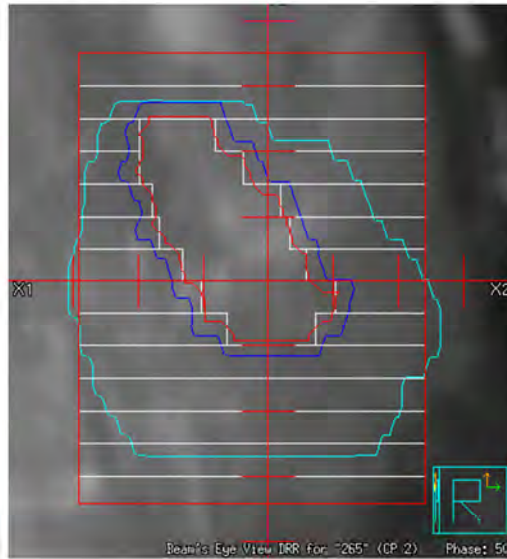
Dose volume histogram



Here is the DVH of the preliminary dose distribution. As you can see most of our goals have already been met.

The 35 Gy covers more than 95% of the PTV35, and only a small improvement to the coverage of the PTV30 seems to be required. Plus most of the nearby critical organs have met their dose constraints, except the duodenum, whose maximum dose should be lower than 38 Gy, which it is already very close to achieving.

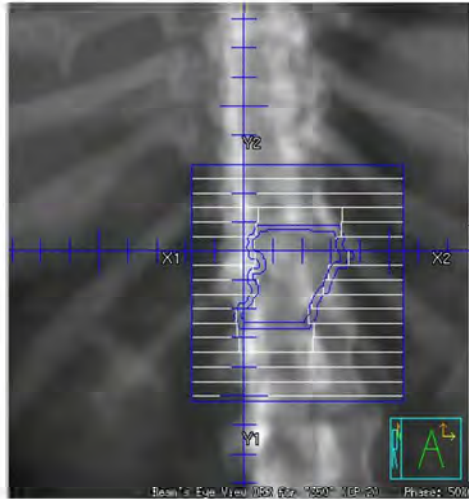
Field-in-field



If further improvement was desired then a field-in-field technique could be employed.

Just as for the low-dose PTV, the leaves are conformed to the high-dose PTV with a -2 mm margin.

MLC setting



Just as before it may be necessary to open the superior and inferior leaves to improve coverage of the PTV.

However, this is not always necessary. It is good practice to save a copy of the previous plan so that it can be returned to if it is obvious that an attempted adjustment results in a poorer plan.

PTV 30

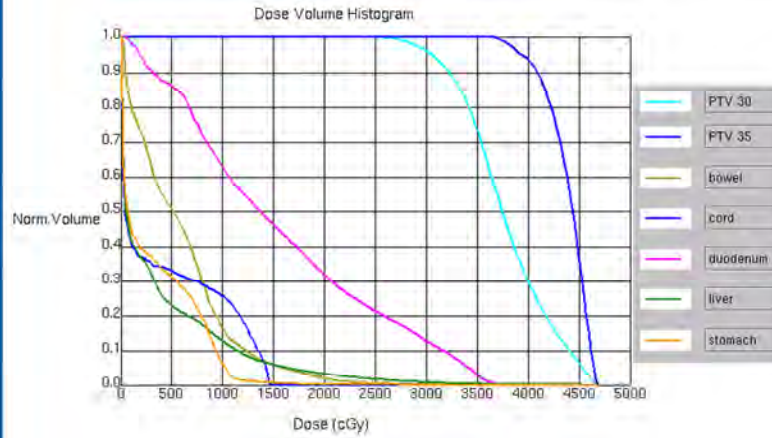
PTV 35

Intermediate dose



As you can see with the intermediate step there does not appear to be a great deal of improvement. This should not be discouraging.

DVH post calculation



As shown by the DVH there has been some improvement to the duodenum, and the coverage of the PTV30. Furthermore, we have yet to optimize the segment weights.



Segment weight optimizer

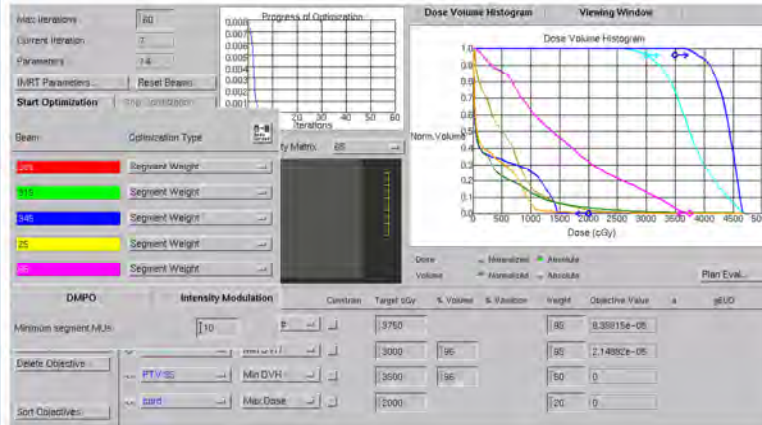
- NOT IMRT!
- SWO will not rescue NCO objectives
- Min MU set to 10.

One feature of our TPS is the SWO. The SWO will automatically adjust the beam weights and segment weights in an attempt to improve plan quality.

Using the segment weight optimizer should not be confused with inverse planning. It is not IMRT!

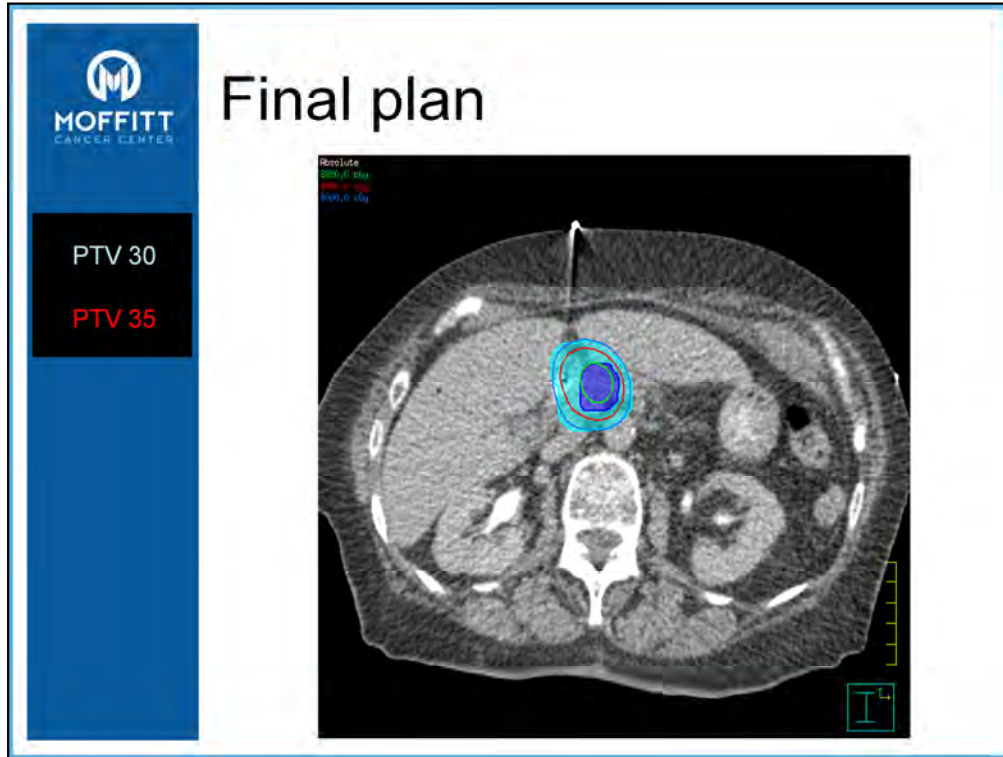
Also, the SWO shall not be relied upon to rescue dose constraints. It won't. What it may achieve is better PTV coverage.

Segment weight optimizer



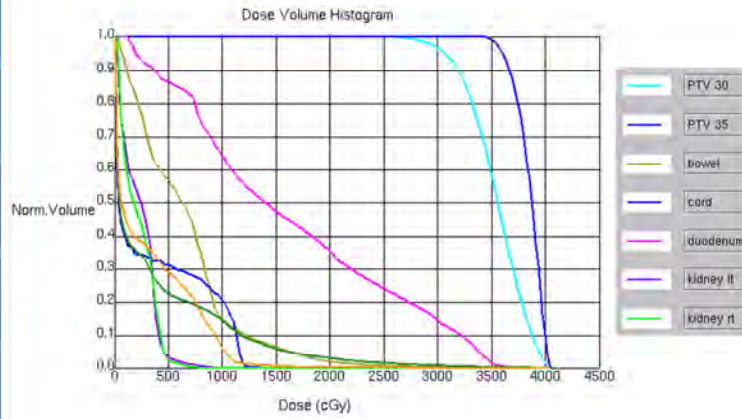
The segment weight optimizer does however take dose objectives. The objectives for the PTV-low and PTV-high should be provided. And we have found that it is a good idea to include some dose constraints for the NCO to prevent the SWO from going too far astray.

The SWO is not infallible. We will often try both manually adjusted weights and computer adjusted weights to see which is more ideal.



Once all the adjustments have been made by an experienced dosimetrist the final plan is shown here. The low isodose conforms nicely to the low-dose PTV. The high isodose may not conform to the high-dose PTV, but the goal is not to produce a homogeneous dose distribution, but rather a heterogeneous one with a hot spot in the high-dose PTV.

Final DVH



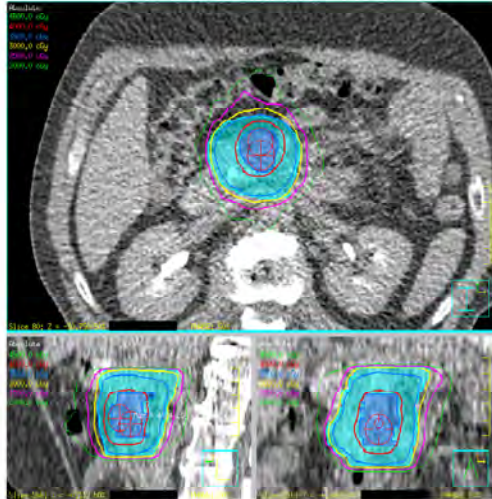
As can be seen from the DVH all the objectives have been achieved.

The dose to the duodenum does not exceed 38 Gy. Plus the PTV 30 and PTV 35 are well covered by the 30 and 35 Gy dose.

PTV 30

PTV 40

Examples of Dose Painted Plans



The planning technique I just illustrated is not limited to 30 and 35 Gy.

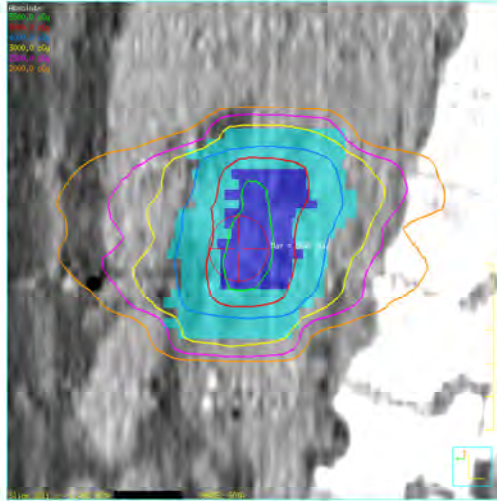
In this CT image we see a dose painted plan with a PTV 35 and a PTV 40. You can see that in this case the isodose lines more closely surround their corresponding targets.



More examples

PTV 40

PTV 50



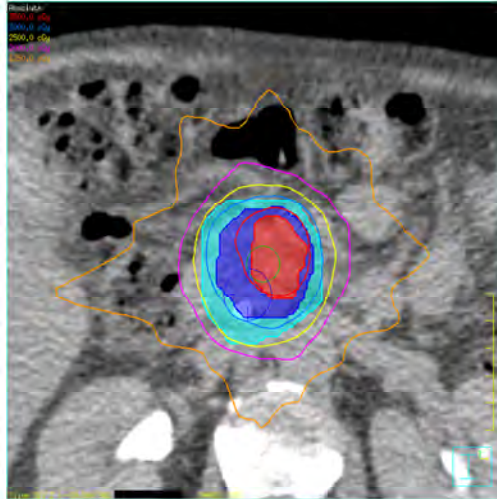
Here is another example.

Interesting examples

PTV 25

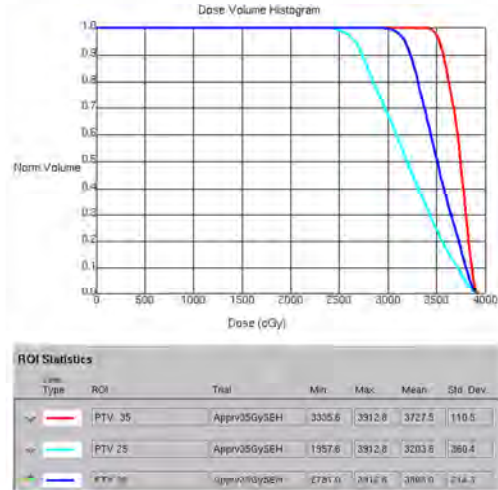
PTV 30

PTV 35



We are also not limited to only two dose-targets. In this example you can see that there are three dose-targets, a light blue 25 Gy PTV, a dark blue 30 Gy PTV, and a red 35 Gy PTV. Once again the corresponding isodose lines match the contours well.

Multiple prescriptions



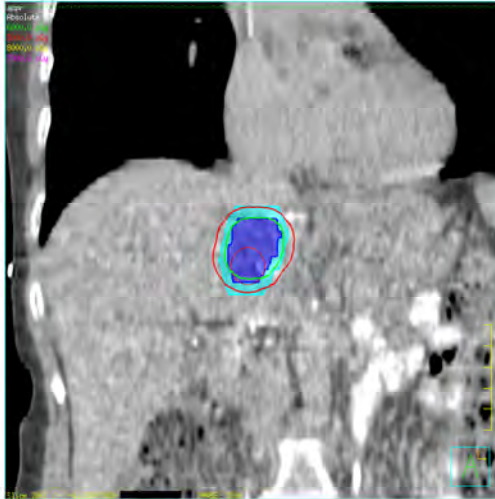
This is of course more convincingly illustrated by the DVH.



Example outside the pancreas

PTV 50

PTV 60



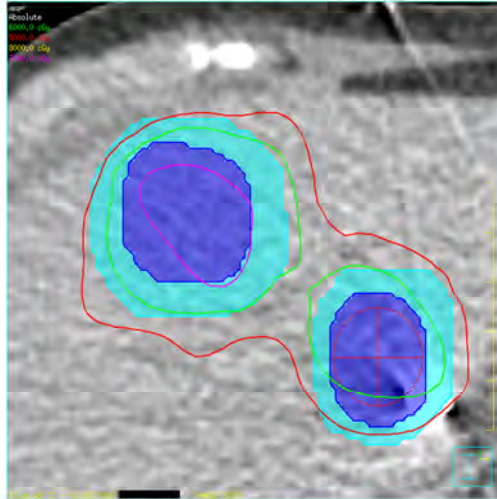
This planning technique is also not limited to the pancreas.
Here is an example where it was used on a tumor in the liver.



Multiple PTV objectives simultaneously achieved

PTV 50

PTV 60



The most interesting application of this planning technique is shown here. In this case the separate lesions in the liver were treated.

These examples help to demonstrate the versatility of this planning technique.



Over the frontier

- Using this technique...
 - Of 18 borderline-resectable patients 11 have been down-staged to resectable
 - Of the 11 patients who received a resection all 11 had a margin status of R0
- The combination of GTX and SBRT is effective in facilitating R0 resection in borderline-resectable patients
- These patients are given the highest chance of long term survival.

Conclusion





Modification to Radiation Therapy

- We introduce a modified therapy whereby the dose is tailored to the tumor *and* its environment.
 - Permits: higher dose to the PTV while mitigating dose to nearby critical organs (NCO)
- A forward planning technique that optimizes the knowledgeable involvement of the Dosimetrist to best determine beam placement – relegating the computer to number-crunching
- Resulting plan achieves the dose objectives.
- Also permits multiple PTV prescriptions, optimizing the involvement of the Oncologist



A cure... provided...

- The only chance a patient has for cure is if surgery is possible
- A sub-class within the unresectable classification that is deemed *borderline-resectable*
- By sufficiently shrinking the tumor with neo-adjuvant therapy these cases can become *resectable*

The diagnosis of pancreatic cancer is a frightening diagnosis.

However, the cancer can be cured, provided a negative margin resection is achieved.

Most patients do not present with ideal tumors, and a resection is often not possible.

However, within the group of unresectable cases there is an emerging sub-class that is deemed *borderline-resectable*

Through successful neoadjuvant therapy it may be possible to shrink the tumor sufficiently so that a resection can be attempted, a resection with negative margins.



Current standard of care

- Hit the tumor with sufficient neo-adjuvant therapy to shrink the tumor
- Combined arms...
 - Immuno-therapy
 - Chemotherapy
 - Radiation therapy
- “Hit it with the kitchen sink”

The current standard of care is a “hit hard”, “use everything” approach, with the intended goal of shrinking the tumor.



Summary

- A significant stride indeed for this terrible disease.

Can pancreatic cancer be cured? Not yet. The probability of long-term survival has significantly improved over the last 5 years. Currently, about 20% of cases can be “cured”. Interestingly, about 20% of patients presenting with pancreatic cancer are resectable. By moving a percentage of the cases that present as non-resectable to resectable – the so-called borderline-resectable case – it will be possible to increase the cure rate. By how much is unclear, but even if the change is from 20% to 25% that still represents a 25% increase!



Questions?

