REVIEW

Stereotactic radiotherapy of pancreatic cancer: a systematic review on pain relief

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Abstract: Locally advanced pancreatic carcinoma (LAPC) has a poor prognosis and the purpose of treatment is survival prolongation and symptom palliation. Radiotherapy has been reported to reduce pain in LAPC. Stereotactic RT (SBRT) is considered as an emerging radiotherapy technique able to achieve high local control rates with acceptable toxicity. However, its role in pain palliation is not clear. To review the impact on pain relief with SBRT in LAPC patients, a literature search was performed on PubMed, Scopus, and Embase (January 2000–December 2017) for prospective and retrospective articles published in English. Fourteen studies (479 patients) reporting the effect of SBRT on pain relief were finally included in this analysis. SBRT was delivered with both standard and/or robotic linear accelerators. The median prescribed SBRT doses ranged from 16.5 to 45 Gy (median: 27.8 Gy), and the number of fractions ranged from 1 to 6 (median: 3.5). Twelve of the 14 studies reported the percentage of pain relief (in patients with pain at presentation) with a global overall response rate (complete and partial response) of 84.9% (95% CI, 75.8%–91.5%), with high heterogeneity (Q^2 test: $P<0.001$; $I^2=83.63\%$). All studies reported toxicity data. Acute and late toxicity (grade ≥3) rates were 3.3%–18.0% and 6.0%–8.2%, respectively. Reported gastrointestinal side effects were duodenal obstruction/ulcer, small bowel obstruction, duodenal bleeding, hemorrhage, and gastric perforation. SBRT achieves pain relief in most patients with pancreatic cancer with an acceptable gastrointestinal toxicity rate. Further prospective studies are needed to define optimal dose/fractionation and the best systemic therapies modality integration to reduce toxicity and improve the palliative outcome. Finally, the quality of life and, particularly, pain control should be considered as an endpoint in all future trials on this emerging treatment technique.

Keywords: radiotherapy, pancreatic neoplasms, systematic review, palliative, pain

Introduction

Locally advanced pancreatic carcinoma (LAPC) is a lethal disease associated with multiple debilitating symptoms and 38.7%–49.1% rates of 1-year survival.[1] Moreover, quality of life (QoL) is poor because of several symptoms such as jaundice, weight loss, obstruction, and, particularly, pain. The latter is very frequent because of pancreatic tissue innervation by networks interacting with both the sympathetic and parasympathetic systems yielding to increased sensitivity. Therefore, pain relief is a major goal of palliative treatment in patients with LAPC.[2]

Radiotherapy (RT) has been used as a noninvasive treatment in the management of these patients to achieve local control and pain relief. Particularly, prolonged (5–6 weeks) concurrent chemoradiation has been considered as a treatment option in LAPC. However, this combined modality treatment may produce discomfort in these patients

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with poor performance status due to treatment duration and not negligible toxicity.

Stereotactic RT (SBRT) is an emerging treatment technique for LAPC patients due to several factors such as the possibility to deliver high biological doses to the tumor because of the lower irradiation of organs at risk.[3] Furthermore, due to the short treatment duration, SBRT produces less discomfort to the patients and can be easily combined with standard chemotherapy. Based on the reported efficacy in terms of local control, SBRT has the theoretical potential to relieve pain in LAPC patients. However, this issue has never been systematically analyzed in prospective studies or meta-analyses.

Therefore, the aim of this study is to systematically review the available evidences on pain control after SBRT in patients with LAPC.

Materials and methods

A systematic search in the electronic databases of PubMed, Embase, and Scopus (January 2000–December 2017) for full-text published studies on SBRT in pancreatic cancer (PC) was performed. Only studies published in English were included in this review. Prospective and retrospective studies on LAPC treated with SBRT and reporting on pain control were included in the review. Case reports, review articles, and published conference abstracts were excluded. The following search strategy was used in PubMed database: ("pancreatic neoplasms" [MeSH Terms]) OR ("pancreatic" [All Fields] AND "neoplasms" [All Fields]) OR "pancreatic neoplasms" [All Fields] OR ("pancreatic" [All Fields] AND "cancer" [All Fields]) OR ("pancreatic cancer" [All Fields]) AND ("radiotherapy" [Subheading] OR "radiotherapy" [All Fields] OR "radiotherapy" [MeSH Terms]) AND ("pain" [MeSH Terms] OR "pain" [All Fields]).

Two independent authors (MB, GM) screened citations at the title and abstract level to identify potentially relevant studies without any duplication. Potentially eligible citations were retrieved for full-text review and any uncertainty was resolved by another author (AGM). The following information was extracted from each study: year of publication, study design, inclusion criteria, total number of patients and number of patients with pain, stage, irradiation technique, planning target volume (PTV) definition, dose prescription, median RT dose, median biologically equivalent doses in 2 Gy fractions (EQD$_2$; α/β: 3 and 10), percentage of patients receiving chemotherapy, pain response rate and evaluation criteria, pain-free survival, and toxicity. The median EQD$_2$ was calculated from the prescribed tumor doses by using

an α/β value of 3 Gy for late effects and 10 Gy for tumor effects.

Outcome measures

The main outcome measure was pain relief evaluated by reduction of analgesic administration, suspension of analgesic administration, and partial response (PR) and complete response (CR). Secondary outcome measures were toxicity and pain-free survival.

Statistical analysis

Proportions and rates were pooled by means of a random-effects model in case of heterogeneity across studies; otherwise, a fixed-effect model was used. The dependent variables were modeled on the logit (log-odds) scale, converted back to percentages, and then presented as point estimates and 95% CI. Statistical heterogeneity was quantified with the I^2 statistic (high heterogeneity level: >50%) and tested using the Q^2 test (statistical significance level: $P<0.1$). All tests were two-sided, and statistical significance was taken as $P<0.05$, except when investigating heterogeneity across studies, in which case it was taken as $P<0.10$. All the analyses were performed using the MEDCALC statistical software.

Results
Search results

From a total of 231 retrieved publications, after applying the selection criteria, 14 studies were found suitable for the analysis (Figure 1).[4–17]

The design of the analyzed papers was prospective in seven studies and retrospective in the other seven studies. According to the extracted data, different scenarios of advanced disease were included (LAPC with or without metastatic disease and locally recurrent PC both after surgery and/or RT). From a total of 469 patients, 190 patients reported with pain before SBRT treatment in 12 studies.[4–7,9–12,14–17] Two studies[8,13] did not report the number of patients with pain before SBRT.

Literature review

Hoyer et al treated 22 patients using a standard linear accelerator (LINAC) and delivering 45 Gy in three fractions (EDQ$_2$: 93.8 Gy) to a PTV defined as the gross tumor volume (GTV) plus edema plus 5–10 mm margin. Chemotherapy was not used, and no pain response was recorded. The authors reported increased pain 2 weeks after treatment and 22.5% of patients experiencing severe gastrointestinal (GI) toxicity.[4]
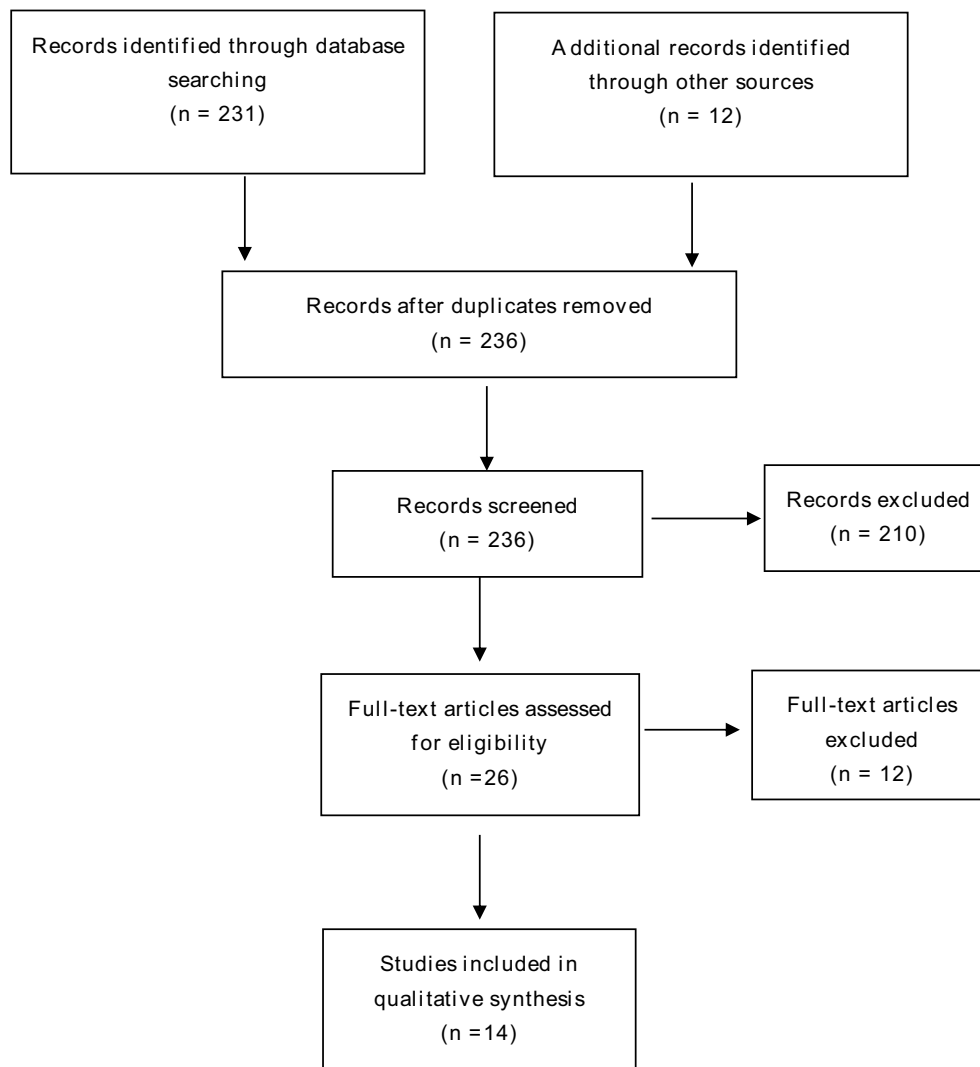
Figure 1 Flow diagram of study identification and selection.

Seo et al treated 30 patients with T4 stage (N1: 30%) in a Phase I dose escalation study using a robotic LINAC. A single SBRT fraction dose between 14 and 17 Gy (median: 16.5 Gy; EDQ_2: 76.4 Gy) was delivered to the PTV (GTV +2–4 mm) as a boost after conformal RT. Seventy percent of patients received induction or adjuvant chemotherapy and 55.6% of patients reported reduced analgesic consumption (RAA).[5]

Didolkar et al treated 85 LAPC patients (24.5% of them also had distant metastases) using a robotic device to deliver a dose between 15 and 30 Gy (median: 25.5 Gy) in three fractions (median EDQ_2: 39.3 Gy) to the PTV (GTV +3 mm). Chemotherapy was administered to 100% of patients after SBRT. The authors reported 48.4% CR and 51.6% PR using a 0–10 scale, 18–24 weeks pain-free survival, and late toxicity (hemorrhage/obstruction) in 8.2% patients.[6]

Shen et al treated 20 LAPC patients using a robotic LINAC to deliver 32–55 Gy (median: 45 Gy; EDQ_2: 79.7 Gy) in three to six fractions (median: 4) to the PTV (GTV +3–5 mm). Chemotherapy was not administered. The authors reported 90% pain relief using a visual analog scale (VAS).[7]

Polistina et al treated 23 patients with LAPC and <6 cm maximum tumor size using a robotic device to deliver 30 Gy in three fractions (EDQ_2: 50.0 Gy). Both induction and adjuvant chemotherapy were administered in all patients before and after SBRT. The authors did not report significant reduction in pain response using a VAS scale.[8]

Rwigema et al treated 71 patients (LAPC: 56; recurrence: 16; metastatic disease: 11; residual disease after surgery: 17) using a standard or robotic LINAC to deliver a single fraction of 18–25 Gy (median: 24; EDQ_2: 68.0 Gy) to the PTV (GTV +2 mm). Ninety percent of patients received

both induction and adjuvant chemotherapy. The authors reported 81.3% CR.[9]

Macchia et al treated 16 PC patients (cT4: 87.5%, local recurrence: 12.5%) using a standard LINAC to deliver 20–35 Gy (median: 25 Gy; EDQ_2: 31.3 Gy) in five fractions prescribed to the PTV (GTV +≥10 mm). All patients received chemotherapy before SBRT. The authors reported CR, PR, and RAA as 25.0%, 31.3%, and 40.0%, respectively. Late toxicity (duodenal bleeding) was recorded in 6.2% of patients.[10]

Wild et al treated 18 patients with LAPC or recurrent disease using a standard LINAC to deliver 20–27 Gy (median: 25 Gy; EDQ_2: 31.3 Gy) in five fractions to the PTV (internal target volume +1–3 mm). Chemotherapy was administered to 28.0% of patients after SBRT. The authors reported 57.0% "effective palliation" and 6.0% late small bowel obstruction.[11]

Tozzi et al treated 30 patients with LAPC or recurrent disease using a standard LINAC to deliver 45 Gy in six fractions (EDQ_2: 65.5 Gy) to the PTV (GTV +5–10 mm). Chemotherapy was administered before SBRT to all patients. The authors reported suspension of analgesic administration (SAA) and RAA in 63.6% and 36.4% of patients, respectively, using a Numerical Rating Scale (NRS).[12]

Herman et al treated 49 LAPC patients using a standard LINAC to deliver 33 Gy in five fractions (EDQ_2: 45.7 Gy) to the PTV (GTV +2–3 mm). Induction chemotherapy was administered to 90.0% of patients and adjuvant chemotherapy to all patients after SBRT. The authors reported a reduction of 8 points of pain from baseline (25 points) using the quality of life questionnaire for patients with pancreatic cancer (QLQ-PAN 26) scoring system. GI late toxicity rate was 6.4%.[13]

Su et al treated 25 patients with LAPC or metastatic disease using a robotic LINAC to deliver 36 Gy in three fractions (EDQ_2: 66.0 Gy) or 30–48 Gy in three to four fractions to the PTV (GTV +1–2 mm). Both induction and adjuvant chemotherapy were used in 8.0% of patients before and after SBRT. The authors reported 50.0% and 15.0% SAA and RAA rates, respectively, using an NRS scale.[14]

Kim et al treated 26 not operable patients using a standard or robotic LINAC to deliver a median dose of 24 Gy (range: 24–36 Gy) in one to three fractions (median EDQ_2: 68.0 Gy) to the PTV (GTV +2 mm). Induction and adjuvant chemotherapy were used in 15.0% and 23.0% of patients, respectively. The authors reported SAA in 35.7% of patients.[15]

Comito et al treated 31 patients with isolated recurrent disease using a Flattening Filter Free Rapidarc technique to deliver 45 Gy in six fractions (EDQ_2: 65.5 Gy) to the PTV (GTV +5–7 mm). Induction and adjuvant chemotherapy was administered in 20.0% and 77.0% of patients before and after SBRT, respec-

tively. The authors reported SAA and RAA in 58.0% and 40.0% of patients, respectively, using an NRS scale.[16]

Koong et al treated 23 previously irradiated patients with local recurrences using a standard or robotic LINAC to deliver 25 Gy in five fractions (EDQ_2: 31.3 Gy) to the PTV (internal target volume +2–3 mm). Induction chemotherapy was delivered in 26.1% of patients. The authors reported "pain improvement" in 57.1% of patients.[17]

Patients' clinical stage was not reported in nine studies.[6,8,11–14,16,17] In one study, 100% of patients had cT4 tumor stage,[5] while in another trial, this rate was 87.5%.[10] In two studies only, patients with stage II–IV were enrolled[7,15] and in another, all patients had T1–3 N0 M0 PC.[4]

Different treatment devices were used including robotic LINACs (six reports),[5–8,14,16] standard LINACs (five studies),[4,10–13] and both (three papers).[9,15,17]

Thirteen studies reported the details of PTV definition: eleven studies used a 1–5 mm GTV/internal tumor volume to PTV margin,[5–7,9,11–17] one study used a >10 mm GTV to PTV margin,[10] and only Hoyer et al defined the PTV as the GTV plus edema plus 5–10 mm.[4]

Dose prescription, reported in 12 of 14 papers, was according to the International Commission on Radiation Units-62 in one study[10] and to specific isodose lines ranging from 67% to 100% in eleven studies.[4–7,9,11–16] The median prescribed SBRT doses ranged from 16.5 to 45 Gy (median: 27.8 Gy), while the number of fractions ranged from 1 to 6 (median: 3.5). The computed median $EQD_{2[\alpha/\beta=10]}$ ranged from 31.3 to 93.8 Gy (median: 65.5 Gy) and the median $EQD_{2[\alpha/\beta=3]}$ from 40.0 to 162.0 Gy (median: 95.0 Gy).

Twelve studies reported induction or adjuvant chemotherapy regimens in patients ranging from 8.0% to 100.0%.[5,6,8–17] The characteristics and main results of these publications are reported in Table 1.

Pain relief

The pain response was scored using different scales: NRS in three studies,[12,14,16] VAS in three studies,[6–8] and QLQ-PAN-26 in one study.[13] Six studies did not report the assessment scale.[4,5,10,11,15,17] Twelve of the 14 studies reported various rates of pain relief.[5–7,9–17] Six studies[5–7,10,12,14–16] reported 69.50% rates of RAA or SAA (95% CI, 59.49%–78.31%), with high heterogeneity between studies (Q^2 test: $P<0.0001$; $I^2=86.44$%) to describe pain relief after SBRT (Figure 2). Three studies reported 54.25% CR rates in 56 patients (95% CI, 40.76%–67.29%), with high heterogeneity (Q^2 test: $P<0.013$; $I^2=76.68$%)[9,5,8] (Figure 3). Overall global response rate to pain in terms of CR or PR as reported in 85 patients from

five studies was 84.9% (95% CI, 75.8%–91.5%), with high heterogeneity again (Q^2 test: $P<0.001$; $I^2=83.63\%$),[5,6,8,9,14,16] as shown in Figure 4. Only one study[6] reported pain-free survival ranging from 18 to 24 weeks. One study reported no significant pain reduction,[8] while another study reported a significant worsening of pain 2 weeks after SBRT.[4]

Toxicity

All studies reported toxicity using the following scoring systems: Radiation Therapy Oncology Group in four studies,[5,7,10,15] CTCAE in five studies,[6,8,12,16,17] and WHO in one study,[4] while four studies did not report the used scale.[9,11,13,14] Acute and late toxicity (grade ≥3) rates were 3.3%–18.0% and 6.0%–8.2%, respectively. Reported gastrointestinal complications were duodenal obstruction/ulcer, small bowel obstruction, duodenal bleeding, hemorrhage, and gastric perforation.

Discussion

We performed a systematic review to analyze the impact of SBRT on pain control in patients with PC. Our analysis has several limitations. Overall, only few studies that reported on pain control were included in the analysis. Secondly, only 4/14 studies had a prospective design, and are therefore more credible in the evaluation of results. Furthermore, in eleven studies, the number of patients with pain before treatment was <20. Inclusion criteria were inconsistent, with some studies including only primary tumors and others also including local recurrences. Treatment techniques were uneven in terms of target definition, dose and fractionation, and dose prescription. In addition, percentages of patients who underwent chemotherapy were variable between the different studies. Finally, criteria and methods for assessing pain and toxicity were widely variable in the analyzed papers.

Another limitation of our study is the lack of a systematic evaluation of the quality of the analyzed studies and, in particular, the risk of bias. However, having clearly observed that no study considered pain palliation as a primary objective and that the description of this endpoint was reported in all the studies in a synthetic and not systematic way, it is obvious that for the purposes of our analysis, all the studies have a low-level quality.

However, despite these limitations, most studies reported pain improvement after SBRT. Only two studies reported no changes[8] or pain worsening.[4] Nevertheless, it should be noted that in the first study, the comparison between VAS before and after SBRT was performed in all treated patients, without any separate analysis on the group with pain before treatment.[8] Obviously, this limitation could have reduced the possibility

to detect a significant improvement of pain. The second study was the one delivering the highest EQD_2 (using α/β values of 3 and 10) from all the analyzed series.[4] Furthermore, the PTV was defined with larger margins compared to those reported in all other studies (GTV+surrounding edema+5–10 mm). This is probably the reason of the high GI complications rate (grade ≥3: 22.5%) and of increased pain due to gastric-duodenal ulcerations.[4]

Except for these two studies, in all other reports, a reduction in pain was achieved, in most cases exceeding 50% of patients. The variability of symptomatic response evaluation hinders the analysis of dose and pain response relationship. However, it could be noted that considering the studies reporting the pain CR rate, this value was <50% in two studies with 31.3 and 39.3 Gy median $EDQ_{2[\alpha/\beta=10]}$[6,10] and was 81.3% in a study with 68.0 Gy median $EDQ_{2[\alpha/\beta=10]}$.[9]

In some studies, cases of severe GI toxicity were recorded. The prevention of toxicity should be pursued to avoid worsening of QoL in these patients with generally poor performance status.[18,19]

Trying to correlate the $EQD_{2[\alpha/\beta=3]}$ with late toxicity, no clear threshold between delivered dose and long-term side effects was observed. In fact, in some series with low (40 Gy) $EQD_{2[\alpha/\beta=3]}$, both late bleeding[10] and bowel obstruction[11] were reported, while in most series with high (104.4–129.6 Gy) $EQD_{2[\alpha/\beta=3]}$, no cases of late toxicity were observed.[5,7,9,14,15]

More specifically, in the studies reporting cases of late toxicity,[4,6,10,11,13] the median $EQD_2(\alpha/\beta: 3)$ was 58.6 Gy (range: 40.0–162.0 Gy), while in the studies not reporting late toxicity,[5,7–9,12,14–17] the median value was 104.4 Gy (range: 40.0–135.0 Gy). On the basis of these paradoxical data, it is difficult to identify a correlation between dose and toxicity. If we consider the series in which >50% of patients received chemotherapy,[5,6,8–10,12,13,16] three out of eight studies reported late toxicity (37.5%). Instead, if we consider studies in which <50% of patients received chemotherapy,[11,14,15,17] only one-fourth reported late toxicity (25%). This is evidently a modest difference that does not allow us to establish a clear correlation between chemotherapy and radiation-induced toxicity. Instead, considering the studies reporting the maximum GTV to PTV radial margin, we observed that the median value was 6.5 mm (range: 3–10 mm) in the studies with late toxicity[4,6,10,13] and 2 mm (range: 2–7 mm) in the studies without late toxicity.[5,7,9,12,14–16] From this simple qualitative assessment, the width of the GTV–PTV margins seems to be the parameter most correlated to toxicity.

The results of our study in terms of the relationship between toxicity and dose are different compared to those of

Table 1 Characteristics and outcomes of analyzed studies

Author, year	Study design	Inclusion criteria	Patients (with pain)	Stage	Technique	PTV	Dose prescription
Hoyer et al, 2005[4]	Phase I–II	LA	22 (15)	$T_{1-3}N_0M_0$	SBRT with standard LINAC	GTV+edema+5–10 mm	PTV encompassed by 67% isodose
Seo et al, 2009[5]	Phase I	LA, no duodenal invasion, <3 N+	30 (18)	T_4: 100.0% N_1: 30.0%	RRS	GTV+2 mm (4 mm CC)	To isodose covering 97% of PTV
Didolkar et al 2010[6]	Retrospective	LA	85 (Moderate: 21.2%, severe: 15.3%)	LA M_1: 24.7[c]	RSBRT	GTV+3 mm	To 80% isodose
Shen et al, 2010[7]	Case series	LA	20 (15)	Stage II–III	RSBRT	GTV+3–5 mm	$V_{75\%}>95\%$
Polistina et al, 2010[8]	Case series	LA <6 cm	23 (NR)	N_1: 60.8%	RSBRT	NR	NR
Rwigema et al, 2011[9]	Retrospective	LA or M1[e]	71 (16)	LA: 56 Rec: 16 M_1: 11 R_1: 17	RRS or LINAC	GTV+2 mm	To 80%–89% isodose
Macchia et al, 2012[10]	Phase I	LA	16 (9)	T_4: 87.5%[f] Rec: 12.5%[f]	SBRT with standard LINAC	GTV+≥10 mm	ICRU-62
Wild et al, 2013[11]	Retrospective	LA or Rec (previous RT)	18 (7)	LA: 16.7% Rec: 83.3%	SBRT	ITV+1–3 mm	To isodose surrounding PTV
Tozzi et al, 2013[12]	Case series	LA or Rec ≤5 cm	30 (11)	LA: 70% Rec: 30%	VMAT FFF	GTV+5 mm (10 mm CC)	CTV $V_{95\%}=100\%$
Herman et al, 2015[13]	Phase II	LA	49 (NR)	NR	SBRT (VMAT)	GTV+2–3 mm	$V_{100\%}>90\%$
Su et al, 2015[14]	Retrospective	LA or M1	25 (20)	LA: 25 M_1: 16	RSBRT	GTV+1–2 mm	$V_{93\%}>97$
Kim et al, 2013[15]	Retrospective	Not surgical candidates	26 (16)	Stage I–IV	LINAC or RRS or RSBRT	GTV+2 mm	To 80%–93% isodose
Comito et al, 2017[16]	Retrospective	Isolated Rec	31 (20)	Local Rec	Rapidarc FFF	ITV+5 mm or GTV+5–7 mm	To mean PTV dose
Koong et al, 2017[17]	Retrospective	Previously irradiated local Rec	23 (14)	Local Rec, M_0	RSBRT or standard LINAC	ITV+2–3 mm	NR

Notes: [a]Induction. [b]Of 12 patients evaluated at 3 months, 50% had "less pain". [c]Previous RT: 34.1%. [d]Only patients with moderate/severe pain. [e]Prior RT: 21%. [f]Ten patients received SBRT as a boost after chemoradiation. [g]Elevated aspartate/alanine aminotransferase: 10%.

Abbreviations: 3D-CRT, 3D-conformal radiation therapy; CC, cranio-caudally; CR, complete response; CTCAE, Common Terminology Criteria for Adverse Events; CTC, Common Toxicity Criteria; CTV, clinical target volume; EORTC, European Organization for Research and Treatment of Cancer; EQD_2, biologically equivalent doses in 2 Gy fractions; FFF, filter flattering free; GI, gastrointestinal; GTV, gross tumor volume; ICRU, International Commission on Radiation Units; ITV, internal tumor volume; LA, locally advanced; LINAC, linear accelerator; M, metastases; NA, not administered; N, nodes; NR, not reported; NRS, Numerical Rating Scale; PR, partial response; PTV, planning target volume; RAA, reduction of analgesic administration; Rec, recurrence; RRS, robotic radiosurgery; RSBRT, stereotactic radiosurgery; RT, radiation therapy; RTOG, Radiation Therapy Oncology Group; SAA, suspension of analgesic administration; SBRT, stereotactic RT; SF, single fraction; VAS, visual analog scale; VMAT, volumetric modulated arc therapy; WHO, World Health Organization.

RT dose, median (range)	EQD2 α/β: 10 (median)	EQD2 α/β: 3 (median)	% of patients receiving chemotherapy[a]	Pain response rate, % (criteria)	Pain-free survival (months)	Grade 3–4 toxicity % (scale)
45 Gy in three fractions	93.8	162.0	NA	NR	At 2 weeks increased pain (*P*: 0.008)[b]	Gastric-duodenal mucositis/ulceration: 18.0 Gastric perforation: 4.5 (WHO)
40 Gy in 2 Gy/fraction (3D-CRT)+16.5 Gy (14–17) SF RRS boost	76.4	104.4	70.0[a] (6 before RT; 15 concurrent to 3D-CRT)	RAA: 55.6 (NR)	NR	Acute: duodenal obstruction 3.3; late 0.0 (RTOG)
25.5 Gy in three fractions (15–30)	39.3	58.6	100 after	CR: 48.4 PR: 51.6[d] (0–10 scale)	18–24 weeks	Acute: duodenitis (14.1) gastritis (12.9) diarrhea (3.5); late: hemorrhage/obstruction (8.2) (CTC 2.0)
45 Gy (32–55) in four (3–6) fractions	79.7	128.2	NA	"Pain relief": 90.0 (VAS)	NR	Acute: 0.0 Late: 0.0 (RTOG)
30 Gy in three fractions	50.0	78.0	100[a] and after	No significant reduction (VAS)	NR	Acute: 0.0 Late: 0.0 (CTC 3.0)
24 Gy SF (18–25)	68.0	129.6	90[a] and/or after	CR: 81.3 (NR)	NR	Acute GI: 4.2 Late: 0.0 (NR)
25 Gy in five fractions (20–35)	31.3	40.0	100[a]	CR: 25.0 PR: 31.3 RAA: 40.0 (NR)	NR	Acute: 0.0 Late: duodenal bleeding: 6.2 (RTOG)
25 Gy in five fractions (20–27)	31.3	40.0	28 after SBRT	57 "Effective palliation" (NR)	NR	Acute: 0.0 Late: small bowel obstruction: 6.0 (NR)
45 Gy in six fractions (36–45)	65.5	95.0	100[a]	SAA: 63.6 RAA 36.4 (NRS)	NR	Acute: 0.0 Late: 0.0 (CTC 3.0)
33 Gy in five fractions	45.7	63.4	90[a] 100 after	Reduction of 8 points from baseline: 25 points (QLQ-PAN 26)	NR	Acute: duodenal ulcer: 2.0[g]; late: duodenal ulcer/bleeding: 6.4 (NR)
36 Gy in three fractions (30–48 in three to four fractions)	66.0	108.0	8[a] 8 after	SAA: 50.0 RAA: 15.0 (NRS)	NR	Acute: 0.0 Late: 0.0 (NR)
24 (24–36) Gy in one to three fractions	68.0	135.0	15.0[a] 23.0 after	Pain relief: 75.0 SAA: 31.3 (NR)	NR	Acute: 0.0 Late: 0.0 (RTOG/EORTC)
45 Gy in six fractions	65.5	95.0	20[a] 77 after	SAA: 58.0 RAA: 40.0 (NRS)	NR	Acute: 0.0 Late: 0.0 (CTCAE V.4.0)
25 Gy in five fractions	31.3	40.0	26.1[a]	"Relative improvement" 57.1 (NR)	NR	Acute: GI (8.7); late: 0.0 (CTCAE v. 4.0)

Author, year	Sample Size	Proportion (%)	95% CI	Weight (%)	
Meta-analysis				Fixed	Random
Seo Y et al., 2009 [4]	18	55.55	30.75 - 78.47	19.00	17.10
Macchia G et al., 2012 [9]	9	40.00	11.05 - 75.45	10.00	15.44
Tozzi A et al., 2013 [11]	11	100.00	71.50 - 100.00	12.00	15.99
Su T et al., 2015 [13]	20	65.00	40.78 - 84.60	21.00	17.30
Kim CH et al., 2013 [14]	16	31.25	11.01 - 58.66	17.00	16.87
Comito T et al., 2017 [15]	20	98.00	79.72 - 100.00	21.00	17.30
Total (fixed effects)	94	69.50	59.49 - 78.31	100.00	100.00
Total (random effects)	94	68.83	42.44 - 89.90	100.00	100.00

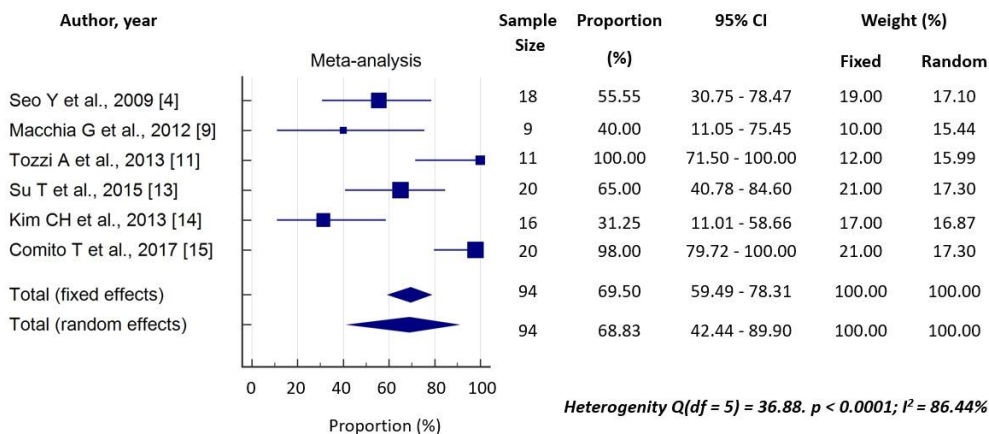*Heterogenity Q(df = 5) = 36.88. p < 0.0001; I^2 = 86.44%*

Figure 2 Overall response rate to analgesic administration in terms of reduction and suspension of analgesic therapy.
Notes: Based on six studies (94 patients), the overall response rate to analgesic administration in terms of reduction or suspension of analgesic therapy was 69.5% (95% CI, 59.5%–78.3%), with high heterogeneity between studies (Q^2 test: $P<0.0001$; I^2=86.44%).
Abbreviation: df, degrees of freedom.

Author, year	Sample size	Proportion (%)	95% CI	Weight (%)	
				Fixed	Random
Didolkar MS et al., 2010 [5]	31	48.38	30.15 - 66.93	54.24	37.75
Rwigema ICM et al., 2011 [8]	16	81.25	54.35 - 95.95	28.81	33.53
Macchia G et al., 2012 [9]	9	25.00	3.81 - 62.66	16.95	28.73
Total (fixed effects)	56	54.25	40.76 - 67.29	100.00	100.00
Total (random effects)	56	53.23	26.08 - 79.38	100.00	100.00

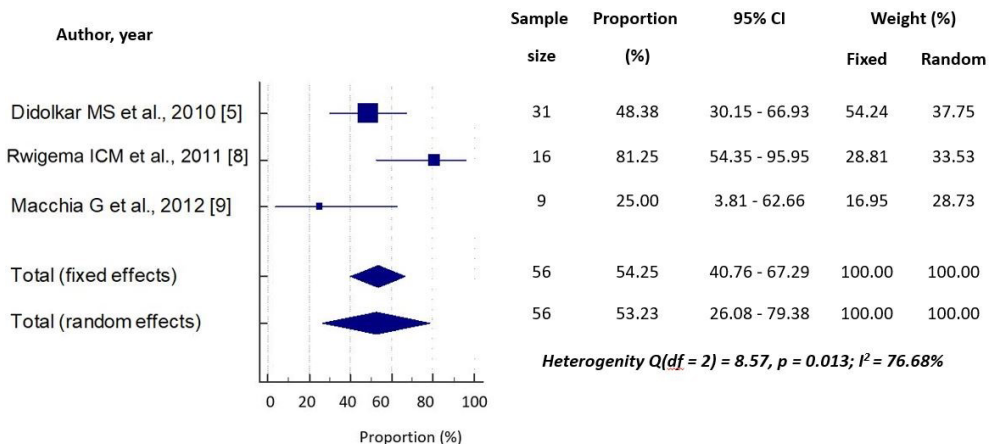*Heterogenity Q(df = 2) = 8.57, p = 0.013; I^2 = 76.68%*

Figure 3 Overall complete response to pain.
Notes: Based on three studies (56 patients), the overall complete response rate to pain was 54.2% (95% CI, 40.8%–67.3%), with high heterogeneity (Q^2 test: $P<0.013$; I^2=76.68%).
Abbreviation: df, degrees of freedom.

Author, year	Sample size	Proportion (%)	95% CI	Weight (%)	
				Fixed	Random
Didolkar MS et al., 2010 [5]	31	100.00	88.78 - 100.00	35.56	21.91
Shen Z et al., 2010 [6]	15	90.00	63.65 - 99.27	17.78	20.00
Macchia G et al., 2012 [9]	9	55.55	21.20 - 86.30	11.11	18.11
Kim CH et al., 2013 [14]	16	75.00	47.62 - 92.73	18.89	20.21
Koong AJ et al., 2017 [16]	14	57.07	28.80 - 82.28	16.67	19.77
Total (fixed effects)	85	84.91	75.82 - 91.59	100.00	100.00
Total (random effects)	85	79.03	54.72 - 95.52	100.00	100.00

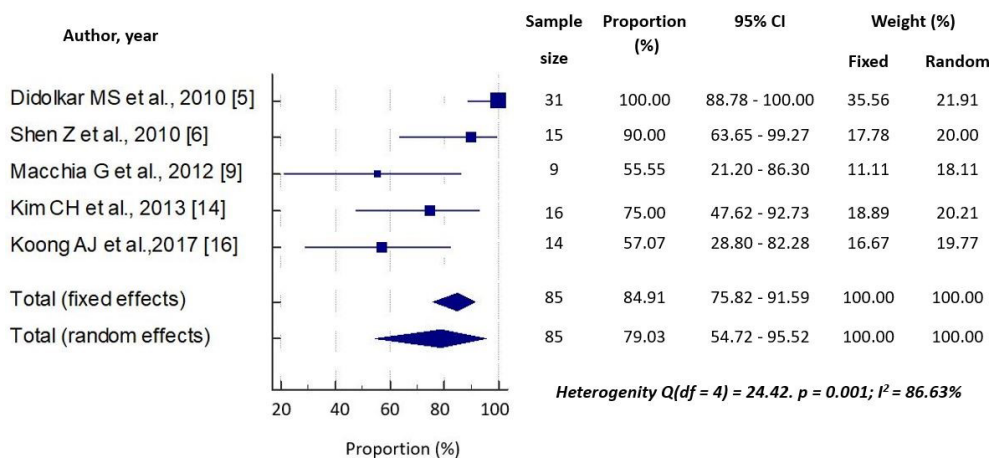*Heterogenity Q(df = 4) = 24.42. p = 0.001; I^2 = 86.63%*

Figure 4 Overall global response to pain.
Notes: Based on five studies (85 patients), the global response rate to pain in terms of complete and partial response rate was 84.9% (95% CI, 75.8%–91.6%), with high heterogeneity (Q^2 test: $P<0.001$; I^2=83.63%).
Abbreviation: df, degrees of freedom.

Brunner et al,[18] but the different methods of analysis and the selection criteria should be considered. In fact, in our analysis, only studies reporting data on pain relief were included.

The efficacy of RT in pain relief in this setting is not new. Patients with LAPC treated with standard chemoradiation experienced pain reduction (in 35%–65% of cases).[20] However, the rate of toxicity recorded in SBRT series seems lower compared to standard radio-chemotherapy. In fact, rates of 36%–79% grade 3–4 toxicity and 41% of grade 4–5 toxicity were reported in concurrent chemoradiation studies.[21–23] Furthermore, the survival outcome recorded in series of chemoradiation and SBRT seems relatively similar.[24]

Also, chemotherapy alone can reduce pain in patients with LAPC.[25] Therefore, it could be interesting to compare the palliation results of chemotherapy with the ones of SBRT or to evaluate the efficacy in terms of pain relief by combining the two treatments. Unfortunately, our analysis is not able to provide indications on these topics because in most series, both SBRT and chemotherapy were administered, and therefore, we cannot compare the two treatments. Furthermore, it is difficult to evaluate the efficacy of combining the two treatments because pain response was evaluated comparing the intensity of this symptom before and after SBRT and not before and after the whole treatment (SBRT+chemotherapy).

Other ablative therapies have been proposed in the treatment of LAPC, such as radiofrequency ablation, irreversible electroporation, high-intensity focused ultrasound, iodine 125, cryosurgery, photodynamic therapy, and microwave ablation. A literature review reported the possibility to reduce pain with some of these treatments such as radiofrequency ablation, irreversible electroporation, SBRT, and high-intensity focused ultrasound. However, among these treatments, SBRT was found to be the only procedure without related mortality and with proven efficacy in QoL improvement.[26]

Based on the results of this analysis, SBRT can be considered as an option in the treatment of symptomatic patients with LAPC. However, a high level of accuracy is required in treatment planning and delivery to reduce the risk of GI complications. Guidelines are available in literature to minimize the probability of side effects.[18,19] Furthermore, more sophisticated and advanced techniques are now available to improve precision in SBRT delivery, such as intensity-modulated RT,[27] simultaneous integrated boost,[3,28] respiratory gating,[29] and adaptive re-planning.[30]

In conclusion, SBRT achieves pain relief in most patients with PC. Furthermore, late toxicity was recorded in only a minority of studies and, even in these, with an incidence of <10%. Therefore, the recorded toxicity can be considered acceptable. Further prospective studies on the palliative role of SBRT in LAPC are needed to define the optimal dose/fractionation and the best systemic therapies modality integration with the aim to reduce toxicity and improve the palliative outcome. Finally, QoL and, particularly, pain control should be considered as an endpoint in all future trials on this emerging treatment technique.

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Disclosure

The authors report no conflicts of interest in this work.

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