Survival of patients with advanced pancreatic cancer after iodine$^{125}$ seeds implantation brachytherapy
A meta-analysis
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Abstract
**Background:** Brachytherapy with iodine$^{125}$-labeled seeds ($^{125}$I-seeds) implantation is increasingly being used to treat tumors because of its positional precision, minimal invasion, least damage to noncancerous tissue due to slow and continuous release of radioactivity and facilitation with modern medical imaging technologies. This study evaluates the survival and pain relief outcomes of the $^{125}$I-seeds implantation brachytherapy in advanced pancreatic cancer patients.

**Methods:** Literature search was carried out in multiple electronic databases (Google Scholar, Embase, Medline/PubMed, and Ovid SP) and studies reporting $^{125}$ seeds implantation brachytherapy in pancreatic cancer patients with unresectable tumor were selected by following predetermined eligibility criteria. Random effects meta-analysis was performed to achieve inverse variance weighted effect size of the overall survival rate after the intervention. Sensitivity and subgroups analyses were also carried out.

**Results:** Twenty-three studies (824 patients’ data) were included in the meta-analysis. $^{125}$I-seeds implantation brachytherapy alone was associated with 8.98 [95% confidence interval (CI): 6.94, 11.03] months ($P < 0.00001$) overall survival with 1-year survival of 25.7 ± 9.3% (mean ± standard deviation; SD) and 2-year survival was 17.9 ± 8.6% (mean ± SD). In stage IV pancreatic cancer patients, overall survival was 7.13 [95% CI: 4.75, 9.51] months ($P < 0.00001$). In patients treated with $^{125}$I-seeds implantation along with 1 or more therapies, overall survival was 11.75 [95% CI: 9.84, 13.65] months ($P < 0.00001$) with 1-year survival of 47.4 ± 22.75% (mean ± SD) and 2-year survival was 16.97 ± 3.1% (mean ± SD). $^{125}$I-seeds brachytherapy was associated with relief of pain in 79.7 ± 9.9% (mean ± SD) of the patients.

**Conclusions:** Survival of pancreatic cancer patients after $^{125}$I-seeds implantation brachytherapy is found to be 9 months, whereas a combined treatment with $^{125}$I-seeds brachytherapy and other therapies was associated with approximately 12 months’ survival. The majority of patients who underwent $^{125}$I-seeds brachytherapy had their pain relieved.

**Abbreviations:** $^{125}$I-seeds = iodine$^{125}$-labeled seeds, cGy/h = centigray/hour, CI = confidence interval, cm = centimeter, CT = computed tomography, EGFR = epidermal growth factor receptor, EUS = endoscopic ultrasonography/ic, G2/M = growth phase-2/mitotic phase, KeV = kiloelectron volt, MBq = megabecquerel, mCi = milliCurie, MeSH = Medical subject heading, mm = millimeter, Na = sodium, Panc-1 = an epithelioid carcinoma cell line derived from human pancreas, PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses, SD = standard deviation.

**Keywords:** brachytherapy, iodine$^{125}$ seed implantation, pain relief, pancreatic cancer, survival

1. Introduction

Pancreatic cancer is the fourth most common cause of cancer-related mortality.[1] In United States of America alone, 12 new cases of pancreatic cancer are diagnosed in every 100,000 individual and 11 in 100,000 persons die from this cancer, each year. Lifetime risk of developing pancreatic cancer is 1.5%.[2] It is a rapidly developing cancer which causes abdominal pain, weight loss, and jaundice.[3] Because the early signs of pancreatic cancer are not much clear, the diagnosis often remains delayed. Even the later symptoms are usually not much specific which leads to diagnosis at middle or terminal stage. By this time, cancer becomes unresectable[4] that may have invaded to surrounding areas and/or metastasized to distant organs.[5]

Whereas, only 15% to 20% of pancreatic cancer patients are diagnosed at an early stage, 5-year survival after tumor resection is 20% to 25%.[6] In patients with exocrine pancreas adenocarcinoma, the 5-year survival rate for is about 3% to 6%.[7-9] and for local tumor, the 5-year survival rate is about 15%.[9] Management of the unresectable pancreatic cancer is carried out with chemotherapy, radiofrequency ablation,
conformal radiotherapy, interstitial brachytherapy, and brachytherapy with radioactive seeds implantation.\textsuperscript{[10–12]} Local tumor control and its metastasis to other parts are the major prognostic factors.\textsuperscript{[13]}

Brachytherapy with iodine\textsuperscript{125} labeled seeds (\textsuperscript{125}I-seeds) implantation has become widespread in oncological use due to the development of modern facilitative medical imaging technologies.\textsuperscript{[14,15]} Computed tomography (CT)-guided percutaneous implantation of \textsuperscript{125}I-seeds provides positional precision with minimal invasion and maintains slow and continuous release of radioactivity for the repair of nonlethal tissue damage and reoxygenation of hypoxic tissues.\textsuperscript{[12,16]}

A number of studies have reported the outcomes of percutaneous \textsuperscript{125}I-seeds implantation in pancreatic cancer patients but survival rates vary across the studies. We have carried out a systematic review of relevant studies and have performed a meta-analysis of the survival rates of the advanced stage pancreatic cancer patients after brachytherapy with \textsuperscript{125}I-seeds implantation alone or in combination with other therapies in order to have a pooled overall as well as subgroup effect sizes of the survival in late-stage patients.

2. Methods

This study was performed by following PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines.\textsuperscript{[17]} Ethics committee and/or institutional board approval was not required for this study.

2.1. Literature search

For the acquisition of relevant research articles, electronic databases (Google Scholar, Embase, Medline/PubMed, and Ovid SP) were searched by using various combinations of MeSH and keywords including pancreatic cancer, brachytherapy, iodine\textsuperscript{125} seeds implantation, \textsuperscript{125}I, percutaneous, pain relief, survival, follow-up, response rate, remission, and Karnofsky Performance Status. Search encompassed original research papers published before February 2016.

2.2. Eligibility criteria

Relevant prospective and retrospective studies investigating brachytherapy with \textsuperscript{125}I-seeds implantation in pancreatic cancer patients with unresectable tumor (stage II, III, IV) were eligible for inclusion. Outcomes of interest (endpoints of the present study) were: overall, 1-year, and 2-year survival rates; and percentage of patients having pain relieved.

Inclusion criterion was: Study reported the outcomes of computed tomographic (CT)-guided or endoscopic ultrasonographic (EUS)-guided \textsuperscript{125}I-seeds implantation brachytherapy with or without other therapies after treating stage II, III, or IV stage pancreatic cancer patients. Exclusion criteria were: Study had follow-up of less than 3 months, study did not treat all patients with \textsuperscript{125}I-seeds implantation brachytherapy, in vitro studies involving clonogenic survival rates, study did not report survival rate.

2.3. Quality assessment

Quality assessment of the included studies was performed by using Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies.\textsuperscript{[18]}

2.4. Data and analyses

Data regarding demographic and clinical characteristics of the patients, study design and outcome measures, and outcome data were taken from the respective research articles. Data were extracted independently by 2 authors. Interrater reliability was good (Cohen kappa = 0.94).

Random effects meta-analyses were performed to achieve inverse variance weighted overall and subgroup effect sizes of the survival rates reported in the individual studies. Subgroup analyses were performed with respect to \textsuperscript{125}I-seeds implantation alone, \textsuperscript{125}I-seeds implantation along with chemotherapy, \textsuperscript{125}I-seeds implantation along with cryoablation, and \textsuperscript{125}I-seeds implantation along with a multimodality treatment.

One- and 2-year survival rates reported by the individual studies were pooled and the significance of difference between \textsuperscript{125}I-seeds implantation brachytherapy alone and \textsuperscript{125}I-seeds implantation brachytherapy with other therapies was assessed with \textit{t} test.

Between studies statistical heterogeneity was assessed with \textit{I}\textsuperscript{2} index. Sensitivity analyses were performed to investigate the source of high heterogeneity. Assessment of the publication bias was performed with the funnel plot asymmetry test followed by trim and fill method of missing studies estimation. All statistical procedures were performed by using Stata software (version 12 SE; Stata Corporation, Lakeway, TX, USA).

3. Results

3.1. Data acquisition

The literature search led to the selection of 23 studies\textsuperscript{[15,19–40]} which fulfilled the eligibility criteria (Fig. 1). Majority of the studies were retrospective in design and of moderate quality (Table 1). A significant publication bias was also evident when tested with funnel plot asymmetry test and trim and fill method...
In these studies, overall 824 patients were treated with $^{125}$I-seeds implantation brachytherapy. Twelve studies treated patients with $^{125}$I-seed implantation alone, whereas, 5 studies treated patients with $^{125}$I-seeds implantation in combination with chemotherapy, 4 studies treated $^{125}$I-seeds implantation in combination with cryosurgery (1 with radiofrequency ablation) and 2 studies utilized multimodality treatment.

3.2. Study characteristics
Average age (mean ± standard deviation; SD) of the patients was 60 ± 11 years of which 60 ± 7.4% were males. Of these, 19% were stage II, 51% stage III, and 30% stage IV pancreatic cancer patients. Anatomically, the tumor was in head of pancreas in 50% of the patients, 32% had tumor in the body of pancreas and 18% had it in the tail. On average, 30 ± 18 $^{125}$I-seeds were used per patient (7 studies data).

3.3. Study outcomes
Median follow-up was 14.2 months (7 studies data). The outcomes of the meta-analysis revealed that $^{125}$I-seeds implantation brachytherapy alone was associated with 8.98 [95% confidence interval (CI): 6.94, 11.03] months ($P < 0.00001$) overall survival after the treatment (Fig. 3) with 1-year survival of 25.70 ± 9.3% (mean ± SD) and 2-year survival was 17.9 0 ± 8.6% (mean ± SD; Fig. 4). In stage IV pancreatic cancer patients, overall survival was 7.13 [95% CI: 4.75, 9.51] months ($P < 0.00001$; Fig. 5).
In the patients treated with $^{125}$I-seeds implantation along with 1 or more therapies, overall survival was 11.75 [95% CI: 9.84, 13.65] months ($P < 0.00001$; Fig. 3) with 1-year survival of 47.4 ± 22.75 (mean ± SD) % and 2-year survival was 16.97 ± 3.1% (mean ± SD; Fig. 4). Difference in 1-year survival rate between $^{125}$I-seeds implantation alone and $^{125}$I-seeds implantation in combination with other therapies was statistically significant ($P = 0.017$).

In subgroup analyses, the overall survival was 13.63 [95% CI: 9.98, 17.28] months ($P < 0.00001$) in patients treated with $^{125}$I-seeds implantation along with cryoablation, 10.05 [95% CI: 8.76, 11.34] months ($P < 0.00001$) in patients treated with $^{125}$I-seeds implantation along with chemotherapy, and 11.50 [95% CI: 8.10, 14.89] months ($P < 0.00001$) in patients treated with $^{125}$I-seeds implantation along with a multimodality treatment (Fig. 6). Statistical heterogeneity was variable with $I^2$ ranged from 0% in $^{125}$I-seeds brachytherapy-chemotherapy combination meta-analysis to 93% in $^{125}$I-seeds brachytherapy alone meta-analysis.

Of the patients who were presented with pain before treatment, 79.7 ± 9.9% (mean ± SD) reported relief from pain after therapy (15 studies data). There was no difference in the percentage of patients receiving either $^{125}$I-seeds brachytherapy alone or in combination with other therapies in this regard (Fig. 4). As mean ± SD, the response rate was 64.1 ± 24.8% (8 studies data) with complete remission was observed in 10.9 ± 13.1% (6 studies data) and partial remission was observed in 26.6 ± 12.7% (6 studies data).

4. Discussion
The present study finds that the overall survival of pancreatic cancer patients after $^{125}$I-seeds brachytherapy is about 9 months. A combined treatment with $^{125}$I-seeds brachytherapy and other therapies is found to be associated with approximately 12 months

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**Figure 3.** A forest plot showing the effect sizes of the overall survival of pancreatic cancer patients treated with $^{125}$I-seeds implantation brachytherapy with or without combinational therapies.

**Figure 4.** A bar chart showing percent pain relief, 1- and 2-year survival of pancreatic cancer patients treated with $^{125}$I-seeds implantation brachytherapy alone and $^{125}$I-seeds implantation brachytherapy with other therapies.
of survival. However, in stage IV patients, the overall survival is about 7 months. The $^{125}$I-seeds brachytherapy is also found to provide adequate pain relief in patients in which presentation symptom was severe pain.

Five-year survival in locally advanced pancreatic cancer patients is about 4% and the overall survival rate is 9 to 15 months which may be 3 to 6 months less in cases with metastases.\[41\] Pancreaticoduodenectomy is the first-line treatment option but depends on the resectability of the tumor. Therefore, the surgery is indicated for just a small proportion of the patients. Moreover, longer operative time, bleeding, and postoperative complications also need extraordinary management. Thus, in general, in the end-stage (III and IV) and in older patients, surgery remains unsuitable.\[42\]

Among the chemotherapeutic regimens, gemcitabine modestly increases the overall survival and offers better clinical benefits in comparison with 5-fluorouracil.\[43\] Gemcitabine improves the overall survival up to 5 to 7 months and 20% increase in 1-year survival rate in metastatic patients.\[43\] Intensity-modulated radiotherapy and image-guided radiotherapy techniques also provide an effective dose while minimizing dispersion to the surrounding tissues. Both these radiotherapy regimens are associated with overall and progression-free survival of 12 and 7.6 months, respectively, to pancreatic cancer patients after preradiation chemotherapy.\[44\]

Radioactive $^{125}$I-seeds implantation provides the interstitial irradiation and can be a suitable option for patients who cannot be benefited by surgery. The half-life of $^{125}$I is 59.7 days which is suitable for rapidly growing pancreatic tumor. In a 4.5 mm long seed with a diameter of 0.8 mm, $^{125}$I is filled as Na$^{125}$I within a sealed titanium alloy tube. Mean photonic energy in a seed is 27 to 35 KeV gamma rays which releases an initial 7cGy/h dose followed by mean radiation of $0.694\pm0.021$ mCi (25.6 MBq) penetrable to 1.7 cm in the human tissue.\[16\]

A continuous low-dose irradiation with $^{125}$I-seeds has been found to cause Panc-1 cell-cycle arrest in the G2/M phase and induce apoptosis.\[45\] However, antiepidermal growth factor receptor (EGFR) monoclonal antibody C225 sensitized irradiation with $^{125}$I-seeds led to apoptosis but not cell-cycle arrest in colorectal cancer cells.\[46\] Best time for chemotherapy is suggested to be is within 3 ± 4 days after implantation of $^{125}$I-seeds as irradiation promotes permeability of the surrounding vasculature during this time.\[47\]

Taken together, brachytherapy with $^{125}$I-seeds implantation provides a comparable option for advanced pancreatic cancer patients whose benefits can be improved with combinational therapies, if feasible. It is a potential treatment for locally advanced pancreatic cancer in terms of feasibility, safety, and pain relief. However, larger and better coordinated studies are required to confirm the long-term effects of this brachytherapeutic regimen.

5. Conclusions

Brachytherapy with $^{125}$I-seeds implantation leads to the overall survival of advanced pancreatic cancer patients of about 9 months and a combined treatment with $^{125}$I-seeds brachytherapy and other therapies is found to be associated with 12 months’ survival. Brachytherapy with $^{125}$I-seeds implantation in combination with cryoablaction is found to be associated with maximum survival (approximately 14 months). However, in stage IV patients, overall survival is about 7 months. The $^{125}$I-seeds brachytherapy is also found to provide adequate pain relief in patients in which presentation symptom was severe pain.
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