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HyTEC Organ-Specific Paper: Abdomen and Pelvis

# Maximizing Tumor Control and Limiting Complications With Stereotactic Body Radiation Therapy for Pancreatic Cancer

**Anand Mahadevan, MD,[*] Shalini Moningi, MD,[†] Jimm Grimm, PhD,[*] X. Allen Li, PhD,[‡] Kenneth M. Forster, PhD,[*] Manisha Palta, MD,[§] Phillip Prior, PhD,[‡] Karyn A. Goodman, MD,[‖] Amol Narang, MD,[¶] Dwight E. Heron, MD, MBA, FACRO, FACR,[#] Simon S. Lo, MD,[**] James Urbanic, MD,[††] and Joseph M. Herman, MD, MSc, MSHCM[‡‡]**

***Department of Radiation Oncology, Geisinger Cancer Institute, Danville, Pennsylvania; [†]Department of Radiation Oncology, Brigham and Women's Hospital, Boston, Massachusetts; [‡]Department of Radiation Oncology, Medical College of Wisconsin, Milwaukee, Wisconsin; [§]Department of Radiation Oncology, Duke University, Durham, North Carolina; [‖]Department of Radiation Oncology, Mount Sinai Hospital, New York, New York; [¶]Department of Radiation Oncology, Johns Hopkins Hospital, Baltimore, Maryland; [#]Department of Radiation Oncology, Bon Secours Mercy Health System, Youngstown, Ohio **Department of Radiation Oncology, Washington University, Seattle, Washington; [††]Department of Radiation Oncology, University of California, San Diego, California; and [‡‡]Department of Radiation Oncology, Northwell Health, New York, New York***

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**Purpose:** Stereotactic body radiation therapy (SBRT) and stereotactic ablative body radiation therapy is being increasingly used for pancreatic cancer (PCa), particularly in patients with locally advanced and borderline resectable disease. A wide variety of dose fractionation schemes have been reported in the literature. This HyTEC review uses tumor control probability models to evaluate the comparative effectiveness of the various SBRT treatment regimens used in the treatment of patients with localized PCa.

**Methods and Materials:** A PubMed search was performed to review the published literature on the use of hypofractionated SBRT (usually in 1-5 fractions) for PCa in various clinical scenarios (eg, preoperative [neoadjuvant], borderline resectable,

Corresponding author: Anand Mahadevan, MD; E-mail: amahadevan@geisinger.edu

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and locally advanced PCa). The linear quadratic model with $\alpha/\beta = 10$ Gy was used to address differences in fractionation. Logistic tumor control probability models were generated using maximum likelihood parameter fitting.

**Results:** After converting to 3-fraction equivalent doses, the pooled reported data and associated models suggests that 1-year local control (LC) without surgery is ≈79% to 86% after the equivalent of 30 to 36 Gy in 3 fractions, showing a dose response in the range of 25 to 36 Gy, and decreasing to less than 70% 1-year LC at doses below 24 Gy in 3 fractions. The 33 Gy in 5 fraction regimen (Alliance A021501) corresponds to 28.2 Gy in 3 fractions, for which the HyTEC pooled model had 77% 1-year LC without surgery. Above an equivalent dose of 28 Gy in 3 fractions, with margin-negative resection the 1-year LC exceeded 90%.

**Conclusions:** Pooled analyses of reported tumor control probabilities for commonly used SBRT dose-fractionation schedules for PCa suggests a dose response. These findings should be viewed with caution given the challenges and limitations of this review. Additional data are needed to better understand the dose or fractionation-response of SBRT for PCa. 

## 1. Clinical Significance

Most patients with pancreatic cancer (PCa) present with locally advanced or metastatic disease. Even when localized, these tumors are often unresectable owing to local invasion of adjacent structures (ie, vessels).[1-3] Even in the minority of patients who present with resectable disease, the 5-year overall survival (OS) is less than 25%.[4,5] Pancreatic cancer comprised only 3% of new cancer diagnoses in the United States in 2019, and yet it is the fourth leading cause of cancer-related death.[6] Local obstructive symptoms can be difficult to manage and contribute to poor quality of life. Because surgery is often considered the critical treatment modality, strategies to downstage locally advanced pancreas cancer (LAPC) and borderline resectable pancreatic cancer (BRPC) and render them operable are popular; eg, neoadjuvant (or induction) chemotherapy and/or radiation (eg, stereotactic body radiation therapy [SBRT]).[7-9] SBRT involves high doses of radiation delivered in 1 to 5 fractions for 1 to 2 weeks. The advent of more effective systemic therapy to control systemic disease progression, and the recognition that some patients (eg, with certain molecular phenotypes such as SMAD-4 intact) are more likely to have persistent local disease progression rather than metastatic spread, has spurred interest in treatments that may provide more durable local control (eg, SBRT).[10]

SBRT is being increasingly seen as an attractive approach for patients with LAPC and BRPC for several reasons. Because SBRT can be given faster than conventional CRT (1-2 weeks vs ≈5-6 weeks), it is less disruptive to the systemic chemotherapy. This consideration has become increasingly important because multiagent systemic therapy developed in the metastatic setting is now being incorporated into the localized settings of LAPC and BRPC. Furthermore, if these newer systemic regimens indeed improve distant disease control in these settings, local control will become ever more important, especially in certain subsets of patients,[11] and SBRT appears to be more efficacious than conventional CRT. This apparent increased efficacy of SBRT compared with conventional fractionation may be due to the higher dose per fraction or a shorter overall treatment time among other factors. Enthusiasm for SBRT is reflected in a recent survey of 28 international academic radiation oncologists from the United States, Europe, and Canada, where 85% favored SBRT compared with conventional CRT for patients with PCa.[3,12]

There is a paucity of prospective data regarding SBRT for LAPC, and no phase 3 trials comparing SBRT to conventionally fractionated RT alone or CRT. Furthermore, the optimal sequencing of chemotherapy and SBRT remains unclear and SBRT is currently being used as upfront treatment[13,14] or as a sandwich regimen during ongoing chemotherapy.[15,16] Several trials are either ongoing or being planned to better address these questions. For example, the ALLIANCE A021501 trial (National Clinical Trial [NCT] 02839343) is a phase 2 trial where patients were randomized at diagnosis to modified FOLinic acid, Fluorouracil, Irinotecan, Oxaliplatin (mFFX) alone or mFFX with SBRT before attempted resection. This trial will provide important information as to which patients with borderline resectable patients are more likely to benefit from SBRT after neoadjuvant mFFX. The SBRT (6.6 Gy x 5 = 33 Gy) was delivered with a simultaneous integrated boost (total doses of 36-40 Gy to the tumor vessel interface [TVI]). The study is closed, and results are pending.

SBRT for PCa is challenging owing to concerns for injury of surrounding organs (eg, duodenum and stomach). Indeed, some of the initial studies using 1- to 3-fraction regimens reported a high incidence of grade 2 to 4 acute and late gastrointestional toxicities,[17,18] mostly duodenal ulceration and perforation. Techniques to reduce planning target volume (PTV) margins, such as image guidance (eg, with magnetic resonance imaging [MRI], cone beam computed tomography [CBCT], CT on rails, stereoscopic x-ray) and respiratory motion assessment and management (eg, with implanted fiducials, tracking, abdominal compression, and breath-hold techniques),[19] and slightly more protracted regimens, may reduce risks to adjacent normal tissues. For example, 5-fraction regimens (6-6.6 Gy × 5 = 30-33 Gy) have recently been reported to be

associated with a low incidence of gastrointestional toxicity while maintaining good local control.[9] Some toxicities associated with abdominal SBRT are discussed in a separate HyTEC report.[20]

With a paucity of prospective randomized data, a wide range on dose fractionation schemes has been used for the treatment of PCa with SBRT. Hence, it is vital to arrive at reasonable estimates of tumor control from published literature. We herein review the available data regarding TCP for SBRT for PCa.

## 2. Endpoints

In this HyTEC article on pancreatic cancer SBRT, the data was initially grouped into the following categories for analysis based on data potentially available for modeling: (1) aggregate over all patient types, (2) neoadjuvant SBRT before surgery, (3) adjuvant SBRT after surgery, (4) BRPC, (5) LAPC, (6) unresected, and (7) resected. Several of these patient categories have overlap, as shown in the Venn diagram in Figure E1, except "unresected" and "resected," which are mutually exclusive. The goal was to develop a dosimetric model of tumor control probabilities across published dose fractionation schedules. In practice, we were unable to address each of these subgroups due to paucity of data in specific subgroups (see the "Mathematical and Biological Models" section).

Definitions for local control varied[21] and consensus guidelines are needed; the Alliance A021501 protocol[1] recommends Response Evaluation Criteria in Solid Tumors.[22] Competing risk analysis is advisable for local control to avoid overstating control rates,[23] but this was only used in the minority of published data sets.[24,25]

Actuarial data from Kaplan-Meier (KM) graphs was used to construct dose-response models for overall survival and local control at 1-year and 2-year time points. The starting definition for KM analysis was widely varying in the literature (Table 1),[8,9,15,17,18,24,26-51] with 42% of the datapoints defining KM from the start of SBRT, 32% from the time of diagnosis, and the remaining 26% with various other definitions including trial registration. This is a serious limitation when evaluating studies with heterogenous reporting of the start of KM analysis.

## 3. Challenges Defining and Segmenting Anatomic Volumes

Proper delineation of the gross tumor volume (GTV) is critical to optimize pancreatic SBRT delivery given the proximity to stomach and duodenum. Underestimation of the GTV could lead to geometric miss, resulting in inferior local control and survival,[52,53] whereas GTV overestimation could result in larger normal tissue volumes irradiated, resulting in excess acute and late toxicity.[17] In conventional radiation therapy, generous clinical target volume and PTV expansions are used to account for some of these uncertainties caused by respiratory motion, bowel or stomach filling and movement and microscopic disease.[54] With SBRT, more stringent (eg, 2-5 mm) expansions are common and vary based on techniques (eg, type of image guidance, respiratory motion management), and nonisotropic expansions are sometimes done (eg, less expansion toward the duodenum).

The standard use of multiphasic contrast-enhanced CT for several anatomic sites has been adopted by diagnostic radiology during the past 2 decades. Fundamentally, multiphasic CT optimizes tumor conspicuity by taking advantage of time-dependent perfusion differences between a tumor and surrounding normal tissues and vasculature.[55] Similarly, oral contrast agents with sufficient density, viscosity, and timing can be optimized to accurately delineate the critical dose limiting organs at risk (OARs) related to PCa, particularly stomach and duodenum. Four-dimensional CT scans now are often used to assess and address the need and effect of motion management.[1]

In clinical practice, and in most of the literature herein reviewed, diagnostic quality multiphasic intravenous and oral contrast-enhanced scans were unlikely to be performed at simulation and rarely during image guided treatment. Adherence to standard protocol segmenting guidelines and reporting of delineation of GTV, PTV, TVI, and OARs are critical for applicability of this analysis.[1,5] This becomes even more challenging with uncertainties in bowel filling and respiratory motion. Fiducial based motion management techniques, including live motion tracking capabilities, gating, and compression have enhanced the confidence in delivery of high doses of radiation close to critical OARs with precision.[56] Thus, there is heterogeneity in the methods used in the reports that are summarized in this review, and this limits the robustness of data-pooling reports like the HyTEC effort.

## 4. Review of Outcomes Data

A PubMed search on June 19, 2019, for "pancreas or duodenum or pancreatic" and "radiosurgery or hypofraction or SBRT or SABR or CyberKnife" returned 414 articles. To be included in the HyTEC pancreatic dose-response models, an article had to report (1) cumulative prescription dose, (2) the number of fractions, (3) the number patients, and KM actuarial OS or LC, or individual patient OS and LC data, (4) at least 75% of the patients without prior pancreatic radiation, and at least 90% of the patients without distant metastases. This resulted in the 48 datapoints as depicted in Tables 1 and E1. The majority of usable SBRT articles used 1 to 5 fractions. Three articles with clear stereotactic intent (eg, $\geq$5 Gy per fraction) that used 6 to 7 fractions[26-28] also are included in the review. Table 1 has separate columns for LC and OS at 1, 2, and 3 years, but only about one-fourth of the studies presented 3-year results. About half of the studies reported 1-year LC,

**Table 1** Reported LC and OS for pancreatic SBRT, sorted chronologically (the differing proportion of categories combined in most reports precluded other logical groupings such as LAPC or BRPC (Appendix E1)

| | Rx | | | | | | | | | | KM |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | N | dose | N | LC | | | OS | | | | starting time |
| Study | Pts | (Gy) | Fx | 1 y, % | 2 y, % | 3 y, % | 1 y, % | 2 y, % | 3 y, % | Institution | definition |
| Passardi et al[28] | 40 | 35 | 7 | NR | NR | NR | 59 | 32 | NR | Italy 4/2011-8/2016 | Enrollment |
| Jung et al[32] | 95 | 28 | 4 | 80 | 40 | 15 | 67 | 20 | 5 | Asan, Korea, 4/2011-7/2016 | Diagnosis |
| Lin et al[31] | 39 | 34.7 | 5 | 92 | 83 | 83 | 69 | 18 | 2 | University of Nebraska, NCT01068327 10/2008-5/2013 | Diagnosis |
| Kharofa et al[33] | 10 | 33 | 5 | NR | NR | NR | 69 | 25 | NR | University of Cincinnati, 11/2014-6/2017 | Surgery |
| Kharofa et al[33] | 8 | 33 | 5 | NR | NR | NR | 80 | 67 | NR | University of Cincinnati, 11/2014-6/2017 | Surgery |
| Bernard et al[34] | 49 | 36 | 3 | NR | NR | NR | 68 | 50 | NR | UPMC NCT01357525 2/2013-1/2018 | Enrollment |
| Bernard et al[34] | 49 | 36 | 3 | 85 | 77 | NR | NR | NR | NR | UPMC NCT01357525 2/2013-1/2018 | SBRT |
| Goldsmith et al[35] | 42 | 26.8 | 3 | 43 | 35 | NR | 39 | 12 | NR | London CyberKnife Center | SBRT |
| Mazzola et al[27] | 33 | 40.2 | 6 | 81 | 65 | NR | 84 | 64 | 47 | Italy 8/2014-12/2016 | SBRT |
| Lischalk et al[36] | 20 | 29.4 | 5 | 43 | NR | NR | 53 | NR | NR | Georgetown Metastatic 2009-2014 | SBRT |
| Zhu et al[37] | 419 | 36 | 5 | NR | NR | NR | 63 | 14 | NR | Changhai Hospital, China 1/2012-12/2016 | Diagnosis |
| Jumeau et al[38] | 17 | 30 | 5 | 57 | 57 | NR | 25 | NR | NR | CHUM, 10/2010-3/2016 | SBRT |
| Quan et al,[30] BRPC with surgery | 10 | 36 | 3 | 80 | 67 | NR | 100 | 90 | NR | UPMC NCT01360593 7/2011-10/2013 | Enrollment |
| Quan et al,[30] BRPC without surgery | 9 | 36 | 3 | 44 | 11 | NR | 66 | 36 | NR | UPMC NCT01360593 7/2011-10/2013 | Enrollment |
| Quan et al,[30] LAPC without surgery | 14 | 36 | 3 | NR | NR | NR | 54 | 10 | NR | UPMC NCT01360593 7/2011-10/2013 | Enrollment |
| Quan et al,[30] LAPC with or without surgery | 16 | 36 | 3 | 78 | 52 | NR | NR | NR | NR | UPMC NCT01360593 7/2011-10/2013 | Enrollment |
| Park et al[39] | 44 | 31.5 | 5 | 66 | 51 | NR | 56 | 26 | NR | MSKCC 2008-2016 | SBRT |
| Sutera et al,[40] 1fx | 92 | 23.4 | 1 | 63 | 53 | 45 | NR | 31 | NR | UPMC 2004-2014 | SBRT |
| Sutera et al,[40] 3fx | 199 | 34.7 | 3 | 79 | 72 | 66 | NR | 38 | NR | UPMC 2004-2014 | SBRT |
| Comito et al,[26] KM from diagnosis | 43 | 45 | 6 | NR | NR | NR | 87 | 33 | 16 | Istituto Clinico Humanitas, Italy 2011-2013 | Diagnosis |
| Comito et al,[26] KM from end of SBRT | 43 | 45 | 6 | 87 | 87 | NR | 61 | 20 | 13 | Istituto Clinico Humanitas, Italy 2011-2013 | SBRT |
| Gurka et al,[41] KM from diagnosis | 37 | 28.2 | 5 | NR | NR | NR | 67 | NR | NR | Georgetown nonmetastatic 1/2008-12/2012 | Diagnosis |
| Gurka et al,[41] KM from SBRT | 37 | 28.2 | 5 | NR | NR | NR | 51 | NR | NR | Georgetown nonmetastatic 1/2008-12/2012 | SBRT |
| Chuong et al[29] | 36 | 35 | 5 | 100 | NR | NR | 93 | NR | NR | Moffitt 2009-2012 | Chemo |
| Moningi et al,[42] KM from diagnosis | 40 | 33 | 5 | 61 | 14 | 2 | 72 | 25 | 4 | JHU 1/2010-2014 | Diagnosis |

(*continued on next page*)

**Table 1** (*continued*)

| Study | Rx N Pts | Rx dose (Gy) | Rx N Fx | LC 1 y, % | LC 2 y, % | LC 3 y, % | OS 1 y, % | OS 2 y, % | OS 3 y, % | Institution | KM starting time definition |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Moningi et al,[42] KM from start of SBRT | 40 | 33 | 5 | NR | NR | NR | 60 | 15 | 3 | JHU 1/2010-2014 | SBRT |
| Song et al[43] | 59 | 45 | 5 | 91 | 80 | 70 | 54 | 35 | 21 | Taipei, Taiwan 10/2006-9/2014 | SBRT |
| Herman et al[9] | 49 | 33 | 5 | 78 | NR | NR | NR | NR | NR | NCT01146054 (JHU + Stanford + MSKCC) | Diagnosis |
| Herman et al,[9] resected | 4 | 33 | 5 | NR | NR | NR | 100 | 38 | NR | NCT01146054 (JHU + Stanford + MSKCC) | Diagnosis |
| Herman et al,[9] unresected | 45 | 33 | 5 | NR | NR | NR | 56 | 17 | NR | NCT01146054 (JHU + Stanford + MSKCC) | Diagnosis |
| Lin et al[44] | 20 | 40 | 5 | 83 | 48 | 16 | 80 | 48 | 32 | Taipei, Taiwan 3/2007-3/2011 | SBRT |
| Pollom et al,[24] 1 fx, KM from start of SBRT | 76 | 25 | 1 | 91 | NR | NR | NR | NR | NR | Stanford 10/2002-6/2013 | SBRT |
| Pollom et al,[24] 1 fx, KM from diagnosis | 76 | 25 | 1 | NR | NR | NR | 35 | NR | NR | Stanford 10/2002-6/2013 | Diagnosis |
| Pollom et al,[24] 5 fx, KM from start of SBRT | 91 | 33 | 5 | 88 | NR | NR | NR | NR | NR | Stanford 10/2002-6/2013 | SBRT |
| Pollom et al,[24] 5 fx, KM from diagnosis | 91 | 33 | 5 | NR | NR | NR | 35 | NR | NR | Stanford 10/2002-6/2013 | Diagnosis |
| Rajagopalan et al[8] | 12 | 31.8 | 2.2 | NR | NR | NR | 92 | 64 | 51 | UPMC resected 2008-2011 | Diagnosis |
| Goyal et al[45] | 19 | 21.4 | 1 | 65 | NR | NR | 56 | NR | NR | Case Western Reserve 11/2007-11/2010 | SBRT |
| Rwigema et al[46] | 24 | 24 | 1 | 66 | 44 | NR | 80 | 57 | NR | UPMC adjuvant 9/2006-1/2010 | SBRT |
| Mahadevan et al[15] | 39 | 25.7 | 3 | NR | NR | NR | 70 | 32 | NR | Harvard BIDMC | Diagnosis |
| Schellenberg et al[18] | 20 | 25 | 1 | 94 | 94 | NR | 50 | 20 | 7 | Stanford 4/2006-10/2007 | NR |
| Didolkar et al[47] | 56 | 25.5 | 3 | NR | NR | NR | 39 | 33 | 18 | Sinai, Baltimore | Diagnosis |
| Polistina et al[48] | 23 | 30 | 3 | NR | NR | NR | 39 | NR | NR | San Bortolo Hospital, Vicenza, Italy 8/2004-5/2007 | Diagnosis |
| Chang et al[49] | 77 | 25 | 1 | 84 | NR | NR | 21 | NR | NR | Stanford 10/2002-10/2007 | SBRT |
| Schellenberg et al,[18] | 16 | 25 | 1 | 100 | NR | NR | 50 | 18 | NR | Stanford 8/2004-2/2006 | SBRT |
| Koong et al[50] | 16 | 25 | 1 | NR | NR | NR | 15 | NR | NR | Stanford 7/2003-8/2004 | NR |
| Hoyer et al[17] | 22 | 30 | 3 | NR | NR | NR | 5 | NR | NR | Aarhus, Denmark | SBRT |
| de Lange et al[51] | 24 | 24 | 3 | NR | NR | NR | 46 | NR | NR | Vrije Universiteit, Amsterdam | NR |

*Abbreviations:* BRPC = borderline resectable pancreatic cancer; fx = fractions; KM = Kaplan-Meier; LAPC = locally advanced pancreatic cancer; LC = local control; N = number; NR = not reported; OS = overall survival; Pts = patients; Rx = prescription; SBRT = stereotactic body radiation therapy.

ranging from 43% to 100%, and all except 7 of the studies reported 1-year OS, ranging from 5% to 100%.

Three articles presented 1-year local control rates for R0 resected cases as well as dose and fractionation information. Chuong[29] prescribed 30 to 40 Gy in 5 fractions for 36 patients, achieving an R0 resection rate of 97.2% and no local recurrences were reported in any patient, with a median follow-up of 13.8 months (range, 6.1-24.8 months), so the KM 1-year LC was 100%. Quan et al[30] prescribed 36 Gy in 3 fractions for 32 patients, of whom 12 (n = 10 BRPC, n = 2 LAPC) had pancreaticoduodenectomy and 11 of 12 (91.7%) received R0 resection. Among the 10 BRPC patients, 1-year local progression free survival was 80%. Lin et al[31] prescribed 30 to 40 Gy in 5 fractions for 12

patients who also underwent pancreaticoduodenectomy, 91.7% achieving R0 resection and no local failures within a year, with 10 of the patients surviving more than a year. Owing to the heterogeneity of prescriptions and sparse data, a weighted average of 96% was used for local control in lieu of a dose-response model. Among 1-year local control results, the 2 local failures in 56 patients with R0 resection was significantly different than the 105 failures in 507 nonresected patients from Table 1 ($P < .001$, Fisher exact test).

To construct a strong dose response model, a large range of doses and fractionations are needed. However, the outcomes must also be stratified by dose and fractionation or they cannot be used for modeling (eg, if an article reported a single local control rate for 15 to 30 Gy in 1 to 5 fractions, the information is not specific enough to be included in a dose response model). It is important to acknowledge that some studies allow prescribing to a low isodose line with correspondingly high target dose heterogeneity, whereas others aim for a more homogeneous target dose, but the detailed dose distribution is rarely reported, thus the HyTEC model only used prescription dose and was therefore unable to account for such dose heterogeneity.

## 5. Factors Affecting Outcomes

Resectability, based largely on the extent of local disease, is likely the strongest factor that affects outcome, with R0 resection having an average 1-year LC of 96% among the 3 studies discussed in the review of outcomes data section,[29-31] whereas the unresected cases in Figure 1 had an average 1-year LC of 79%, which was significantly different ($P < .001$, Fisher exact test). Among resected cases, the extent to which the tumor is amenable to resection is similarly critical; for example a surgical series found that median tumor-related survival in R0 and R1 resections was 19 (range, 4-85) versus 14 months (range, 2-48) in PCa ($P < .04$).[57] Although there is no consensus regarding the ideal timing between SBRT and resection, the interval has been about 2 months in most reports, as summarized in Tables E3 and E4.

Selective boosting of tumor subvolumes (often termed "simultaneous integrated boost") has been a hallmark of radiosurgery for decades[58,59] and, as elucidated by Tome and Fowler,[60] may affect outcomes. For example, tumor extent near the major vessels may be a dominant factor affecting resectability, as defined in Table E2, from the Alliance A021501 protocol,[1] and thus delivering higher or tumoricidal doses to the vessels at (or adjacent to) the TVI may be helpful as long as tolerance limits are not exceeded. Indeed, the TVI is an important OAR or target volume in current protocols (Alliance A021501). Chuong et al[7] applied this concept delivering a simultaneous boost up to 50 Gy in 5 fractions to the region of vessel abutment and encasement, thereby achieving local control in all patients within their life span in the study period. Hence, such regional dose escalation to the TVI, which is the main area limiting resectability, could affect local control.

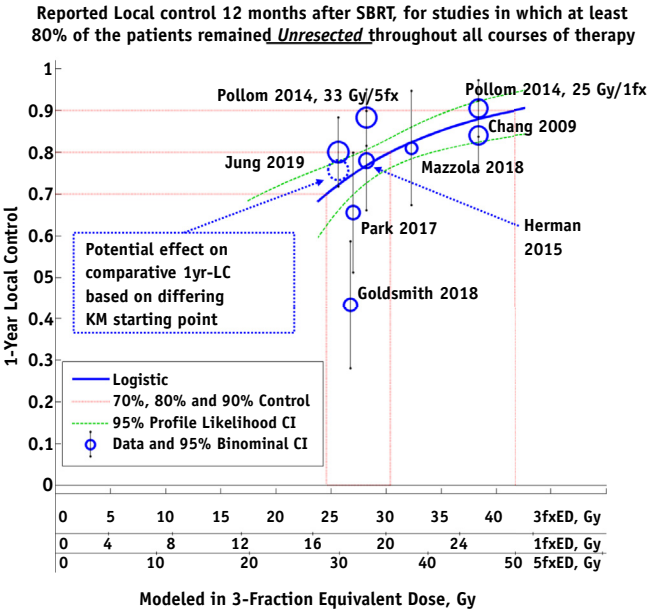


**Fig. 1.** Dose response model for unresected (mostly locally advanced) patients. For studies using a fraction number other than 3, doses were converted to 3-fraction equivalents using the linear quadratic model and $\alpha/\beta = 10$ Gy.[35,63,64] Y-axis values were digitized from reported Kaplan-Meier (KM) graphs. The area of the circle is roughly proportional to the number of patients in the individual reports. Binomial confidence intervals for each study and profile likelihood confidence intervals for the model are partially overlapping, and potential reasons for the remaining differences are discussed in the Factors Affecting Outcomes and Reporting Standards for Outcomes sections. For maximum likelihood parameter fitting[67] the 1-year LC rates from the figure were converted to a proportionate number of binary outcomes according to the number of patients in each study, to ensure each patient was only accounted for once in the model. The dashed arrows denote the 2 articles that started KM calculation from the time of diagnosis, rather than the time of stereotactic body radiation therapy (as for the other studies). The dashed circle estimates the possible magnitude of the effect for the Jung et al[32] data set if the average time difference was 2 months from the time of diagnosis to stereotactic body radiation therapy, based on their KM graph. No similar estimate could be done for Herman et al[9] because the full KM graph was not reported in that study. Studies were included if ≥80% of the patients in the reported series did not have a resection.

The use of varying treatment techniques and platforms may affect outcomes. For example, more accurate target delineation methods (eg, MRI, positron emission tomography, etc) and methods that address daily localization and intrafraction motion would be expected to improve outcomes.

## 6. Mathematical and Biological Models

Prescriptions varied from 1 to 5 fractions across most studies, with a majority of studies using 3 to 5 fractions. More recent publications and clinical trials have used 5-fraction regimens. To facilitate data pooling, doses were converted to a 3-fraction equivalent using the linear quadratic model[61,62] and $\alpha/\beta = 10$ Gy.[35,63,64] Logistic modeling[65,66] via maximum likelihood parameter fitting[67] of the resultant 3-fraction equivalent doses was then performed using the formula Tumor Control Probability (TCP) $= 1/(1 + (D50/D)^{4*g50})$, where D50 is the 50% control rate, D is the prescription dose, and g50 is the slope parameter.

Construction of separate dose-response models were attempted for each of the 7 groups: (1) aggregate, (2) neoadjuvant, (3) adjuvant, (4) BRPC, (5) LAPC, (6) unresected, and (7) resected. This was infeasible owing to the heterogenous mixture of patients in many reports (Table E1). There were a number of studies with at least 80% of the patients having pancreas tumors that were not resected before or after SBRT (see the 8 datapoints in Fig. 1), and these were grouped together in the analysis. We needed to use this 80% threshold approach (albeit arbitrarily defined) because most of the articles reported on aggregate mixtures of patients without clear reporting of differential outcomes in these 7 groups. A "symmetrically opposing" group of data sets was defined in which 80% of the patients did have margin-negative surgery (eg, including the subgroups of patients receiving preoperative SBRT, or with BRPC, or downstaged LAPC who were subsequently able have surgery), and the 3 data sets in this category[29-31] were averaged as discussed in the Review Of Outcomes Data section. The estimated local control rates for both groups are shown in Table 2. Note that studies with fewer than 80% of the patients in a group were omitted from the analysis of that group, except in the aggregate model of all cases. Models from the other groups were not as robust as those in Figure 1 and Table 2, and examples of a few additional scenarios are shown in Figure E2. For the unresected 1-year LC model in Figure 1, the logistic parameters were D50 = 17.6 (95% confidence interval [CI], 8.8-21.5), g50 = 0.64 (95% CI, 0.27-1.02), and the data had a significant dose response ($P = .002$, Fisher exact test).

Surgical resectability of PCa has been known to be one of the most significant factors affecting survival,[57] and in Table 2 differences in LC were observed, with 1-year LC for the unresected model remaining <90%, whereas the average 1-year LC with R0 resection was >90%. Among patients eligible for pancreas SBRT, the main reason for unresectability is classic LAPC, but the model in Fig. 1 also includes unresected patients for any other reason, such as metastatic disease or medical inoperability.

Among the studies in Table 1 that were used to generate Fig. 1, the times for KM estimates were relatively uniform (6 of 8 were done from the time of SBRT). There was more variation in the times for KM estimates in the other subgroups considered (see Appendix E1), perhaps explaining the lesser degree of dose response seen in those other subgroups. This variation in start times for KM estimates is not ideal and is discussed further in the Reporting Standards section.

## 7. Special Situations

Neoadjuvant SBRT in clearly resectable PCa is an active area of study for many reasons. Tissues at risk for potential acute and long-term complications (eg, duodenum) will be

**Table 2** Estimated TCP of common pancreatic SBRT regimens, sorted by 3-fraction equivalent dose (linear quadratic model, $\alpha/\beta = 10$ Gy[35,63,64]

| No. of fractions | Total dose (Gy) | 3-fraction equivalent dose (Gy) | 1-y LC when unresected, % | 1-y LC when R0 resected, % |
|---|---|---|---|---|
| 1 | 25 | 38.4 | 88 | 90 |
| 3 | 36 | 36 | 86 | 90 |
| 3 | 30 | 30 | 79 | 90 |
| 1 | 20 | 30 | 79 | 90 |
| 5 | 33 | 28.2 | 77 | 90 |
| 5 | 30 | 25.8 | 73 | 90 |
| 3 | 24 | 24 | 69 | - |
| 5 | 25 | 21.7 | 63 | - |
| 1 | 15 | 21.7 | 63 | - |

*Abbreviations*: LC = local control; SBRT = stereotactic body radiation therapy; TCP = tumor control probability

Notes: The first 2 columns are common prescriptions from the literature, the third column is the computed 3-fraction equivalent dose (per linear quadratic model with $\alpha/\beta = 10$), and the last 2 columns are the corresponding 1-year LC. The somewhat overlapping definitions of the 7 groups (described earlier in the Mathematical and Biological Models section), including both with and without resection are shown in Fig. E1. The "unresected" column is from maximum likelihood parameter fitting of the 8 datapoints in Figure 1 ($P = .002$, Fisher exact test), and the "R0 resected" column is from the average of 3 studies in review of outcomes data,[29-31] which were significantly different than the "unresected" data ($P < .001$, Fisher exact test).

The numbers are generated by pooling data from series where ≥80% of the reported cases did not have surgery (for the unresected column), or where ≥80% did have R0 resections either before or after SBRT (far right-hand R0 resected column).

removed at the subsequent Whipple procedure, this perhaps lessening one barrier for dose escalation. Reconstruction of bowel, biliary and pancreatic tissues could conceivably be done with tissues that received relatively low RT doses. Similarly, neoadjuvant SBRT might make borderline resectable cancers operable,[29] again allowing removal of some of the at-risk normal tissues. Surgery after SBRT enables study of histopathologic, molecular, and genetic effects of radiation (eg, enabling assessment of potential radiation-responsive predictive biomarkers).

Tumors arising from the body or tail of the pancreas are often adjacent to the stomach, and thus doses to the stomach might limit SBRT target doses. Even if SBRT is given preoperatively, portions of the stomach are typically not resected during a distal or total pancreatectomy, so stomach doses remain an important consideration for SBRT-associated toxicities. The stomach tends to be mobile (and much more mobile than the duodenum), and this raises the possibility of applying maneuvers to move the stomach away from the target (eg, by altering the degree of stomach filling, varying patient position) that can alter the therapeutic ratio. Similarly, this mobility can result in the portions of the stomach receiving higher doses than depicted on the planning scan (eg, if a portion of the stomach moves closer to the target). Thus, consideration should be made to monitor or assess stomach position during the course of SBRT (eg, with daily pre-SBRT imaging). In many situations, dose heterogeneity within the PTV can be tailored based on the tumor location and the bordering critical normal structures.

The postoperative setting is also an opportunity for additional study. Conventional postoperative radiation has largely fallen out of favor based on multiple European studies,[69,70] but with intensification of adjuvant chemotherapy possibly reducing the risk of metastases, and existence of clear predictors of local failure (eg, R1 resection, N+ and high post OP CA19-9), postoperative RT might become increasingly important, and SBRT may emerge as a useful approach in this setting. A short course of SBRT without interrupting the standard adjuvant chemotherapy would be appealing in the high-risk postoperative setting. A few retrospective studies have evaluated SBRT after R1 or R2 resections with favorable results.[34,46] However, postoperatively, portions of small bowel are often present in the volume where the GTV previously resided, perhaps making SBRT particularly challenging in this setting.

## 8. Recommended Dose and Volume Objectives

The pooled data suggests that there is a dose response (Fig. 1 and Table 2). The 33 Gy in 5 fraction regimen corresponds to 28.2 Gy in 3 fractions and the modeled 1-year LC was 77% without surgery and >90% with R0 resection at or above this dose (Table 2). An equivalent dose of 36 Gy in 3 fractions is estimated to correspond to 1-year LC of 86% without surgery. It appears that beyond this, grade 3 toxicity may outweigh any potential incremental benefit.[17] Below 24 Gy in 3 fractions, the tumor control was <70%. In clinical practice, prescription doses should be selected based on criteria such as the likelihood of local control impacting outcome, the risks of normal tissue risks, patient risk-tolerance, etc. Also, purposeful target dose heterogeneity (eg, with higher doses to target regions such as the TVI where it can be safely delivered, and lower doses to target regions adjacent to dose-limiting normal tissues) can be useful.

These dose or outcome estimates should be viewed within the context of challenges and limitations, including those in defining and segmentation of target volumes (see the "Challenges Defining and Segmenting Anatomic Volumes" section), the multiple treatment related factors (see the "Factors Affecting Outcomes" section), the challenges detecting a local failure,[11] and statistical issues related to competing risks and patient selection (issues that may tend to overestimate the rates of local control). This also highlights the need for minimum reporting standards to understand TCP and NTCP (see the "Reporting Standards for Outcomes" section).

We acknowledge that the 1-year time horizon used in this analysis is short, and that these estimated local control rates are likely overstated. At the same time, this is a reasonable endpoint given the available data and the pace of growth of many PCa cases. Some limited available 2-year data are included in Appendix E1. We also acknowledge that the linear quadratic model is imperfect and thus the comparisons, pooling and projections related to the model are uncertain.

## 9. Future Studies

As alluded to in section 7, neoadjuvant SBRT in clearly-resectable PCa, and adjuvant SBRT in resected PCa, may also improve outcomes. Preoperative SBRT (with resected tumor tissue available for study) may increase our understanding of the biology, and response to RT, of PCa, tolerance and radiosensitivity of PCa and the OARs[8,71,72] by enabling histologic quantification of tissue damage. It is expected that outcomes would be progressively better as one moves from locally advanced or unresectable, to borderline resectable, and to resectable; and similarly, among resectable cases according to the extent of tumor resection as one moves from R2 to R1 and to R0.[57] These classifications of extent of resectability should all be quantified in future studies and used to stratify patients when reporting LC and OS as a function of SBRT dose, volume, and fractionation.

**Table 3** Reporting standards for assessing outcomes for pancreas cancer SBRT

| | |
|---|---|
| Disease-related factors | Resectability determination by accepted criteria (eg, Alliance[1], ASTRO[5], ASCO[3], or NCCN[2] should be reported. |
| Planning-related factors | Simulation imaging standards, target volume and OAR delineation according to accepted guidelines should all be standardized within range and reported as such in each protocol and publication.[1,5] The dose distribution or equivalent uniform dose needs to be reported in addition to just the prescription to account for dose heterogeneity; for example the Alliance A021501 protocol allows up to 21% higher dose to the TVI than the PTV, so these distributions must be reported quantitatively to generate meaningful statistics. |
| Treatment-related factors | Prior, concomitant or adjuvant use of surgery, radiation, and systemic therapies, including chemotherapy, immunotherapy, or targeted therapies could affect outcome and should be reported, including the time elapsed between each course of therapy. Furthermore, image guidance techniques and respiratory motion management strategies during treatment should be used and described. |
| Post-treatment assessments | Assessment of local control is typically performed according to the widely accepted RECIST criteria.[1,22] This was not uniformly reported in the analyzed reports. In patients who received preoperative SBRT the goal of attaining adequate local control and eventually survival, would be to achieve a microscopic margin negative (R0) resection and pathologic response (partial or complete). These parameters should be reported in preoperative and neoadjuvant studies.<br>There are various clinical scenarios in PCa with different outcomes and it would be helpful if future studies stratified outcomes by such categories: (1) aggregate, (2) neoadjuvant, (3) adjuvant, (4) BRPC, (5) LAPC, (6) unresected, and (7) resected. As Table E1 shows, many article had varied mixtures of these categories but did not stratify their reported outcomes, which made it impossible for us to construct separate models for all categories; therefore, this level of reporting is needed in future studies. |
| Statistical considerations | To avoid overestimating local control rates, competing risk analysis is preferred.[23-25]<br>For fair comparisons of multidisciplinary management, starting KM analysis from the time of diagnosis is preferable. When authors wish to report KM analysis starting from the time of protocol enrollment or the time of SBRT, they should also report KM analysis from the time of diagnosis, for comparison to other reports. See note below. |

*Abbreviations*: ASCO = American Society of Clinical Oncology; ASTRO = American Society for Radiation Oncology; NCCN = National Comprehensive Cancer Network; OAR = organ at risk; PTV = planning target volume; RECIST, Response Evaluation Criteria in Solid Tumors; SBRT = stereotactic body radiation therapy; TVI = tumor vessel interface.

The utility of various approaches in the areas of imaging guidance (eg, x-ray, CT, or MRI), motion management, adaptive replanning, and dose escalation, to improve the therapeutic ratio, need to be addressed.

## 10. Reporting Standards for Outcomes

To enable data pooling and analysis initiatives such as QUANTEC and HyTEC to achieve reliable estimates of tumor control and dose tolerance, we need journal papers to report dose distribution, fractionation, volume and outcome *per patient,* or at least stratified into clearly demarcated groups of patients.[68,73] In addition, specific considerations needed to assess pancreas TCP are addressed in Table 3

## 11. Statistical considerations note

Among 39 usable studies, there were 7 different definitions of the starting point for KM actuarial analysis, and 3 studies did not define the starting point, as may be seen in Table 1. This introduces potential for immortality bias in estimating survival.[74] For patients in clinical trials, date of registration (which could be months before SBRT due to inclusion of neoadjuvant chemotherapy) is usually the starting point of survival estimation. With median survival in the region of 15 to 20 months, a lead time of 3 to 6 months of chemotherapy before SBRT may skew reported outcomes compared with studies of upfront SBRT. For a disease as rapidly progressing as PCa, it is remarkable that dose-response models could apparently prevail despite these large variations in definitions. However, because PCa is a multidisciplinary endeavor, to make fair comparisons among the different therapies, measuring KM from the date of diagnosis is likely the most equitable. Some papers presented results in terms of both definitions and this is valuable and should be standardized moving forward.[26,47,49]

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