

Comparing Chemoradiation, ^{125}I Seed Implantation Combined with Chemotherapy, and Chemotherapy Alone Efficacy in Treating Unresectable Locally Advanced Pancreatic Cancer

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Research Article

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Abstract

Background: The prognosis of unresectable locally advanced pancreatic cancer (LAPC) remains dismal, and the optimal modality is unclear. This study compared four common treatments for LAPC, including concurrent chemotherapy combined with high-dose radiation (DT>50Gy) (CCHRT), concurrent chemotherapy combined with low-dose radiation (DT50 Gy) (CCLRT), ¹²⁵I seed implantation combined with chemotherapy, and chemotherapy alone (CA).

Materials/Methods: 89 patients with unresectable locally advanced pancreatic cancer were enrolled in this retrospective study. Overall survival was assessed using the Kaplan-Meier method and Cox regression. All four groups were first compared simultaneously and then in every two.

Results: In the parallel comparison of all four groups, CCHRT-receiving patients demonstrated better OS benefits than their CCLRT-, ¹²⁵I seed implantation combined with chemotherapy-, or CA-receiving counterparts ($P=0.030$). Comparisons in pairs revealed that patients given CCHRT showed significantly better OS benefits than those receiving CCLRT (13 vs. 7 months, $P=0.006$). CCHRT-receiving patients also had significantly better OS than their ¹²⁵I seed implantation combined with chemotherapy-receiving counterparts (13 vs. 10 months, $P=0.003$). However, there was no statistical difference in OS between CCHRT- and CA-receiving patients, CCLRT- and ¹²⁵I seed implantation combined with chemotherapy-receiving patients, CCLRT- and CA-receiving patients, ¹²⁵I seed implantation combined with chemotherapy- and CA-receiving patients.

Conclusions: CCHRT-receiving patients with unresectable LAPC demonstrated better OS than those on CCLRT, ¹²⁵I seed implantation combined with chemotherapy, or CA. Further randomized clinical trials are warranted.

Background

Pancreatic cancer is the fourth leading cause of cancer-related deaths globally, with a high degree of malignancy, poor prognosis, short survival time, and a 5-year survival rate of 5%[1]. For resectable locally advanced pancreatic cancer (LAPC), surgery followed by adjuvant chemotherapy combined with/without adjuvant radiotherapy is the primary treatment strategy[2]. For borderline resectable LAPC, multi-agent chemotherapy, such as gemcitabine/Abiraterone or FOLFIRINOX followed by fluoropyrimidine-based concurrent chemoradiation (CCRT) and surgery or gemcitabine-based concurrent chemoradiation and surgery, is the treatment paradigm[3]. Common treatment modalities for unresectable LAPC include CCRT, CA, and ¹²⁵I seed implantation; however, its optimal treatment remains controversial. Some studies, including the ECOG 4201 trial, demonstrated that CCRT prolongs patient's OS than CA[4–6]. However, other investigations, including the LAP07 clinical trial, have found little difference between CCRT and CA in extending patient survival[7–9].

Furthermore, radiation dose for cancer remains hotly debated. In the 1980s, the Gastrointestinal Tumor Study Group (GITSG) protocol GITSG 9273 found that increased radiation dose did not improve patients' OS[10]. In contrast, *Jinsil Seong et al.* demonstrated that increased radiation dose was associated with prolonged survival[11].

With the development of modern medical imaging technology, CT-guided percutaneous ^{125}I seed implantation has been widely used in clinical practice; however, its efficacy and safety for unresectable LAPC remain controversial. Some studies have suggested that ^{125}I seed implantation is safe and effective[12, 13], but *Schuricht et al.* found no proof that it improves patients' OS[14].

Therefore, we compared four common treatments strategies for LAPC, including concurrent chemotherapy combined with high-dose radiation (DT > 50Gy) (CCHRT), concurrent chemotherapy combined with low-dose radiation (DT \leq 50 Gy) (CCLRT), ^{125}I seed implantation combined with chemotherapy, and chemotherapy alone (CA), to determine the most effective modality for LAPC based on overall survival (OS).

Methods

Patient information collection

This study was a retrospective investigation conducted at the Shandong Cancer Hospital and the third hospital affiliated with Shandong First Medical University in line with the moral code of the Helsinki Declaration of 1975 and approved by the Ethics Committee of the relevant institutions of the Shandong Cancer Hospital and the third hospital affiliated with Shandong First medical university. Data were gathered with the patients' informed consent and were digitally encoded, anonymized, and stored in a secure database.

Following the criteria of the tumor (T), nodes (N), and metastases (M) staging (TNM staging) of pancreatic cancer in the eighth edition of the American Joint Committee on Cancer (AJCC) staging system, we collected the clinical data of 89 patients with unresectable LAPC from January 2014 to December 2019. All patients were diagnosed with pancreatic cancer based on abdominal imaging and histopathological diagnosis. Pancreatic cancer unresectability was determined at the Shandong Cancer Hospital and Institute and the third hospital affiliated to Shandong First medical university using Multi-disciplinary Treatment (MDT). The MDT determination was based on the extent of the tumor in the superior mesenteric artery (SMA), celiac artery, common hepatic artery, superior mesenteric vein, and portal vein. The enrolled patients were divided into four groups: CCHRT, CCLRT, ^{125}I seed implantation combined with chemotherapy, and CA.

Statistical analysis

All the data were analyzed using the SPSS 22.0 data statistics software. The classified data were compared utilizing the Chi2 test or Fisher's exact test, and the continuous data were compared with the

Kruskal-Wallis H test. Overall survival (OS) was estimated using the Kaplan-Meier method; first, all four groups were compared together for survival analysis and then in sets of two. Following pairwise comparisons, p values were corrected using Bonferroni's method, and $P < 0.0083$ was considered a statistically significant difference. Univariate and multivariate analyses were performed with Cox regression. $P < 0.3$ variables in the univariate analysis were included in the multivariate analysis. $P < 0.05$ was considered a statistically significant difference.

Results

Patient information

The clinical data of 89 LAPC patients, including 54 males and 36 females, were analyzed retrospectively. The median age of the patients was 63 years old (ranging from 35 to 81 years old), with a KPS score of 70 to 90. Patients and tumor characteristics (including age, gender, presentation status of the Eastern Cooperative Tumor Group (ECOG), primary tumor site, T stage, and N stage) were well balanced in the four groups (Table 1). Twenty-three patients received CCHRT, with a median OS of 13 months (ranging from 6 months to 33 months), 21 received CCLRT, with a median OS of 7 months (ranging from 1 month to 25 months), another 21 received ^{125}I seed implantation combined with chemotherapy, with a median OS of 10 months (ranging from 2 months to 22 months), and 24 received CA, with a median OS of 11 months (ranging from 3 months to 31 months).

Table 1
Patient and Tumor Characteristics

	CCHRT (n = 23)	CCLRT (n = 21)	125I (n = 21)	CA (n = 24)	P value
Age(years)					
Median(range)	63.5(50–78)	63(35–80)	66(35–75)	55(37–81)	0.098
Gender					
Male	11 (47.8%)	12 (57.1%)	12 (57.1%)	18 (75.0%)	0.285
Female	12 (52.2%)	9 (42.9%)	9 (42.9%)	6 (25.0%)	
KPS					
Median(range)	80 (80–90)	80 (70–90)	80 (70–90)	80 (80–90)	0.119
≤ 80	18 (78.3%)	11 (52.4%)	13 (61.9%)	13 (52.2%)	0.259
> 80	5 (21.7%)	10 (47.6%)	8 (38.1%)	11 (45.8%)	
ECOG performance status					
0	11(47.8%)	10(47.6%)	10(47.6%)	12(50.0%)	0.998
1	12(52.2%)	11(52.4%)	11(52.4%)	12(50.0%)	
Clinical T stage					
T3	2(8.7%)	0(0)	3(14.3%)	3(12.5%)	0.341
T4	21(91.3%)	21(100.0%)	18(85.7%)	21(87.5%)	
Clinical N stage					
N0	8(34.8%)	10(47.6%)	9(42.9%)	7(29.2%)	0.498
N1	8(34.8%)	7(33.3%)	7(33.3%)	14(58.3%)	
N2	7(30.4%)	4(19.1%)	5(23.8%)	3(12.5%)	
Primary site of tumor					
Pancreatic head	8(34.8%)	11(52.4%)	11(52.4%)	10(41.7%)	0.933
Pancreatic neck	5(21.7%)	2(9.5%)	4(19.0%)	5(20.8%)	
Pancreatic body	7(30.4%)	6(28.6%)	4(19.0%)	5(20.8%)	

Abbreviations: CCHRT: concurrent chemotherapy combined with high-dose radiation (DT > 50Gy); CCLRT: concurrent chemotherapy combined with low-dose radiation (DT ≤ 50Gy); 125I: 125I seed implantation combined with chemotherapy; CA: chemotherapy alone; KPS: karnofsky performance status; ECOG performance status: Eastern American Oncology Collaboration performance.

	CCHRT (n = 23)	CCLRT (n = 21)	¹²⁵ I (n = 21)	CA (n = 24)	P value
Pancreatic tail	3(13.1%)	2(9.5%)	2(9.5%)	4(16.7%)	

Abbreviations: CCHRT: concurrent chemotherapy combined with high-dose radiation (DT > 50Gy); CCLRT: concurrent chemotherapy combined with low-dose radiation (DT ≤ 50Gy); ¹²⁵I: ¹²⁵I seed implantation combined with chemotherapy; CA: chemotherapy alone; KPS: karnofsky performance status; ECOG performance status: Eastern American Oncology Collaboration performance.

Survival Analysis

Comparing all four groups together revealed significant differences in OS ($P = 0.030$); CCHRT-receiving patients with unresectable LAPC demonstrated better OS benefits than CCLRT-, ¹²⁵I seed implantation combined with chemotherapy-, or CA-receiving patients (Figure.1). Per comparisons in sets of two, CCHRT-receiving patients exhibited significantly better OS benefits than their CCLRT-receiving counterparts ($P = 0.006$) (Figure.2A). CCHRT also provided substantially better OS benefits than ¹²⁵I seed implantation combined with chemotherapy ($P = 0.003$) (Figure.2B). However, there was no statistical difference in OS between the impacts of CCHRT and CA, CCLRT and ¹²⁵I seed implantation combined with chemotherapy, CCLRT and CA, and ¹²⁵I seed implantation combined with chemotherapy and CA (Figure.2C-F).

Prognostic Factors Associated With Os

As shown in Table 2, the CCLRT ($P = 0.009$) and ¹²⁵I seed implantation combined with chemotherapy ($P = 0.011$) treatment modality were significantly associated with poor OS in the univariate analysis; other factors' associations did not reach statistical significance. Being male ($P = 0.037$), the CCLRT ($P = 0.017$) and ¹²⁵I seed implantation combined with chemotherapy ($P = 0.044$) treatment modality were also associated with poor OS in the multivariate analysis.

Table 2
Univariate and Multivariate Analysis for OS.

Variable	Univariate analysis			Multivariate analysis		
	HR	95% CI	<i>P</i>	HR	95% CI	<i>P</i>
Age(years)	0.998	0.976–1.020	0.832			
Gender						
Male vs Female	0.620	0.361–1.063	0.082	0.525	0.286–0.962	0.037
KPS						
> 80 vs ≤ 80	1.269	0.752–2.144	0.372			
ECOG PS						
0 vs 1	1.236	0.735–2.077	0.424			
Clinical T stage						
T3 vs T4	0.830	0.329–2.095c	0.693			
Clinical N stage			0.724			
N0 vs N1	0.792	0.448–1.399	0.421			
vs N2	0.890	0.444–1.782	0.741			
Primary site of tumor			0.266			0.175
Pancreatic head vs pancreatic neck	0.602	0.298–1.216	0.157	0.554	0.271–1.130	0.104
vs pancreatic body	0.542	0.275–1.066	0.076	0.514	0.256–1.032	0.061
vs pancreatic tail	0.783	0.341–1.795	0.563	0.578	0.239–1.399	0.224
Treatment modality			0.021			0.028
CCHRT vs CCLRT	2.759	1.282–5.936	0.009	2.553	1.178–5.529	0.017
vs 125I	2.586	1.241–5.389	0.011	2.159	1.021–4.566	0.044
vs CA	1.346	0.648–2.793	0.425	1.028	0.473–2.235	0.943

Abbreviations: CCHRT: concurrent chemotherapy combined with high-dose radiation (DT > 50Gy); CCLRT: concurrent chemotherapy combined with low-dose radiation (DT ≤ 50Gy); 125I: 125I seed implantation combined with chemotherapy; CA: chemotherapy alone; KPS: karnofsky performance status; ECOG performance status: Eastern American Oncology Collaboration performance.

Discussion

The most effective treatment methods for unresectable LAPC remain controversial, but few studies have sought to determine its best therapy. To the best of our knowledge, ours was the first study to compare OS among CCHRT-, CCLRT-, ¹²⁵I seed implantation combined with chemotherapy-, and CA-receiving patients with unresectable LAPC. We found that CCHRT conferred better OS than CCLRT, ¹²⁵I seed implantation combined with chemotherapy, or CA for this group of patients.

Upon simultaneously comparing the efficacy of all four modalities, we found OS to be statistically different among groups, with CCHRT providing better OS benefits than the other treatments. To further evaluate the advantages and disadvantages of each treatment, comparative analyses of treatment models were conducted in sets of two. CCHRT conferred significantly better OS benefits than CCLRT; this finding is similar to that of *Jinsil Seong et al.*, which indicated that increasing radiotherapy dose significantly improved patients' OS[11]. However, in the 1980s, the Gastrointestinal Tumor Study Group (GITSG) protocol GITSG 9273 found no statistically significant difference in survival among patients randomly assigned to high-dose radiation (60Gy) combined with 5-FU and low-dose radiation (40Gy) combined with 5-FU[10]. Because the head of the pancreas predominantly constituted the primary tumor site in the CCLRT group of our study, the radiotherapy dose was maintained below 50Gy to protect the surrounding duodenum.

Some studies have explored unresectable LAPC's best treatment modalities for many years, but results remain controversial. The Gastrointestinal Tumor Study Group (GITSG) found CCRT to be more effective than CA in the 80s[4]. Some studies have also demonstrated that patients with unresectable LAPC receiving CCRT therapy tend to have longer OS than those treated with CA[4, 5]. The ECOG 4201 test also previously showed that LAPC patients receiving CCRT, *i.e.*, gemcitabine combined with radiation therapy, have longer OS compared to their CA-receiving counterparts[6]. However, several studies have also argued against using CCRT over CA. An FFCD-SFRO study reported that CCRT prompted increased toxicity and decreased effectiveness than gemcitabine alone[7], and the LAP07 clinical trial revealed that CCRT conferred no better survival benefits than CA[8]. In one retrospective study, Groupe Cooperateur Multidisciplinaire en Oncologie (GERCOR) reported an increase in OS in patients receiving CCRT compared to patients receiving CA[15]. However, both the French Association for Digestive Cancer and the French Radiation Oncology Study found that the addition of conventional chemoradiation (CRT) to chemotherapy resulted in poorer OS and more severe toxicity[16]. *Ivy Weishan Ng* did not see any improvement in survival or delay in disease progression in patients with unresectable LAPC in her comparison of chemotherapy combined with radiation dose and CA[9]. CCHRT showed a slightly better OS benefit than CA in our study, but CCLRT provided an inferior OS than CA; both differences were not statistically significant. Further randomized clinical trials exploring unresectable LAPC's best treatment modalities must be performed.

With the development of modern medical imaging technology in recent years, the CT-guided percutaneous implantation procedure has been widely used clinically[17]. ¹²⁵I seed implantation is not a

new radiotherapy technique; it was used initially to treat prostate cancer, and its efficacy in local tumor control is well documented[14]. Per some investigations, percutaneous ^{125}I seed implantation combined with chemotherapy to treat pancreatic cancer under CT guidance is a safe and effective method for treating LAPC; patients with advanced pancreatic cancer implanted with ^{125}I particles had fewer incidences of postoperative side effects and complications[12, 13]. A series of preliminary studies have shown that ^{125}I seed implantation may benefit patients in pain relief, control of local tumor growth, and survival[18–20]. However, *Schuricht et al.* found no improvement in the OS of patients with pancreatic cancer treated with ^{125}I seed implantation[14]. In our study, ^{125}I seed implantation failed to show any OS benefit to patients than other treatment regimens.

There are several limitations to this research. First, our findings are based on limited cases; yet, we cannot discount the fact that CCHRT-receiving LAPC patients had longer OS than their CCLRT- and ^{125}I -receiving counterparts. More subjects are required to further explore optimal treatment regimens for LAPC patients. Second, this was a retrospective study with inevitable inherent selection biases and limitations. Still, patients were strictly controlled according to tumor staging and treatment regimen, and, therefore, the biases were avoided as much as possible. Finally, a prospective study must be conducted to explore the most effective treatment modality for unresectable LAPC. A randomized clinical trial examining whether external radiation therapy can be combined with ^{125}I seed implantation irradiation to increase radiotherapy dose for tumors (such as pancreatic head cancer) is ongoing at our center.

Conclusions

CCHRT conferred better OS benefits than CCLRT, ^{125}I seed implantation combined with chemotherapy or chemotherapy alone to patients with unresectable LAPC. This treatment modality could provide some guidance in the battle to treat this disease. Prospective clinical trials must be performed to explore further which modality is optimal for this group of patients.

Abbreviations

LAPC: locally advanced pancreatic cancer; CCHRT: concurrent chemotherapy combined with high-dose radiation (DT>50Gy); CCLRT: concurrent chemotherapy combined with low-dose radiation (DT50Gy); CA: chemotherapy alone; OS: overall survival.

Declarations

Ethics approval and consent to participate

It was human data, not human participants, that participated in the study. The study did not involve experiments on animals.

Consent for publication

Not applicable.

Availability of data and materials

The datasets generated and/or analyzed during the current study are available from the corresponding author upon request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

Jinbo Yue, Hongxin Niu and Shumei Jiang designed the study. Yanfen Zheng wrote the manuscript, collected patients and analyze data. Chao Liu, Rui Huang and Wenxue Zou contributed to collect patients and analyze data. All authors read and approved the final manuscript.

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Figures

Overall survival (n=89)

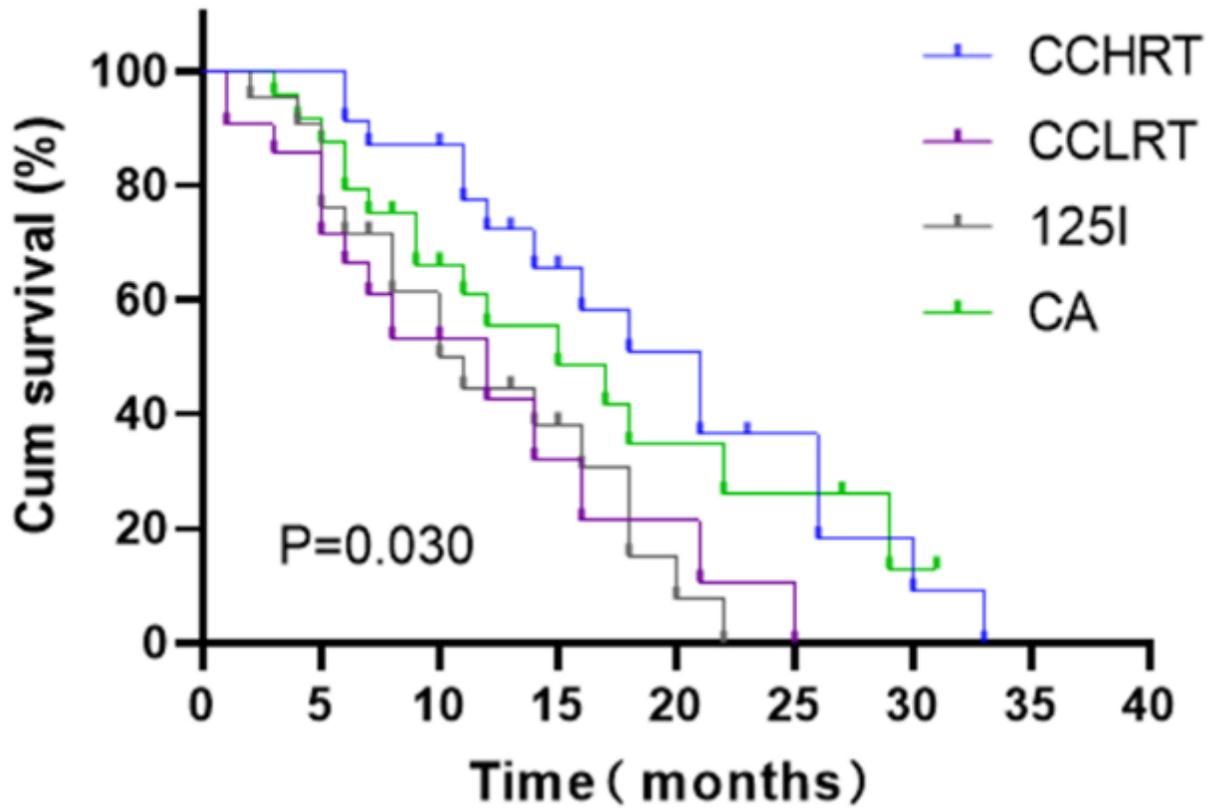


Figure 1

Abbreviations: CCHRT: concurrent chemotherapy combined with high-dose radiation (DT>50Gy); CCLRT: concurrent chemotherapy combined with low-dose radiation (DT≤50Gy); 125I: 125I seed implantation combined with chemotherapy; CA: chemotherapy alone.

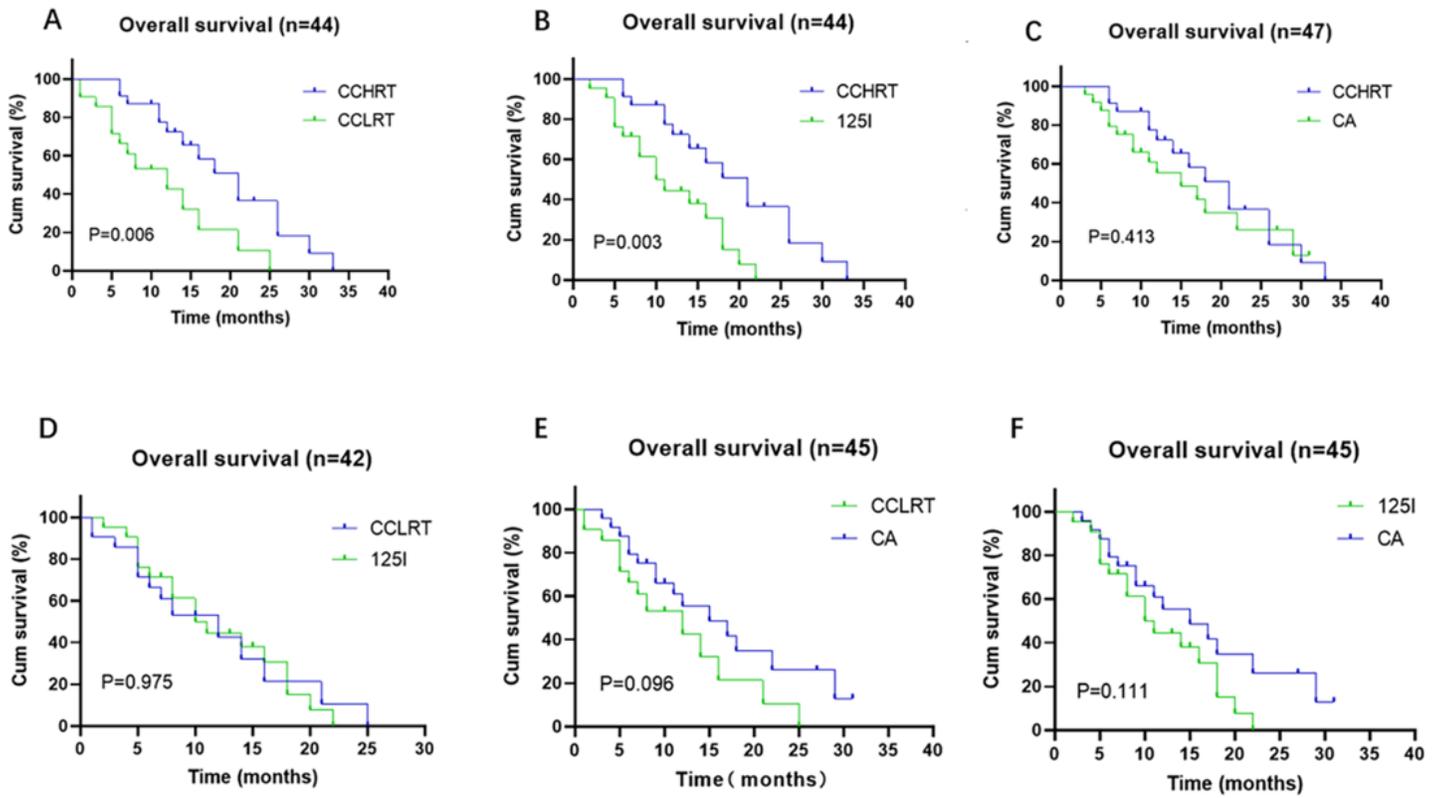


Figure 2

Abbreviations: CCHRT: concurrent chemotherapy combined with high-dose radiation (DT>50Gy); CCLRT: concurrent chemotherapy combined with low-dose radiation (DT≤50Gy); 125I: 125I seed implantation combined with chemotherapy; CA: chemotherapy alone.