

Radiation Therapy for Pancreatic Cancer: An ASTRO Evidence-Based Guideline

Developed in collaboration with the American Society for
Clinical Oncology and the Society of Surgical Oncology

Endorsed by European Society for Radiotherapy & Oncology

Supported by Royal Australian and New Zealand College of Radiologists

Citation

This slide set is adapted from the [***Radiation Therapy for Pancreatic Cancer Guideline***](#), published in the September 2019 issue of Practical Radiation Oncology (PRO).

The full-text guideline is also available on the ASTRO Web site:
www.astro.org

Guideline Task Force

Chairs

- Albert Koong, MD, PhD
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Members

- Devon Godfrey, PhD
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- Arti Parekh, MD
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- Joseph Salama, MD
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Task Force Composition

- Radiation oncology
 - Drawn from academic practice, private or community practice, and the Veterans Health Administration system
 - Include a RO resident and A member of the Guidelines Subcommittee
- Related specialties/disciplines
 - Medical oncology
 - Surgery

Non-RO physicians nominated by their respective societies

- Patient representative

Guideline Scope

To provide recommendations on indications, dose, target volumes, and sequencing with chemotherapy for conventionally fractionated RT and SBRT in pancreatic cancer.

The guideline also considers technical aspects of RT delivery and use of prophylactic medications to mitigate toxicity.

Systematic Review

- MEDLINE® PubMed - 05/01/2007 – 06/05/2017
 - Both MeSH terms and text words used
 - Supplemented with handsearches
- Outcomes: survival; tumor control; acute + late toxicity; quality of life; target + normal tissue delineation; treatment planning technique + delivery; and dose to organs at risk
- Inclusion: Age ≥ 18 years, pancreatic cancer treated with RT with or without chemo
- Exclusion: recurrent disease, salvage therapy/re-irradiation; pre-clinical/non-human; lack of clinical outcomes, non-English, case report, not relevant to KQs
- Restricted for KQs 1-3 and 6 to studies with ≥ 40 patients for conventional fractionation and ≥ 20 patients for SBRT; for KQs 4-5 to studies with ≥ 10 patients with pancreatic cancer. No restrictions on KQ7.
- 735 abstracts retrieved \rightarrow 179 articles included and abstracted into evidence tables

Grading Recommendations

<i>Strength of Recommendation</i>	<i>Definition*</i>	<i>Quality of Evidence</i>	<i>Recommendation Wording</i>
Strong	<ul style="list-style-type: none"> • Benefits clearly outweigh risks and burden, or risks and burden clearly outweigh benefits. • All or almost all informed people would make the recommended choice for or against an intervention. 	Any (usually high or moderate)	“Recommend”
Conditional	<ul style="list-style-type: none"> • Benefits are finely balanced with risks and burden or appreciable uncertainty exists about the magnitude of benefits and risks. • Most informed people would choose the recommended course of action, but a substantial number would not. • There is a strong role for patient preferences & shared-decision making. 	Any (usually moderate to low)	“Conditionally Recommend”

* Andrews J, Guyatt G, Oxman AD, et al. GRADE guidelines: 14. Going from evidence to recommendations: the significance and presentation of recommendations. *J Clin Epidemiol.* 2013;66(7):719-725.

Grading Evidence

<i>Quality of Evidence</i>	<i>Definition[^]</i>
High	We are very confident that the true effect lies close to that of the estimate of the effect
Moderate	We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low	Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate.
Very Low	We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate.

[^] Balshem H, Helfand M, Schunemann HJ, et al. GRADE guidelines: 3. Rating the quality of evidence. *J Clin Epidemiol.* 2011;64(4):401-406.

Consensus Methodology

- Modified Delphi approach
- Task force members rate their agreement with each recommendation using an online consensus survey
 - Five-point Likert scale from “strongly disagree” to “strongly agree”
 - Consensus defined using pre-specified threshold of $\geq 75\%$ agreement
- Recommendations for which consensus is not achieved are removed or are revised and re-surveyed.
- Recommendations achieving consensus edited after the first round are also re-surveyed.

Key Question 1: In patients with pancreatic cancer, what are the appropriate indications for regimens that include conventionally fractionated RT or SBRT as:

- Adjuvant therapy?
- Neoadjuvant therapy?
- Definitive therapy?

KQ1 Recommendation Statements

1. Following surgical resection of pancreatic cancer, adjuvant conventionally fractionated RT with chemotherapy in select high-risk patients is conditionally recommended.

Implementation Remark: High-risk clinical features would include positive lymph nodes and margins regardless of tumor location within the pancreas.

Recommendation strength
Conditional

Quality of evidence
Low

Consensus
92%*

2. Following surgical resection of pancreatic cancer, adjuvant SBRT is only recommended on a clinical trial or multi-institutional registry.

Recommendation strength
Strong

Quality of evidence
Very Low

Consensus
100%*

* The medical physics representative abstained from rating these recommendations.

KQ1 Recommendation Statements

3. For patients with resectable pancreatic cancer, neoadjuvant therapy is conditionally recommended.

Recommendation strength	Quality of evidence	Consensus
Conditional	Low	92%*

4. For patients with borderline resectable pancreatic cancer and select locally advanced pancreatic cancer appropriate for downstaging prior to surgery, a neoadjuvant therapy regimen of systemic chemotherapy, followed by conventionally fractionated RT with chemotherapy is conditionally recommended.

Recommendation strength	Quality of evidence	Consensus
Conditional	Moderate	85%*

* The medical physics representative abstained from rating these recommendations.

KQ1 Recommendation Statements

5. For patients with borderline resectable pancreatic cancer and select locally advanced pancreatic cancer appropriate for downstaging prior to surgery, a neoadjuvant therapy regimen of systemic chemotherapy followed by multifraction SBRT is conditionally recommended.

Recommendation strength	Quality of evidence	Consensus
Conditional	Low	77%*

6. For patients with locally advanced pancreatic cancer not appropriate for downstaging to eventual surgery, a definitive therapy regimen of systemic chemotherapy followed by either (1) conventionally fractionated RT with chemotherapy, (2) dose-escalated chemoradiation, or (3) multifraction SBRT without chemotherapy is conditionally recommended.

Recommendation strength	Quality of evidence	Consensus
Conditional	Low	85%*

* The medical physics representative abstained from rating these recommendations.

Key Question 2: In patients with pancreatic cancer receiving RT, what are the appropriate dose-fractionation schemes and target volumes for:

- Conventionally fractionated RT and chemotherapy?
- SBRT?

KQ2 Recommendation Statements

1. For patients with resected pancreatic cancer selected for adjuvant conventionally fractionated RT and chemotherapy, 4500-5400 cGy in 180-200 cGy fractions with concurrent 5-fluorouracil-based chemotherapy is recommended.

Recommendation strength
Strong

Quality of evidence
Moderate

Consensus
85%*

2. For patients with borderline resectable pancreatic cancer selected for neoadjuvant conventionally fractionated RT and chemotherapy, 4500-5040 cGy in 180-200 cGy fractions is conditionally recommended.

Recommendation strength
Conditional

Quality of evidence
Low

Consensus
92%*

* The medical physics representative abstained from rating these recommendations.

KQ2 Recommendation Statements

3. For patients with locally advanced pancreatic cancer selected for definitive conventionally fractionated or dose-escalated RT with chemotherapy, 5040-5600 cGy in 175-220 cGy fractions with concurrent chemotherapy is conditionally recommended.

Recommendation strength	Quality of evidence	Consensus
Conditional	Low	100% [†]

Implementation Remark: A number of fractionation schemes are used for locally advanced disease; see Appendix Table 1 in full-text guideline for a selection of the regimens tested in trials.

4. For patients with borderline resectable pancreatic cancer selected for SBRT, 3000-3300 cGy in 600-660 cGy fractions with a consideration for a simultaneous integrated boost of up to 4000 cGy to the tumor vessel interface is conditionally recommended.

Recommendation strength	Quality of evidence	Consensus
Conditional	Moderate	100% [†]

[†] The medical physics and surgical oncology representatives abstained from rating this recommendation.

KQ2 Recommendation Statements

5. For patients with locally advanced pancreatic cancer selected for SBRT, 3300-4000 cGy in 660-800 cGy fractions is recommended.

Recommendation strength
Strong

Quality of evidence
Moderate

Consensus
100% [†]

6. For patients with resected pancreatic head cancer receiving adjuvant RT, use of the NRG Oncology consensus panel guidance for clinical target volume delineation is recommended.

Recommendation strength
Strong

Quality of evidence
Moderate

Consensus
100% [†]

[†] The medical physics and surgical oncology representatives abstained from rating this recommendation.

KQ2 Recommendation Statements

7. For patients with resected pancreatic body and tail tumors receiving adjuvant RT, a clinical target volume including the pancreatic resection margin and regional nodal basins indicated in the NRG Oncology consensus panel guidance for pancreatic head lesions but excluding the periportal/liver hilum nodal region is recommended.

Recommendation strength	Quality of evidence	Consensus
Strong	Moderate	100% [†]

8. For patients with borderline resectable pancreatic cancer selected for SBRT, a treatment volume including the gross tumor volume with a small margin is recommended.

Recommendation strength	Quality of evidence	Consensus
Strong	Moderate	92% [†]

Implementation Remark: SBRT does not routinely treat elective nodes.

[†] The medical physics and surgical oncology representatives abstained from rating this recommendation.

KQ2 Recommendation Statements

9. For patients with locally advanced pancreatic cancer selected for SBRT, a treatment volume including the gross tumor volume with a small margin is recommended.

Recommendation strength
Strong

Quality of evidence
High

Consensus
100% [†]

Implementation Remark: SBRT does not routinely treat elective nodes.

10. For patients with locally advanced pancreatic cancer selected for definitive conventionally fractionated RT and chemotherapy, selective nodal treatment is conditionally recommended.

Recommendation strength
Conditional

Quality of evidence
Moderate

Consensus
83% [†]

[†] The medical physics and surgical oncology representatives abstained from rating this recommendation.

Key Question 3: In patients with pancreatic cancer receiving RT, what is the appropriate sequencing of chemotherapy with RT as:

- Adjuvant therapy?
- Neoadjuvant therapy?
- Definitive therapy?

KQ3 Recommendation Statements

1. For patients with resected pancreatic cancer receiving adjuvant therapy, delivery of chemoradiation following 4 to 6 months of systemic chemotherapy is recommended.

Recommendation strength
Strong

Quality of evidence
Moderate

Consensus
92%*

2. For patients with borderline resectable pancreatic cancer receiving neoadjuvant therapy, delivery of RT following 2 to 6 months of systemic chemotherapy is recommended.

Recommendation strength
Strong

Quality of evidence
Moderate

Consensus
92%*

* The medical physics representative abstained from rating these recommendations.

KQ3 Recommendation Statements

3. For patients with unresectable or locally advanced pancreatic cancer without systemic progression after 4 to 6+ months of chemotherapy, definitive RT is recommended.

Recommendation strength	Quality of evidence	Consensus
Strong	Moderate	85%*

* The medical physics representative abstained from rating these recommendations.

Key Question 4: In patients with pancreatic cancer receiving RT, how do the following impact target and normal tissue delineation, treatment planning techniques, and treatment delivery accuracy for conventionally fractionated RT and SBRT:

- Motion management?
- Image guidance?
- Contrast administration during CT simulation?

KQ4 Recommendation Statements

1. For patients with pancreatic cancer receiving conventionally fractionated pancreatic RT or SBRT without breath-hold, a patient-specific respiratory motion assessment (eg, 4-D CT simulation) is recommended.
2. For patients with pancreatic cancer receiving conventionally fractionated RT for whom free-breathing target motion is significant (>1 cm), a respiratory motion reduction technique is conditionally recommended.

Recommendation strength
Strong

Quality of evidence
High

Consensus
100%*

Recommendation strength
Conditional

Quality of evidence
Moderate

Consensus
100%*

Implementation Remarks:

- For palliative or postoperative RT, motion assessment and management may not be required.
- For respiratory motion management techniques, the end-exhalation position may be more reproducible than inhalation positions.

* The surgical oncology representative abstained from rating these recommendations.

KQ4 Recommendation Statements

3. For patients with pancreatic cancer receiving SBRT, a respiratory motion management technique is recommended.

Implementation Remarks:

- For palliative or postoperative RT, motion assessment and management may not be required.
- For respiratory motion management techniques, the end-exhalation position may be more reproducible than inhalation positions.

Recommendation strength	Quality of evidence	Consensus
Strong	High	100%

* The surgical oncology representative abstained from rating these recommendations.

KQ4 Recommendation Statements

4. For patients receiving conventionally fractionated RT for pancreatic cancer, daily image guidance is recommended.

Recommendation strength
Strong

Quality of evidence
Moderate

Consensus
100%*

5. For patients receiving SBRT for pancreatic cancer, daily image guidance with fiducial markers and volumetric imaging is recommended.

Recommendation strength
Strong

Quality of evidence
Moderate

Consensus
100%*

Implementation Remarks:

- Bony anatomy and surgical stents are each poor surrogates for pancreas target positioning; if used for image guidance, large ITV margins are necessary.
- Where possible, the use of cine (fluoroscopic) imaging is suggested, in addition to 2-dimensional or 3-dimensional image guidance, to confirm that the ITV adequately accounts for respiratory motion variations or intra-breath-hold drift.

* The surgical oncology representative abstained from rating these recommendations.

KQ4 Recommendation Statements

6. Unless there is a contraindication to IV contrast, patients with pancreatic cancer receiving RT should receive IV contrast at CT simulation; multiphasic CT with a high contrast flow rate and injection volume and patient-specific scan timing is recommended.

Recommendation strength	Quality of evidence	Consensus
Strong	High	100%*

* The surgical oncology representative abstained from rating these recommendations.

Key Question 5: In patients with pancreatic cancer receiving RT, how do different treatment planning techniques (3-D CRT, IMRT, VMAT) impact treatment delivery and dose to OARs?

KQ5 Recommendation Statements

1. For treatment of localized pancreatic cancer, modulated treatment techniques such as IMRT and VMAT for planning and delivery of both conventionally fractionated and hypofractionated RT are recommended.

Recommendation strength	Quality of evidence	Consensus
Strong	Moderate	100%*

* The medical physics and surgical oncology representatives abstained from rating this recommendation.

Key Question 6: In patients with metastatic pancreatic cancer, what are the appropriate indications for RT in palliative therapy?

KQ6 Recommendation Statements

1. For selected patients with metastatic pancreatic cancer, palliative RT to either the primary or select metastatic sites for symptom management is recommended.

Recommendation strength	Quality of evidence	Consensus
Strong	Moderate	100%*

* The medical physics representative abstained from rating these recommendations.

Key Question 7: In patients with pancreatic cancer receiving RT, how do prophylactic medications impact the incidence and severity of acute and late toxicities?

KQ7 Recommendation Statements

1. For patients with pancreatic cancer undergoing RT, prophylactic use of anti-emetic medications to reduce the rate of nausea is recommended.

Recommendation strength
Strong

Quality of evidence
Low

Consensus
100%*

2. For patients with pancreatic cancer undergoing RT, prophylactic use of medications to reduce acid is conditionally recommended.

Recommendation strength
Conditional

Quality of evidence
Very Low

Consensus
100%*

* One task force member was recused from voting on this KQ based on disclosures.