Curr Oncol Rep (2015) 17:419
DOI 10.1007/s11912-014-0419-8

GASTROINTESTINAL CANCERS (B CZITO, SECTION EDITOR)

Intraoperative Radiotherapy for Gastrointestinal Malignancies: Contemporary Outcomes With Multimodality Therapy

Felipe A. Calvo · Claudio V. Sole · Hugo Marsiglia · Eduardo Alvarado · Carlos Ferrer · Brian Czito

Published online: 22 November 2014

Abstract The integration of intraoperative radiotherapy (IORT) into the multimodal treatment of gastrointestinal cancer is feasible and leads to high rates of local control. In-field tumoral control using IORT-containing strategies can be achieved in over 90 % of most cases, regardless of the site or status of the tumor (primary or recurrent). Electron beam IORT, or intraoperative electron radiation therapy, is the dominant technology used in institutions reporting data in publications the 21st century. Neither surgery nor systemic therapy is compromised by the integration of IORT-containing radiotherapy.

Keywords Gastrointestinal malignancies · Intraoperative radiotherapy · Local control

Supported in part by a grant from the Carlos III Institute of Health Research, Spanish Ministry of Science and Innovation (project code PI11-02908)

This article is part of the Topical collection on *Gastrointestinal Cancers*

F. A. Calvo · E. Alvarado
Department of Oncology, Hospital General Universitario Gregorio Marañón, Ave. Doctor Esquerdo 46, 28007 Madrid, Spain

C. V. Sole (✉)
Department of Radiation Oncology, Instituto de Radiomedicina, Ave. Americo Vespucio Norte 1314, 7630370 Santiago, PC, Chile
e-mail: cvsole@uc.cl

H. Marsiglia
Department of Radiation Oncology, Institute Gustave Roussy, Ave. 114 Rue Édouard Vaillant, 94805 Villejuif, France

C. Ferrer
Oncology Institute, Hospital Provincial de Castellón, Spain Avda. Doctor Clara 19, 12002 Castellon, Spain

B. Czito
Department of Radiation Oncology, Duke University Hospital, Box 3085, Durham, NC 27710, USA

Introduction

The incidence of digestive tract tumors has increased considerably over the last decade [1]. In contemporary treatment approaches, multimodal strategies have become the cornerstone of therapy for locally advanced and borderline resectable gastrointestinal tumors. By the end of this decade, indications for radiotherapy are anticipated to increase by 20–30 % relative to current levels [2]. Despite therapeutic improvements such as the integration of chemoradiotherapy (CRT) with surgery, as well as increasingly efficacious chemotherapeutic agents, locoregional failure remains common in many gastrointestinal malignancies and cure rates suboptimal [3••]. Current treatment options to improve tumor outcomes through enhancing locoregional control rates include radiotherapy dose escalation. Factors limiting the implementation of this approach include the high sensitivity of normal digestive tract tissues to higher radiation doses (including a higher risk of fibrosis, stenosis, and necrosis which increases exponentially when conventionally fractionated doses of 50 Gy are exceeded, particularly to larger volumes). Similarly, gastrointestinal tumors frequently recur at challenging anatomical sites where it is not feasible to re-irradiate to significant or curative doses of external beam radiotherapy (EBRT) [4]. In this clinical scenario, intraoperative radiotherapy (IORT) is an attractive option for maximizing local cancer control, given areas of residual disease can be treated appropriately and to higher radiation doses, without damage to critical organs through normal organ shielding and temporary mobilization away from the treatment field [5••].

In this article, we review the indications for and outcomes of IORT administered in the treatment of tumors at various gastrointestinal sites and provide updated clinical data.

Gastric Cancer

Historically, treatment of gastric cancer has been challenging, and disease-related outcomes suboptimal, even with the use of adjuvant treatments. Based on improved survival outcomes from the Intergroup/SWOG 0116 trial, postoperative 5-FU-based chemoradiotherapy (45 Gy in 25 fractions) has become the standard adjuvant treatment approach for locally advanced gastric cancer patients in the USA [6]. The role of perioperative chemotherapy was addressed in the Medical Research Council Adjuvant Gastric Infusional Chemotherapy trial [7], also demonstrating a survival advantage in these patients. However, both trials showed that outcomes following multimodal therapy remain suboptimal, with local or regional recurrences of approximately 19 and 65 %, respectively [6, 7]. Although the addition of IORT has been associated with improved locoregional control in these patients, an overall survival (OS) benefit has not been proven [8, 9]. Zhang et al. [9] analyzed 97 patients with gastric adenocarcinoma (T3/4 or N+) treated with adjuvant CRT combined with (47 %) and without (53 %) intraoperative electron radiation therapy (IOERT; dose range, 12–15 Gy). Five-year locoregional control rates were 50 and 35 % for patients treated with and without IOERT (p=0.04), respectively. It has also been reported that following IORT, the primary pattern of cancer progression within the upper abdominal region (80 %) involved the hepatic hilum area, with no progression observed within the IORT-treated field, highlighting the need to carefully define the treatment field when metastatic nodal disease is present [8].

Treatment-related toxicity remains a long-term clinical challenge in the multimodal treatment of gastric cancer [6–9]. The tolerance of upper abdominal organs and structures to EBRT following gastric resection was evaluated in a clinical trial, which showed that although local control rates were improved, complication rates increased with the use of IORT when compared with non-IORT approaches (44 vs 20 %; p<0.05) [10]. These results should be interpreted in the context that IORT doses utilized in this trial were higher than standardly recommended. The evaluation of the efficacy of IORT in combination with other (neo) adjuvant modalities is relevant when investigating synergistic or additive therapeutic effects in gastric cancer patients. Similarly, the benefits of improved locoregional control should be weighed against the increased risk of toxicity in these patients.

Esophageal and Gastroesophageal Cancer

Recognition of the high risk of locoregional recurrence after surgery-alone or definitive combined-modality therapy in esophageal and gastroesophageal cancer [11] has led to increased interest and investigation in the use of IORT to promote improved control through dose escalation beyond the standard limits of EBRT. Recent prospective experiences have reported locoregional recurrence rates from 20 to 40 % at 2, 3, and 5 years following trimodality treatment [11]. Studies focusing on the implementation of IORT in esophageal and gastroesophageal cancers [12–15] have demonstrated a reduced risk of locoregional recurrence in the upper abdomen or mediastinum, although similar to gastric cancer, a convincing survival benefit has not been demonstrated. Hosokawa et al. [12] reported on 121 patients who received IORT (range, 12–25 Gy) following surgery. Of these, 85 % received adjuvant mediastinal radiotherapy (45 Gy in 16 fractions). Five-year OS and disease-free survival (DFS) were 34 and 55 %, respectively; no mediastinal lymph node recurrence was observed. Miller et al. [14] reported on 24 patients with esophageal (n=7) and gastroesophageal tumors (n=17) as part of a larger cohort of 50 patients with primary and recurrent stomach cancer. No central failures were detected after a median follow-up of 20 months. Calvo et al. [15] analyzed 53 patients with primary esophageal carcinoma (44 %) or gastroesophageal carcinoma (56 %) and locoregional disease (clinical stage IIb [n=30; 57 %], IIIa [n=14; 26 %], IIIb [n=6; 11 %], IIIc [n=3; 6 %]) who received preoperative CRT and complete resection. Thirty-seven patients also received a preanastomotic reconstruction IOERT boost (10–15 Gy) to the tumor bed (mediastinum and/or the celiac lymph node basin). With a median follow-up time of 27.9 months, locoregional recurrence rate was 15 %. Five-year OS and DFS rates were 48 and 36 %, respectively. Multivariate analysis demonstrated only the IOERT group retained significance in relation to locoregional recurrence (p=0.01). Postoperative mortality was 11 % (n=6) and the frequency of perioperative complications 30 % (n=16).

Assessment of the toxicity of IORT for esophageal cancer has been variable, with many investigators reporting few complications. Specific types of toxicity have been associated with IOERT (e.g., upper gastrointestinal tract bleeding for gastric and pancreatic carcinomas); however, the frequency of toxicity is generally acceptable if IORT dose does not exceed 20 Gy [16].

Pancreatic Cancer

The relative ineffectiveness of standard doses (45–54 Gy) of postoperative EBRT in patients with resected pancreatic carcinoma and the recognition of high rates of locoregional recurrence following surgery or combined-modality therapy [17] have led to increased interest in the use of IORT as a means of improving locoregional control through dose escalation, beyond the limits of what is attainable with EBRT-alone approaches [18]. Few studies have focused on combined CRT and IORT in pancreatic cancer [19–22], with a decrease in the risk of locoregional recurrence consistently reported. The most extensive (n=270) analysis evaluating EBRT plus

IORT was performed by Valentini et al. [19], who found that pooled group 5-year local control was 23.3 % and 5-year survival was 17.7 %. In this series, improved locoregional control and survival were observed in patients receiving preoperative EBRT (locoregional control, median not reached; OS, median 30 months) compared to patients receiving postoperative EBRT (locoregional control, median 28 months; OS, median 22 months) and in patients who underwent postresection IORT exclusively (locoregional control, median 8 months; OS, median 13 months) ($p<0.0001$). Jingu et al. [21] reported the largest single-center experience, spanning over 30 years. Among 192 patients receiving IOERT (R0 resection, 48; R1, 35; R2, 109), 29 % received additional adjuvant EBRT and 65 % received adjuvant chemotherapy. Multivariate analysis showed that the degree of resection (R0-1 vs. R2, $p=0.001$) and adjuvant chemotherapy ($p=0.028$) had a significant impact on OS. Ogawa et al. [20] reported data from a multicenter analysis of 210 patients treated with gross total resection (R0, 70 %; R1, 30 %) and IORT (median, 25 Gy), with and without EBRT (70 %). Fifty-four percent of patients received chemotherapy. Local failure was observed in 14.8 %, and the 2-year local control rate was 83.7 %. On multivariate analysis, chemotherapy, completeness of resection, carbohydrate antigen 19–9, and pathological N stage had a significant impact on OS. Our group recently reported on 60 patients with pancreatic adenocarcinoma (clinical stage IB [$n=13$; 22 %], IIA [$n=16$; 27 %], IIB [$n=22$; 36 %], IIIC [$n=9$; 15 %]) treated with CRT (45–50.4 Gy) and curative resection [22]. Forty-eight percent of patients also received an IOERT boost (range, 10–15 Gy). With a median follow-up of 15.9 months, 5-year OS, DFS, and locoregional control were 20, 13, and 58 %, respectively. On multivariate analysis, only margin status (HR, 3.0; $p=0.05$) and omission of IOERT (HR, 6.75; $p=0.01$) retained significance with regard to locoregional recurrence. Treatment-related toxicity with combined modality therapy should also be considered (perioperative mortality, 3.8–6.0 %; perioperative complications, 23–36 %), which can limit the therapeutic index following surgery, EBRT, and chemotherapy [23]. Similar to a surgery-alone approach, complications related to the use of IORT and surgery include pancreatic fistula development, delayed gastric emptying, hemorrhage, and abdominal abscesses formation [19].

Colorectal Cancer

Dubois et al. [24] reported a phase III randomized clinical trial assessing the efficacy and tolerance of IORT (18 Gy) in patients with locally advanced rectal cancer ($n=142$; cT3, T4, or N+) treated with preoperative radiotherapy (40 Gy) and surgical resection. With a median follow-up of 61 months, 5-year OS (69.8 vs. 63.1 %, $p=0.26$), 5-year local control (91.8 vs. 92.8 %, $p=0.60$), and postoperative complication rates (29.6 vs. 19.1 % $p=0.15$) were not significantly different between the groups. These trial results confirmed the technical feasibility and acceptable tolerance profile of IORT delivery in this setting, although no long-term clinical benefit was observed, particularly in the context of inclusion of patients with less advanced disease in the study. Given there are limited options in terms of safe dose escalation or re-irradiating in certain clinical settings, IORT is an attractive option to further explore in clinical studies [25]. In contrast to the above, several analyses from expert IORT institutions have shown IORT use to be beneficial in patients with advanced T4 or recurrent disease, making it an attractive option in these settings where there is limited opportunity for dose escalation or re-irradiation [26]. Kusters et al. [25] performed the largest study to date ($n=605$) in a European multicenter cooperative analysis, including patients with locally advanced rectal cancer treated with preoperative radiotherapy (±CT), radical surgery, IORT, and elective adjuvant chemotherapy (42 %). Local relapse, distant metastasis, and OS rates were 12.0, 29.2, and 67.1 %, respectively. Risk factors associated with locoregional recurrence included lymph node metastasis, margin involvement, failure to achieve downstaging, and failure to deliver postoperative chemotherapy. The importance of obtaining an R0 resection is evident in primary and locally recurrent colorectal cancer patients. In locally advanced rectal cancer patients, IORT has been reported to compensate for positive margins [27, 28]. Advanced surgical techniques, including laparoscopic resection in locally advanced rectal cancer, can incorporate an IORT boost to the presacral area with equivalent cancer-related outcomes and improved clinical tolerance [29]. Haddock et al. [30] evaluated 607 patients with recurrent colorectal cancer treated with IOERT (range, 7.5–30 Gy) and external radiation (96 %; median dose, 45.5 Gy). Survival estimates at 5 years were 46, 27, and 16 % for R0, R1, and R2 surgical resections, respectively. Multivariate analysis revealed that R0 resection and no prior chemotherapy were associated with improved survival. Other factors associated with favorable outcomes included combined treatment with EBRT and IORT and lack of fragmentation of the tumor specimen [31]. Similar to other sites, secondary IORT-related complications range from 10 to 40 %, including wound-healing complications, fistulas, ureteral obstruction, and neuropathy [16].

Cancer of the Anal Canal

For patients with residual or recurrent squamous-cell carcinoma of the anus following definitive CRT, surgery is considered standard salvage treatment. Outcomes are worse in patients with unresectable or borderline unresectable disease; therefore, additional local therapeutic options to enhance disease control are appropriate [32]. Wright et al. [33] reported on 14 patients with locally recurrent squamous-cell carcinoma of the

Table 1 Select series of gastrointestinal malignancies receiving IORT and/or EBRT

Cancer/Author	*N*	Stage/status	IOERT Dose (Gy)	EBRT (%)	Adjuvant CT (%)	In-field LR (%)	LR (%)	DFS (%)	OS (%)	Comments
Esophagus										
Hosokawa [12]	121	I–IV	12–25	85	0	0	0	54	34.5	Improved survival pN0
Miller [14]	50	III–IV or recurrent	12.5 (10–25)	96	92		10	16	15	
Calvo [15]	37 16	IIb–IIIc	10–15 (med 10) 0	100 100	30 25	5.4 18.7	5 38	48 44	48 48	Significant improvement in LR/in-field LR with IORT
Gastric										
Calvo [8]	32	T2-4 N0-1 (stage II/III)	10–15	50	30	0	16	42 months	54	No significant difference in LRC based on adju vant treatment or TNM. No in-field recurrences
Zhang [9]	51 46	T3-4 or N+ T3-4 or N+	0 12–15	100 100	100 100		41 28			
Droguitz [10]	61 61	I–IV	23 (15–25) 0	0 0	0 0		10 NR		58 59	Historical controls
Pancreas										
Valentini [19]	270	pT1-4 pN0-1	15	64	12		77		17.7	Preoperative CRT associated with better LC. Started in 1980s, prior to CRT standardization
Ogawa [20]	210	pT1-4 pN0-1	25	30	54		16.3[a]	31.2[a]	42.1[a]	Association of IORT and CT improved OS. Use of chemotherapy, completeness of resection and N stage impacted on OS
Jingu [21]	192	IA-III (UICC 2002)	25	29	65		39[a]		16.9[a]	57 % R2 (palliative or biopsy only). EBRT had no correlation with LC. Degree of resection, adjuvant CT improved OS
Calvo [22]	29 31	IB, IIA, IIIC	15 –	100 100	62 61		42 (Overall) –	13 (Overall) –	20 (Overall) –	R2 excluded. No IORT associated with worse LC
Rectal										
Dubois [24]	69	T3/T4 or N+	–	100 Neoadjuvant	19 %	6	7	63	74.8	Phase III study, under-recruitment (50 %)
	73		18	100 Neoadjuvant	25 %	4	8	64	70	LRF: 3 patients (4.1 %) IF IORT and 3 patients (4.1 %) IF EBRT
Kusters [25]	605	T3-4	10–12.5	100 (Neo or adj)			12		67.1	

Table 1 (continued)

Cancer/Author	*N*	Stage/status	IOERT Dose (Gy)	EBRT (%)	Adjuvant CT (%)	In-field LR (%)	LR (%)	DFS (%)	OS (%)	Comments
Dresen [26]	147	Recurrent	10–17.5	38.7 (EBRT re-irradiation for recurrence)	100 % (Neo or adj) 30 (For recurrence)		46	34.1	35.1	Locally recurrent patients. IORT and re-irradiation used in dose escalation
Mirnezami [27]	3003	III–IV or recurrent	7.5–25				(Local control) OR 0.22 (95 %CI 0.05–0.86)	HR 0.51 (95 % CI 0.31–0.85)	HR 0.33 (95 % CI 0.2–0.54)	Systemic review/meta-analysis showing improved LC, DFS and OS with IORT
Alberda [28]	21 22	T3-4 N0/+or Tx N + (non-mesorectal). *CRM negative but <2 mm*	10 0	100 100	~1 ~1		30 21		63 % 81 %	Non-statistically significant difference
	31	T3-4 N0/+or Tx N + (non-mesorectal). *CRM affected*	10	100	~1		16		41	Significant difference in LR and OS favoring IORT treatment
	17		0	100	~1		59		13	Univariate analysis: IORT only significant OS predictor
Haddock [30]	607	Recurrent	15	96	99 (Concur/adj)	14	28		30	OS higher than previously published experience in non-IORT pts. Long-term survivors not seen in previous experience
Calvo [31]	60	Locally recurrent	10–15 (med 12.5)	47	50		56	37	43	
Zhang [35]	46 45	pT3N0	0 15–25 (mean 20)	100 0	100 100		14 16	73 71	86 84	No significant difference in disease-related outcomes. Significantly less toxicity for IORT
Anus										
Wright [33]	14	Locally recurrent	15 (15–17.5)	14	28		92.9[a]		21.4[a]	High-dose-rate IORT
Hallemeier [34]	32	Residual or recurrent	12.5 (7.5–20)	100	100	21	51	23	17	CMT including salvage surgery and IORT associated with long-term survival in a small, but significant subset

OS overall survival, *DFS* disease-free survival, *EBRT* external beam radiation therapy, *LR* local relapse

[a] 2 years

anal canal managed with surgery and IORT. After a median follow-up of 17 months, disease recurred in 11 cases at a median of 8 months from treatment. Two-year actuarial control was 7.1 and OS 21.4 %. Acute toxicity included wound-healing complications (n=6), gastrointestinal obstruction (n=5), neurogenic bladder (n=1), ureteral stricture (n=3), and peripheral neuropathy (n=2). Hallemeier et al. [34] reported outcomes of salvage resection and IORT (median, 12.5 Gy) for 32 patients (residual disease [28 %], first recurrence [53 %], and second recurrence [19 %]) following primary CRT (patients with recurrent disease received preoperative CRT). Extent of surgical resection was R0 (50 %), R1 (41 %), and R2 (9 %). The 5-year estimates of OS, DFS, and locoregional control were 23, 17, and 49 %, respectively.

Conclusions

Integration of IORT in the contemporary multimodal approach to treating gastrointestinal cancer is feasible and promotes high local control rates (Table 1). In-field control using IORT-containing strategies is over 90 % in the majority of malignancies, regardless of the cancer site or status (primary or recurrent). Although patients with R0 resection appear to experience the largest benefit with EBRT, poorer prognosis patients (e.g., R1 resection) may achieve superior outcomes with combined EBRT + IORT. Neither surgery nor systemic therapy appears to be compromised by the integration of an IORT-containing regimen. Future clinical research should further focus on the potential benefit of IORT in these patients as well as anatomical-functional outcomes and quality of life.

Compliance With Ethics Guidelines

Conflict of Interest Felipe A. Calvo, Claudio V. Sole, Hugo Marsiglia, Eduardo Alvarado, Carlos Ferrer, and Brian Czito declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
•• Of major importance

1. Siegel R, Ma J, Zou Z, et al. Cancer statistics, 2014. CA Cancer J Clin. 2014;64:9–29.
2. Smith BD, Haffty BG, Wilson LD, et al. The future of radiation Oncology in the United States from 2010 to 2020: will supply keep pace with demand? J Clin Oncol. 2010;31:4151–7.
3.•• Gunderson LL, Ashman JB, Haddock MG, et al. Integration of radiation oncology with surgery as combined-modality treatment. Surg Oncol Clin N Am. 2013;22:405–32. *Patient selection and contemporary integration of radiation (EBRT and IORT) and surgery has become the standard treatment for patients with locally advanced primary cancers and those with local-regional relapse*.
4. Valentini V, Morganti AG, Gambacorta MA, et al. Preoperative hyperfractionated chemoradiation for locally recurrent rectal cancer in patients previously irradiated to the pelvis: a multicentric phase II study. Int J Radiat Oncol Biol Phys. 2006;64:1129–39.
5.•• Debenham BJ, Hu KS, Harrison LB. Present status and future directions of intraoperative radiotherapy. Lancet Oncol. 2013;14:e457–64. *Intraoperative radiotherapy is part of the multimodality armamentarium to treat common tumour sites in the primary or recurrent setting. Several new techniques, radiobiology, and physics of intraoperative radiotherapy are currently being explored*.
6. Smalley SR, Benedetti JK, Haller DG, et al. Updated analysis of SWOG-directed intergroup study 0116: a phase III trial of adjuvant radiochemotherapy versus observation after curative gastric cancer resection. J Clin Oncol. 2012;30:2327–33.
7. Cunningham D, Allum WH, Stenning SP, et al. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. N Engl J Med. 2006;335:11–20.
8. Calvo FA, Sole CV, Obregón R, et al. Intraoperative radiotherapy for the treatment of resectable locally advanced gastric adenocarcinoma: topography of locoregional recurrences and long-term outcomes. Clin Transl Oncol. 2013;15:443–9.
9. Zhang Q, Tey J, Peng L, et al. Adjuvant chemoradiotherapy with or without intraoperative radiotherapy for the treatment of resectable locally advanced gastric adenocarcinoma. Radiother Oncol. 2012;102:51–5.
10. Drognitz O, Henne K, Weissenberger C, et al. Long-term results after intraoperative radiation therapy for gastric cancer. Int J Radiat Oncol Biol Phys. 2008;70:715–21.
11. Sjoquist KM, Burmeister BH, Smithers BM, Zalcberg JR, Simes RH, Barbour A, et al. Survival after neoadjuvant chemotherapy or chemoradiotherapy for resectable oesophageal carcinoma: an updated meta-analysis. Lancet Oncol. 2001;12:681–92.
12. Hosokawa M, Shirato H, Ohara M, et al. Intraoperative radiation therapy to the upper mediastinum and nerve-sparing three-field lymphadenectomy followed by external beam radiotherapy for patients with thoracic esophageal carcinoma. Cancer. 1999;86:6–13.
13. Murakami M, Kuroda Y, Nakajima T, et al. Intraoperative radiotherapy for the abdominal lymphatic system in patients with esophageal carcinoma. Dis Esophagus. 1999;12:270–5.
14. Miller RC, Haddock MG, Gunderson LL, Donohue JH, Trastek VF, Alberts SR, et al. Intraoperative radiotherapy for treatment of locally advanced and recurrent esophageal and gastric adenocarcinomas. Dis Esophagus. 2006;19:487–95.
15. Calvo FA, Sole CV, Obregón R, et al. Postchemoradiation resected locally advanced esophageal and gastroesophageal junction carcinoma: long-term outcome with or without intraoperative radiotherapy. Ann Surg Oncol. 2013;20:1962–9.
16. Azinovic I, Calvo FA, Puebla F, et al. Long-term normal tissue effects of intraoperative electron radiation therapy (IOERT): late sequelae, tumor recurrence, and second malignancies. Int J Radiat Oncol Biol Phys. 2001;49:597–604.
17. Neoptolemos JP, Dunn JA, Stocken DD, Almond J, Link K, Beger H, et al. Adjuvant chemoradiation and chemotherapy in resectable pancreatic cancer: a randomized controlled trial. Lancet. 2001;358:1576–85.
18. Calvo FA, Valentini V. Radiotherapy for pancreatic cancer: systematic nihilism or intraoperative realism. Radiother Oncol. 2008;87:314–7.
19. Valentini V, Calvo F, Reni M, Krempien R, Sedlmayer F, Buchler MW, et al. Intra-operative radiotherapy (IORT) in pancreatic

cancer: joint analysis of the ISIORT-Europe experience. Radiother Oncol. 2009;91:54–9.
20. Ogawa K, Karasawa K, Ito Y, Ogawa Y, Jingu K, Onishi H, et al. Intraoperative radiotherapy for resected pancreatic cancer: a multi-institutional retrospective analysis of 210 patients. Int J Radiat Oncol Biol Phys. 2010;77:734–42.
21. Jingu K, Tanabe T, Nemoto K, Ariga H, Umezawa R, Ogawa Y, et al. Intraoperative radiotherapy for pancreatic cancer: 30-year experience in a single institution in Japan. Int J Radiat Oncol Biol Phys. 2012;83:507–11.
22. Calvo FA, Sole CV, Atahualpa F, et al. Chemoradiation for resected pancreatic adenocarcinoma with or without intraoperative radiation therapy boost: long-term outcomes. Pancreatology. 2013;13:576–82.
23. Birkmeyer JD, Siewers AE, Finlayson EV, et al. Hospital volume and surgical mortality in the United States. N Engl J Med. 2002;346:1128–37.
24. Dubois JB, Bussieres E, Richaud P, et al. Intra-operative radiotherapy of rectal cancer: results of the French multi-institutional randomized study. Radiother Oncol. 2011;98:298–303.
25. Kusters M, Valentini V, Calvo FA, et al. Results of European pooled analysis of IORT-containing multimodality treatment for locally advanced rectal cancer: adjuvant chemotherapy prevents local recurrence rather than distant metastases. Ann Oncol. 2010;21:1279–84.
26. Dresen RC, Gosens MJ, Martijn H, et al. Radical resection after IORT-containing multimodality treatment is the most important determinant for outcome in patients treated for locally recurrent rectal cancer. Ann Surg Oncol. 2008;15:1937–47.
27. Mirnezami R, Chang GJ, Das P, et al. Intraoperative radiotherapy in colorectal cancer: systematic review and meta-analysis of techniques, long-term outcomes, and complications. Surg Oncol. 2013;22:22–35.
28. Alberda WJ, Verhoef C, Nuyttens JJ, et al. Intraoperative radiation therapy reduces local recurrence rates in patients with microscopically involved circumferential resection margins after resection of locally advanced rectal cancer. Int J Radiat Oncol Biol Phys. 2014;88:1032–40.
29. Calvo FA, Sole CV, Serrano J, et al. Postchemoradiation laparoscopic resection and intraoperative electron-beam radiation boost in locally advanced rectal cancer: long-term outcomes. J Cancer Res Clin Oncol. 2013;139:1825–33.
30. Haddock MG, Miller RC, Nelson H, et al. Combined modality therapy including intraoperative electron irradiation for locally recurrent colorectal cancer. Int J Radiat Oncol Biol Phys. 2011;79:143–50.
31. Calvo FA, Sole CV, Alvarez de Sierra P, et al. Prognostic impact of external beam radiation therapy in patients treated with and without extended surgery and intraoperative electrons for locally recurrent rectal cancer: 16-year experience in a single institution. Int J Radiat Oncol Biol Phys. 2013;86:892–900.
32. James RD, Glynne-Jones R, Meadows HM, et al. Mitomycin or cisplatin chemoradiation with or without maintenance chemotherapy for treatment of squamous-cell carcinoma of the anus (ACT II): a randomised, phase 3, open-label, 2×2 factorial trial. Lancet Oncol. 2013;14:516–24.
33. Wright JL, Gollub MJ, Weiser MR, et al. Surgery and high-dose-rate intraoperative radiation therapy for recurrent squamous-cell carcinoma of the anal canal. Dis Colon Rectum. 2011;54:1090–7.
34. Hallemeier CL, You YN, Larson DW, et al. Multimodality therapy including salvage surgical resection and intraoperative radiotherapy for patients with squamous-cell carcinoma of the anus with residual or recurrent disease after primary chemoradiotherapy. Dis Colon Rectum. 2014;57:442–8.
35. Zhang Q, Tey J, Yang Z, et al. Intraoperative radiotherapy in the combination of adjuvant chemotherapy for the treatment of pT3N0M0 rectal cancer after radical surgery. Am J Clin Oncol. 2014;37:8–12.