Role of Chemoradiation (CRT) in the Adjuvant Treatment of Radically Resected Pancreatic Cancer (PC) Patients: A Mono-Institutional Retrospective Analysis.

Gian Carlo Mattiucci

Università Cattolica del Sacro Cuore, Roma

Lisa Salvatore

Comprehensive Cancer Center, Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Roma

Andrea D'Aviero (✉ andreadav89@gmail.com)

Università Cattolica del Sacro Cuore <https://orcid.org/0000-0002-9194-620X>

Cinzia Bagalà

Comprehensive Cancer Center, Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Roma

Maria Bensi

Università Cattolica del Sacro Cuore, Roma

Francesco Mosè Castronovo

Radioterapia Oncologica, Università degli Studi di Palermo

Francesco Cellini

Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Dipartimento di Diagnostica per Immagini, Radioterapia Oncologica ed Ematologia, Roma

Paola De Franco

Università Cattolica del Sacro Cuore, Roma

Brunella Di Stefano

Università Cattolica del Sacro Cuore, Roma

Gabriella Macchia

Gemelli Molise Hospital, Unità Operativa di Radioterapia, Campobasso

Valeria Masiello

Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Dipartimento di Diagnostica per Immagini, Radioterapia Oncologica ed Ematologia, Roma

Roberta Menghi

Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Digestive Surgery Unit, CRMPG (Advanced Pancreatic Research), Roma

Giuseppe Quero

Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Digestive Surgery Unit, CRMPG (Advanced Pancreatic Research), Roma

Sara Reina

Università Cattolica del Sacro Cuore, Roma

Alessio Giuseppe Morganti

Radiation Oncology Center, Department of Experimental, Diagnostic and Specialty Medicine DIMES,
University of Bologna, S. Orsola-Malpighi Hospital, Bologna

Sergio Alfieri

Università Cattolica del Sacro Cuore, Roma

Giampaolo Tortora

Università Cattolica del Sacro Cuore, Roma

Vincenzo Valentini

Università Cattolica del Sacro Cuore, Roma

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Abstract

Background

Pancreatic cancer (PC) represents an unfavorable prognosis disease, even in patients with resectable disease. The aim of this series was to investigate the role of treatment intensification with adjuvant chemoradiation (CRT) in radically resected PC patients.

Methods

Data from PC patients undergone radical surgery, adjuvant chemotherapy (CT) and CRT throughout a 20-year period were retrospectively collected. Actuarial local control (LC) and the overall survival (OS) were the primary endpoints, while secondary end-points were the disease-free-survival (DFS) and metastases-free-survival (MFS).

Results

The analysis included 108 PC patients treated with adjuvant CRT and CT from January 2000 to August 2019. Median age was 66 years (range: 40-83), all patients underwent radical surgical resection with adjuvant chemotherapy (88, 81,5%) plus concomitant chemoradiation (101, 93,5%) or radiotherapy alone (7, 6,5%).

The median dose delivered on tumor bed was 50,4 Gy (range: 45-50,6 Gy), while median dose on regional lymphatic drainage stations was 39,6 Gy (range 39,6-45 Gy. Concomitant CT was gemcitabine-based regimen in the vast majority of patients (87, 80.6%). Median follow-up time was 21 months; the 2- and 5-years LC rate were 75,8% and 59,1%, respectively. Perineural invasion (PNI) at pathological assessment was found significantly associated to LC ($p=0.028$). Median OS was 40 months with 2- and 5-years OS rate of 73.9% and 41,6 % respectively.

Conclusions

The outcomes of this series strongly suggest that the impact of adjuvant CRT should be deeply investigated in PC patients. Timing, combination of modern CRT with new systemic therapies need to be further investigated to personalize therapy and optimize clinical advantages.

Introduction

Pancreatic cancer (PC) with 132.600 estimated new diagnoses and 128.000 deaths per year is projecting to become the second leading cause of cancer-related deaths for both genders in 2030 [1,2].

Radical surgery represents the only potentially curative approach, but only the 20% of patients have resectable disease at diagnosis [3–5].

Important prognostic information could be assessed on the basis of pathologic examination. The definition of margin status, tumor grade and size; lymph-vascular space invasion (LVSI); perineural invasion (PNI) and lymph node involvement have been demonstrated to modify PC resected patients' prognosis [6–8] .

Prognosis in PC, even in patients with resectable disease, remains unfavorable with high rates of local and distant recurrences [8,9].

These disappointing outcomes underline the need of effective adjuvant treatments to improve survival outcomes in patients with resected pancreatic adenocarcinoma.

The role of adjuvant chemotherapy (CT) has been widely assessed in randomized trials mainly with gemcitabine-based schedules as standard of care [10–12]. A phase III trial of the Canadian Cancer Trials Group and the Unicancer-GI–PRODIGE Group, recently showed the impact of adjuvant FOLFIRINOX regimen on survival outcomes even if with higher incidence of toxic effects [13,14].

The impact of treatment intensification with adjuvant chemoradiation (CRT) is still under debate with main focus on the combination timing with adjuvant CT.

The Gastrointestinal Tumor Study Group (GITSG) randomized trials showed an improved overall survival (OS) in patients undergoing CRT plus adjuvant CT after definitive surgery [15,16].

Furthermore, the European Organization for Research and Treatment of Cancer (EORTC) designed a randomized trials to confirm the impact of CRT on survival outcomes shown by GITSG trial [17]. Adjuvant radiotherapy in combination with 5-fluorouracil was shown to be safe and well tolerated, even if no significant improvement in median survival was shown. A late re-analysis of the EORTC trial addressed a significant impact of CRT in specific subgroups of patients [18].

The ESPAC-1 trial showed a detrimental effect on survival for patients undergoing CRT compared to CT or surgery alone [19–21]. Following studies seemed to suggest that the slightly low prescription dose for CRT in the ESPAC-1 study (split course 40Gy schedule), could affect LC and OS outcomes [22,23].

In this pattern of uncertainty also meta-analysis [24,25], pooled analysis [26,27] and single center analysis [28,29] have been carried out also in order to identify specific subset of patients with poor prognostic factors in which CRT could have a relevant role.

The aim of this analysis was to report our series of radically resected PC managed postoperatively with CRT and adjuvant CT, also to suggest a possible role of postoperative CRT in maximizing adjuvant treatment in poor prognostic factors subsets.

Methods

Eligibility criteria

This is an observational monocentric study aimed to investigate the impact of adjuvant chemoradiation in radically resected pancreatic cancer (PC) patients treated at Fondazione Policlinico Universitario A. Gemelli IRCCS.

Clinic-pathologic and outcome data from pancreatic cancer patients, who had undergone primary radical surgery and adjuvant chemotherapy plus concomitant chemoradiotherapy from 2000 to 2019, were collected. Inclusion criteria were age ≥ 18 years, ECOG performance status ≤ 2 and complete macroscopic resection of histologically proven PC. Exclusion criteria were: lack of pathological tumor (pT) and/or nodal stage assessment, neoadjuvant treatment, synchronous or metachronous cancer metastatic disease (M1).

The variables collected for analysis were: age, sex, tumor location (head, body, tail), tumor grade (1-3), microscopic residual disease (R0/R1), lymph vascular space invasion (LVSI), perineural invasion (PNI), pathological tumor stage, and pathological nodal stage (pN0/pN+).

Treatment protocol

Patients included in the analysis underwent radical surgery on primary disease. Adjuvant gemcitabine-, 5-fluorouracil- or capecitabine-based CRT was delivered, with CT (gemcitabine alone or FOLFIRINOX schedule).

Clinical Target Volumes (CTVs) were defined according to pathological and clinical pre-operative and post-operative contrasted enhanced CT scan. CTV1 included the tumor bed, while CTV covered regional lymphatic drainage stations according to national and European guidelines [30,31].

Patients received 3D-Conformal Radiation Therapy (3D-CRT) or Intensity Modulated RT (IMRT) technique based chemoradiation. Total dose ranged between 45 and 50,4 Gy was prescribed according to the guidelines of International Commission on Radiation Units (ICRU) Measurements Report guidelines 62 and 83 for 3D-CRT and IMRT respectively.

Endpoints and analysis of data

Primary study endpoints were the actuarial local control (LC) and the overall survival (OS) rates; secondary end-points were the disease-free survival (DFS) and metastases-free survival (MFS) rates.

LC was defined as the time from the date of adjuvant CRT and the date of in-field radiotherapy relapse/progression of disease or the last follow-up visit. OS was calculated from the date of diagnosis to death or last follow-up visit. The time from the date of adjuvant CRT and the date of distant failure was considered for Metastasis-free survival (MFS); while DFS was considered as the time from the date of adjuvant CRT to local control failure or distant progression.

Actuarial outcomes results were analyzed through the Kaplan-Meier method; log-rank tests were used to evaluate subgroups differences. Prism version 8.31 for macOS software (1994-2019 GraphPad Software,

La Jolla California USA, www.graphpad.com) was used to perform statistical analysis.

Results

The analysis enrolled 108 patients with PC treated with adjuvant CRT from January 2000 to August 2019.

Median age was 66 years (range: 40-83), male female ratio was 62/46.

All patients underwent radical surgical resection, followed by adjuvant chemotherapy (88, 81,5%) plus concomitant chemoradiation (101, 93,5%) or radiotherapy alone (7, 6,5%) on the basis of risk factors at pathological examination.

Pathological examination revealed Pancreatic Ductal AdenoCarcinoma (PDAC) histology in 107 patients (99,1%) and Colloid Carcinoma (CC) histology in 1 patient (0,9%). Pathological tumor stage, according to the 7th edition of the AJCC cancer staging manual [32], was pT3 in the large majority of patients (70, 65%); nodal involvement was found in 61 patients (56.5%) while positive surgical margins in 31 patients (28,7%). LVSI and PNI were found in 50 (46,3%) and 52 (48,1%) patients respectively. Table 1 summarizes patients characteristics.

All patients completed adjuvant (C-)RT treatment, only 4 patients had major treatment interruption longer than 7 days, RT technique was 3D-CRT and IMRT in 80 (74,1%) and 26 (24,1%) cases respectively.

The median dose on CTV2 regional lymphatic drainage stations was 39,6 Gy (range 39,6-45 Gy), while CTV1 tumor bed received median 50,4 Gy (range: 45-50,6 Gy). Concomitant chemotherapy was gemcitabine-based regimen (87, 80.6%); 5-fluorouracil-based (6, 5,6%) or capecitabine-based (5, 4,6%).

With a median follow-up time of 21 months from adjuvant (C-)RT (range; 1-200), the 2- and 5-years LC rate were 75,8% and 59,1%, respectively (Figure 1). The presence of PNI at pathological examination was found significantly associated to LC ($p=0.028$). No significant association of margin status ($p=0.073$), nodal status ($p=0.511$) or LVSI ($p=0.769$) with local recurrence was found (Figure 2).

Median OS was 40 months with 2- and 5-years OS rate of 73.9% and 41,6 % respectively; no significant association with clinic-pathological assessment was found.

As per secondary endpoints median DFS was 29 months with 2- and 5-years rate of 54,4% and 35,3 % respectively. The 2- and 5-years rate MFS were 62,1% 46,8% respectively, with a median value of 44 months. Table 3 resumes 2- and 5-years LC and OS analysis.

Discussion

Despite the impact of CT adjuvant therapeutic strategies in PC has widely been assessed, the role of CRT is still controversial.

This study was designed with the aim to report the outcomes of CRT adjuvant treatment intensification in radically resected PC .

The role of CRT in patients with resected PC was firstly investigated by the GITSG randomized trial [15]. This multicentric prospective trial showed an improvement in terms of OS (mOS: 20 versus 11 months; $p=0.03$) in patients with resected PC undergoing adjuvant CRT compared to surgery alone. Data of GITSG were further confirmed by a sequential enrollment of additional 30 patients treated with adjuvant CRT [16].

Furthermore, the EORTC designed a prospective randomized multicenter trial to evaluate the potential benefit of adjuvant CRT on survival outcomes, compared to observation [17]. Two hundred eighteen patients were randomly assigned to CRT (40 Gy split course with concurrent infusional 5-fluorouracil) plus sequential CT, or to observation. No significant improvement in median survival (19 months for observation versus 24.5 months for CRT) was demonstrated.

However, a late re-analysis of the EORTC trial addressed a significant impact of CRT on 2-years OS (37% CRT vs 23% observation; $p=0.049$) in the cluster of patients with negative-margins resected head PC [18].

The ESPAC-1 trial was also designed to address the choice of appropriate adjuvant therapy for resected PC patients. The trial was structured into four arms in which patients were randomized to CRT alone, CT alone, both CRT and CT or observation.

The long term results of ESPAC-1 trial, with a 47 months median follow-up, showed a survival benefit for adjuvant CT (mOS 20 vs. 16 months; $p=0.011$). On the other hand CRT was found to be detrimental with a mOS of 14 months compared to no CRT mOS of 17 months [19–21].

In the present analysis survival and loco-regional control following adjuvant CRT were found to be interesting; median OS was 40 months with 2- and 5-years OS rate of 73.9% and 41,6 % respectively. Also LC rates were appealing with 2- and 5-years LC rate of 75,8% and 59,1%, respectively.

Furthermore, mOS of the presented series seem to be comparable, and even slightly superior, to outcomes presented in series of patients treated with exclusive adjuvant CT, addressing a potential role of CRT in adjuvant setting [10–12].

As far as radiotherapy schedule is concerned, both GITSG EORTC and ESPAC-1 trials were designed to deliver a RT was delivered a split course 40 Gy RT. Controversial results of the previous mentioned trials were address to the low-dose RT schedule delivered and received criticism from authors who further analyzed the impact of dose escalation on OS [22,23].

Hall et al. compared survival outcomes of PC cancer patients treated with different dose levels of adjuvant CRT. Dose level between 50-55 Gy was shown to led to higher survival rates (mOS 23 months) as compared to dose levels of <40 Gy, 40-55 Gy and >55 Gy (mOS 15, 20, 16 months respectively) [22].

Morganti et al. performed a multicentric pooled-analysis of 1248 resected PC cancer patients treated with adjuvant CRT. A total of 514 patients were addressed for the analysis, four dose level groups (group 1: < 45 Gy, group 2: ≥ 45 and < 50 Gy, group 3: ≥ 50 and < 55 Gy, group 4: ≥ 55 Gy) were defined a significant impact of higher dose was demonstrated as group 4 (≥ 55 Gy) showed a 28.0 months OS ($p= 0.004$) compared to the other groups [23].

The outcomes of the presented series seem to confirm good results related to higher CRT doses, as the whole population analyzed received at least 45 Gy maximum dose (with over 90% patient receiving >50,4 Gy maximum dose). Despite this evidence, the maximum dose level was not found to be significantly correlated to OS and LC.

IMRT technique has been shown to be useful to lower the dose to OAR with good outcomes in terms of LC [33,34]. In our series the RT technique was not significantly correlated to LC and OS.

In the definition of best adjuvant treatment approach, the evaluation of clinic-pathological risk factors is a challenging task. Several studies showed a significant impact surgical margins extent on local recurrence and consequently on survival [7–9]. Also the relationship between survival outcomes and other prognostic factors have been analyzed such as pre- and post-surgical Ca 19.9 levels, tumor dimension, positive lymph-node status, LVSI and PNI evidence at pathological examination [7,27,35–40].

In the presented analysis a log-rank tests showed no significant association of margin and nodal status with survival outcomes. The relationship of OS and LC such as for DFS and MFS with other prognostic risk factors was analyzed, assessing the significant association of LC with the presence of PNI at pathological examination ($p=0.028$). As previously mentioned PNI has been shown to be a relevant independent prognostic factor for both OS and LC; the results of our series seem to strengthen the impact of adjuvant CRT in presence of high-risk factors[37–40].

The authors are aware of limits regarding this analysis, such as the small sample size, the retrospective nature of the study and the related lack of some relevant clinical data. Furthermore, the impact of the study could be strengthened with a more efficacious adjuvant CT schedule such as Folfirinox [13,14] combined to modern RT approach [41–43].

However, the results of our series seem to suggest a favorable impact of treatment intensification with CRT in association to adjuvant CT, even if previously mentioned randomized trial have not strongly supported this evidence.

Conclusions

The role of CRT in resectable PC patients following upfront radical surgery and adjuvant CT is still controversial.

Our study showed encouraging rates of survival and local control. Median OS of 40 months and the 2- and 5-years survival rate of 73.9% and 41,6 % respectively, strongly suggest that the impact of adjuvant

CRT should be deeply investigated in particular in patients with poor prognostic factors such as positive lymph-nodes, positive margins, lymph vascular space invasion and perineural invasion.

Furthermore, pursuing an integrated effective treatment strategy, new prospective studies should be designed to investigate the impact and the best combination of modern CRT with new systemic therapies

Abbreviations

3D-CRT: 3D-Conformal Radiation Therapy; CC: Colloid Carcinoma; CRT: Chemoradiation; CT: Chemotherapy; CTV: Clinical Target Volume; DFS: Disease-Free-Survival; IMRT: Intensity Modulated Radiotherapy; LC: Local Control; LVSI: Lymph-Vascular-Space-Invasion; MFS: Metastases-Free-Survival; OS: Overall Survival; PC: Pancreatic Cancer; PDAC: Pancreatic Ductal AdenoCarcinoma; PNI: Perineural Invasion; RT: Radiotherapy.

Declarations

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ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Ethics approval was not necessary for the comprehensive review article. All co-authors have agreed to participate.

CONSENT FOR PUBLICATION

All co-authors have read and approved the final manuscript.

COMPETING INTERESTS

The authors declare there are not competing interests.

AVAILABILITY OF DATA AND MATERIALS

All references are cited in the manuscript. The datasets used and analyzed for this study could be provided upon reasonable request.

AUTHORS' CONTRIBUTIONS

Conception and design: G.C. Mattiucci, L. Salvatore, A.G. Morganti, S. Alfieri, G. Tortora, V. Valentini

Data Collection: A. D'Aviero, M.Bensi, F. Castronovo, P. De Franco, B. Di Stefano, S. Reina

Analysis and Interpretation of Data: C. Bagalà, F. Cellini, G. Macchia, V. Masiello, R. Menghi, G. Quero

Manuscript Writing: G.C. Mattiucci, Andrea D'Aviero, L. Salvatore

The Final Manuscript Approval: G.C. Mattiucci, L. Salvatore, A. D'Aviero, C. Bagalà, M. Bensi, F. Castronovo, F. Cellini, G. Macchia, P. De Franco, B. Di Stefano, V. Masiello, R. Menghi, G. Quero, S. Reina, A.G. Morganti, S. Alfieri, G. Tortora, V. Valentini.

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Tables

Table 1: Patients characteristics

Characteristics	N° (range)	(%)
Total patients	108	100
Age, years mean (range)	66 (40-83)	
Gender		
Male	62	57,4
Female	46	42,6
Tumor site		
Head	80	74,1
Body	7	6,5
Tail	10	9,2
Other	11	10,2
Histotype		
Pancreatic Ductal AdenoCarcinoma	107	99,1
Colloid Carcinoma	1	0,9
Grading (G)		
G1	3	2,8
G2	65	60,2
G3	32	29,6
NK	8	7,4
Tumor stage		
pT1	2	1,9
pT2	23	21,3

pT3	70	64,8
pT4	13	12
Nodal Stage		
pN0	47	43,5
pN+	61	56,5
Margin status		
R0	77	71,3
R+	31	28,7
Lymph Vascular Space Invasion (LVSI)		
Negative	38	35,2
Positive	50	46,3
NK	20	18,5
Perineural Invasion (PNI)		
Negative	37	34,3
Close	52	48,1
NK	19	17,6

Table 2: Treatment protocol

Characteristics	N° (range)	(%)
Adjuvant Chemotherapy	102	94,4
Gemcitabine	79	73,1
Folfirinox	6	5,6
Other	17	15,7
Adjuvant ChemoRadiation	101	93,5
Gemcitabine	87	80,6
5-FU	6	5,6
Other	8	7,4
Exclusive RT	7	6,5
RT Dmax		
<50,4 Gy	8	7,4
>50,4 Gy	100	92,6
RT Technique		
3D-CRT	80	74,1
IMRT	28	25,9

RT: Radiotherapy; 3D-CRT: Conformal Radiation Therapy; IMRT: Intensity Modulated RT

Table 3: Analysis of 2-, 5-year, and median actuarial local control (LC) and overall survival (OS) time

Variable	N° patients	2-years LC (%)	5-years LC (%)	2-years OS (%)	5-years OS (%)
Gender				p=0.973	p=0.060
Male	62	80,7	56,4	87,1	35,9
Female	46	69,2	64,2	95,6	52,6
Tumor site				p=0.846	p=0.849
Head	80	74,1	59,0	73,5	40,2
Body	7	80,0	60,0	57,1	38,1
Tail	10	68,6	68,6	80,0	45,7
Other	11	91,0	54,5	80,8	47,1
Grading (G)				p=0.309	p=0.456
G1	3	100	100	100	100
G2	65	71,9	52,4	77,3	40,3
G3	32	78,0	61,4	67,1	38,0
Tumor stage				p=0.809	p=0.419
pT1	2	100	50,0	100	50,0
pT2	23	81,7	68,1	85,3	63,2
pT3	70	73,0	59,1	68,1	38,8
pT4	13	77,0	52,7	84,6	38,5
Nodal Stage				p=0.511	p=0.121
pN0	47	76,0	66,8	73,4	45,7
pN+	58	75,6	58,8	74,3	37,8
Margin status (R)				p=0.115	p=0.700

R0	77	77,9	71,8	72,1	42,0
R+	31	58,7	61,6	78,3	39,2
LVSI		p=0.769		p=0.483	
Negative	38	73,7	65,0	58,9	34,3
Positive	50	75,8	51,8	83,0	42,1
PNI		<i>p=0.028</i>		p=0.180	
Negative	37	82,0	68,4	62,0	44,3
Close	52	68,2	50,4	79,3	32,2

LVSI: Lymph Vascular Space Invasion; PNI: Perineural Invasion

Figures

Figure 1

Kaplan-Meier Plot: Local Control (LC), Overall survival (OS), Disease-Free Survival (DFS) and Metastases Free Survival (MFS) for whole population.

Figure 2

Kaplan-Meier Plot: Local Control (LC) and Overall survival (OS) for Nodal Status (N); Margin Status (R); Lymph Vascular Space Invasion Status (LVSI) and Perineural Invasion Status (PNI).