ORIGINAL ARTICLE

IMPACT OF DEMOGRAPHIC AND IMAGING PARAMETERS OF BASELINE FDG PET/CT UPON OVER-ALL SURVIVAL IN UN-RESECTABLE PANCREATIC DUCT ADENOCARCINOMA TREATED WITH CHEMORADIATION WITH OR WITHOUT IMMUNOTHERAPY

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ABSTRACT

AIM/INTRODUCTION: Pancreatic duct adenocarcinomas (PDAC) are known to have dismal survival as more than 80% tumors are un-resectable at diagnosis. Chemotherapy with or without radiation is the standard regime in these patients with lower over-all survival (OS). In recent year immunotherapy has been introduced with reported better OS. FDG PET/CT is an effective tool for staging and response evaluation in these patients. Aims of this study were to compare OS in patients with un-resectable PDACs who had chemoradiation with or without immunotherapy and its predictor(s) using demographic and imaging parameters of baseline FDG PET/CT scan. **METHODS:** This retro-prospective study was conducted at PET/CT Imaging facility of JCIA accredited healthcare facility of Pakistan from (March 2017 till December 2020). Total 29 patients with un-resectable PDACs were included who had FDG PET/CT for staging. Seventeen patients (17/29) received only chemoradiation (CRT-Group) while 12/29 received CRT with immunotherapy (CRT+Im Group). These patients were followed for a median period of 4 months (2-10 months). Kaplan Meier s survival curves were analyzed to measure OS in both groups. Using Receiver operating characteristics (ROC) curve, demographic and baseline FDG PET/CT parameters were plotted to find out significant predictor(s) of OS in both groups. **RESULTS:** Patients with CRT had mean OS 6.9 month (5.3 8.5) compared to 8.3 months (6.3 10.2) who had CRT+Im (p value > 0.5). Using ROC analysis, age, gender, body mass index (BMI), primary tumor size (PTS) and SUVmax of primary tumor in baseline FDG PET/CT did not show significant impact on OS in either group. However, hypermetabolic bony and pulmonary metastases were found to be significant predictors of shorter OS in both groups (AUC: 0.879 and 0.875 in CRT and CRT+Im respectively; p value <0.05). **CONCLUSION:** In un-resectable PDAC no significant difference in mean OS was found in patients treated with CRT and CRT+Im. Age, gender, BMI, PTS and SUVmax of primary tumor in baseline FDG PET/CT were found non-significant predictors for OS in either group. Hypermetabolic bony and pulmonary metastases on baseline FDG PET/CT were found to be significant predictors of shorter OS in both groups.

Key Words: Pancreatic Duct Adenocarcinoma; FDG PET/CT; Chemoradiationtherapy; Immunotherapy; over-all survival; predictors

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Introduction

Currently pancreatic duct adenocarcinoma (PDAC) is the 3rd leading cause of cancer-related deaths and expected to become 2nd in next 10 years in United States.[1,2] Eighty percent (80%) of patients have un-respectable disease due to locally advanced disease with or without distant metastasis.[3] In these patients, neoadjuvant treatment like combination chemotherapy (folinic acid, 5-fluorouracil, irinotecan and oxaliplatin-FOLFIRINOX), or chemoradiotherapy (CRT) protocols may result in successful resection in up to 60% of patients with locally advanced PDAC.[4] However, median OS of metastatic PDAC is 11 months in patients who receive FOLFIRINOX.[5] Federal Drug Administration (FDA) has approved pembrolizumab (immune checkpoint inhibitor) for the treatment of patients with un-resectable PDAC with microsatellite instability high (MSI-H) or mis-match-repair deficient (dMMR) features.[6] Evolving data discourage the use of immunotherapy as a monotherapy and favor its use with chemotherapy and radiotherapy as these options make tumor environment favorable for immunotherapy.[7] Early phase trials of combining immunotherapy, especially checkpoint inhibitors with chemotherapy in PDAC, have reported some encouraging findings.[8,9]

Objectives of this study were to compare OS in patients with un-resectable PDACs who had chemoradiation with or without immunotherapy and its predictor(s) using demographic and imaging parameters of baseline FDG PET/CT scan.

Material and Methods

This retro-prospective study was conducted at PET/CT Imaging facility of JCIA healthcare facility of Pakistan from (March 2017 till December 2020). Total 29 patients with un-resectable PDAC were included who had FDG PET/CT for staging. Cohort included 18 males and 11 females with a mean age 59 years. Seventeen patients (17/29) received only chemoradiation (CRT-Group) while 12/29 received CRT with immunotherapy [Pembrolizumab] (CRT+Im Group). CRT-group had M:F ratio of 10:7 with a mean age of 58 58 – 13 years. CRT+Im group had M:F of 8:4 with a mean age of 60 – 09 years. Primary tumor size (mm) and SUVmax of primary tumor were 51 – 19 mm and 6.5 – 3.4 in CRT-group respectively. CRT+Im group had primary tumor size of 39 – 14 mm having SUVmax 9.2 – 6.0 (Table 1). These patients were followed for a median period of 4 months (2-10 months). Kaplan Meier s survival curves were analyzed to measure OS in both groups. Using receiver operating characteristics (ROC) curve, demographic and baseline FDG PET/CT parameters were plotted to find out significant predictor(s) of OS in both groups.

Inclusion Criteria: During study period patients with biopsy proven PDAC referred for 18FDG PET/CT imaging for staging were reviewed. Patients found to have locally advanced disease without or without metastases were recruited.

^{18}FDG PET/CT Imaging: FDG PET/CT was performed as per institutional protocol adopted from EANM guidelines (Boellaard et al., 2015). All patients had 4-6 hour fasting (only plain water was allowed) and a fasting blood sugar less than 200 mg% before receiving an intravenous ^{18}FDG dose of 3 MBq/Kg in the uptake room. During uptake period (55 -75 minute) patients were requested to lie comfortably and allowed to take about 500-1000 ml of plain water. Bladder was emptied prior to call the patient for PET/CT imaging suite equipped with Celesteion, Toshiba, Japan. A low dose CT examination (mid brain to mid-thigh) from head to toe followed by acquisition of PET imaging using 3 minute/bed position from toe to head in all patients. Follow up scans were performed with same protocols, keeping FDG dose, uptake time and hepatic SUVmean of baseline and follow-up studies within – 10%, – 15% and 20% minutes respectively as per PET response criteria in solid tumor (PERCIST) (Wahl et al., 2009). SUV_{max} of primary lesions and nodal disease were measured in both studies and also % change in highest SUV_{max} of baseline and follow-up studies for response evaluation as recommended by PERCIST criteria.

Statistical Analysis: Continuous variables were described by mean – standard deviation (SD). Com-

parisons between patient groups based on CRT and CRT+Im in unresectable PDAC were performed using Student s t test for continuous variables and the χ† test for categorical variables. Statistical significance was defined as P<0.05. Mean survival and criterion values against variables in both groups of unresectable PDAC were analyzed by Kaplan Meier analysis. Commercially available packages Microsoft excel 2010, Medcalcfi and statistical package for social sciences (SPSS 19fi) were used.

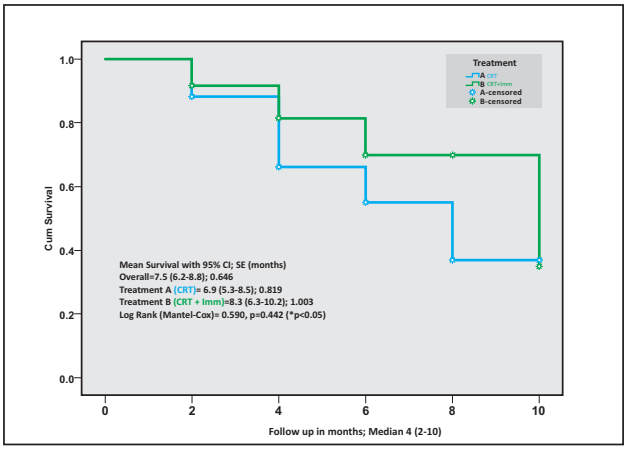
Results

No significant difference was found for age, gender distribution, and primary tumor size in CRTI and CRT+Im groups seen (p >0.05) (Tab.2 and 3). Similarly, no significant difference was observed for PTS and SUV_{max} of primary tumor between two groups (p>0.05) (Tab.2 and 3). No statistical significance was observed for presence of hypermetabolic regional node and non-nodal metastasis in both groups. Patients with CRT only had mean OS 6.9 month (5.3 8.5) compared to 8.3 months (6.3 10.2) who had CRT+Im (p value > 0.05) (Fig.1). Using ROC analysis, age, gender, body mass index (BMI), primary tumor size (PTS) and SUVmax of primary tumor in baseline FDG PET/CT did not show significant impact on OS in either group. However, presence of hypermetabolic bony and pulmonary metastases were found to be significant predictors of shorter OS in both groups (AUC: 0.879 and 0.875 in CRT and CRT+Im respectively; p value <0.05) (Tab.2 and 3).

Variables	Group A (n=17) Un-resectable Pancreatic cancer; CRT group	Group B (n=12) Un-resectable Pancreatic cancer; CRT+Im group	X² or t-test values	p value
Age in years Mean ± SD (range)	58 ± 13 (30-76)	60 ± 09 (50-75)	0.460	0.6494
Gender (Male: Female)	10: 07 (59% v: 41%)	08: 04 (67% v: 33%)	0.185	0.6670
BMI (Kg/m²) Mean ± SD	25.586 ± 4.765	25.422 ± 5.991	-0.082	0.9352
Primary tumor SUV max Mean ± SD (range)	6.5 ± 3.4 (1.2-14.2)	9.2 ± 6.0 (2.8-24)	1.544	0.1343
Primary tumor size in mm Mean ± SD (range)	51 ± 19 (27-92mm)	39 ± 14 (21-61mm)	-1.857	0.0743
%Overall Survival (OS)	58.8%	66.7%	0.180	0.6713

*p<0.05
CRT = Chemoradiation therapy
Imm = Immunotherapy
SD = Standard Deviation
BMI = Body Mass Index
SUVmax = Standardized uptake value
OS = Overall survival

Table 1: Patient s demographics of un-resectable pancreatic duct adenocarcinoma on baseline FDG PET/CT prior to therapy.



CRT = Chemoradiation therapy
Imm = Immunotherapy
CI = Confidence Interval

Figure 1: Kaplan Meier Survival analysis of Overall survival on FDG PET/CT in un-resectable pancreatic cancer using chemoradiation therapy and chemoradiation plus immunotherapy.

Variables		AUC	Criterion	SE	95%CI	Z statistics	P value
Demographics	Age	0.557	>51	0.155	0.254 - 0.860	0.369	0.7118
	Male Gender	0.636	NA	0.127	0.388 - 0.884	1.072	0.2839
	BMI	0.586	>25.344	0.150	0.293 - 0.879	0.573	0.5665
Baseline FDG PET/CT	Baseline SUVmax	0.717	>4.9	0.184	0.356 -1.000	1.176	0.2396
	PTS	0.500	>45	0.236	0.038- 0.962	0.004	1.000
	Lung and Bony Mets	0.879	NA	0.0872	0.708-1.000	4.342	<0.001*

*p<0.05
CRT = Chemoradiation therapy
SUVmax = Standardized uptake value
BMI = Body mass index
PTS = Primary Tumor Size

Table 2: Predictors for shorter survival in un-resectable pancreatic duct adenocarcinoma patients in Group A (CRT group).

Variables		AUC	Criterion	SE	95%CI	Z statistics	P value
Demographics	Age	0.641	>57	0.220	0.209 - 1.000	0.639	0.5230
	Male Gender	0.563	NA	0.155	0.259 - 0.866	0.403	0.6866
	BMI	0.500	>20.761	0.197	0.114 - 0.886	0.000	1.000
Baseline FDG PET/CT	Baseline SUVmax	0.547	>8.7	0.218	0.119 - 0.975	0.215	0.8301
	PTS	0.732	>36	0.180	0.380 - 1.000	1.291	0.1966
	Lung and Bony Mets	0.875	NA	0.125	0.630 - 1.000	3.000	0.0027*

*p<0.05
CRT = Chemoradiation therapy
Im = Immunotherapy
SUVmax = Standardized uptake value
BMI = Body mass index
PTS = Primary Tumor Size

Table 3: Predictors for shorter survival in un-resectable pancreatic duct adenocarcinoma patients in Group B (CRT+ immunotherapy group).

Discussion

Pancreatic ductal adenocarcinoma (PDAC) being an aggressive tumor which is unresectable in 80% at time of diagnosis and has a dismal five-year overall survival (OS) of 6%.[1] In these patients systemic palliative chemotherapy (most commonly FOLFRINOX) with local radiotherapy is used to improve survival moderately.[4,5] In recent years, an anti-PD1 immunotherapy agent (Pembrolizumab) has been approved by FDA in PDAC. However, in PDAC the currently available immunotherapies have only demonstrated marginal efficacy in terms of survival.[10]

In this study OS was lower (6.9 months in CRT group and 8.3 months in CRT+Im group) and did not show a significant benefit of adding immunotherapy (Pembrolizumab) to CRT. This is in contrast to recently published data favoring addition of immunotherapy to chemotherapy and chemoradiation therapy was associated with significantly improved OS in PDAC patients without definitive surgery.[11] In NCT02331251 trial including 17 patients treated with Pembrolizumab and chemotherapy, the overall survival was 15 months compared to 8.3 month in our study group having 12 /29 patients.[12] In NCT02309177 trial including 42 treatment na ve patients with advanced pancreatic cancer, chemotherapy and Nivolumab showed an overall survival of 9.9 months which is comparable to our CRT+Im group (8.3 months).[13] With these published results from small sample sized trials and current study, larger clinical trials and meta-analysis are warranted to ascertain the real benefit of adding immunotherapy to CRT in unresectable PDAC.

Various studies have been performed to see the impact of race, age and genders upon survival in PDAC. Our study population included only Pakistani individuals and OS in both groups was less than 1 year. This is in contrast to a study published in 2021 revealing longer survival in Asians followed by blacks and lowest in Indians and Americans.[14] In another study published in 2020, when disease stage and treatment were controlled for, black patients had no decrease in survival.[15] The possible reason of lower survival in our Pakistani (Asian) might be higher unresectable disease burden at the time of diagnosis. Important to note that race in our study albeit with small sample size, failed to show any significance of race in either treatment group. Our finding is in concordance with a study published in 2013 showing no significant difference in survival rates by race in patients having an equal access to health care system.[16]

Survival analysis based on sex suggested that females had measurably increased odds of survival earlier in disease progression which became indistinguishable after first 10 months.[14] However, our study failed to show any significant impact of gender upon survival in both groups. Plausible reason could be that none of patients in either group could survive beyond 10 months.

In our study, primary tumor size and SUVmax in either group did not show significant difference upon OS. This is in contrary to published studies favoring negative correlation between size and SUVmax with survival in PDAC.[17] The reason could be due to an altered tumor biology in our region resulting in aggressive tumor behavior independent of intensity of FDG uptake and SUVmax which needs to be studied in depth in future studies. Presence of hypermetabolic bony and pulmonary metastasis in our study were found to be associated with lower OS. This is an expected finding which stands valid for most malignancies.

Limitation and Strength: Small sample size of our

study is a major limitation. This primary reason is lower referral to our tertiary care facility and affordability of patients towards Immunotherapy. Another limitation of study is lack of adequate information about microsatellite instability high (MSI-H) or mismatch-repair deficient (dMMR) features of primary tumor. This is an important limitation as it has direct impact on efficacy of immunotherapy of PDAC. The major strength of this study is standardized imaging and reporting protocol of FDG PET/CT studies as this minimize possibility of impact of various factor on SUVmax of primary tumors and their metastases. Another strength of our study is that patients in both groups had no significant difference for demographic, PTS and imaging (SUV_{max}) parameters.

Conclusion

Conclusion:In un-resectable PDAC no significant difference in mean OS was found in patients treated with CRT and CRT+Im. Age, gender, BMI, PTS and SUV_{max} of primary tumor in baseline FDG PET/CT were found non-significant predictors for OS in either group. Hypermetabolic bony and pulmonary metastases on baseline FDG PET/CT were found to be significant predictors of shorter OS in both groups. Large sample study with precise details of tumor microenvironment is warranted to ascertain the role immunotherapy in PDAC in local Pakistani population.

Conflict of Interest: Authors declared no institutional or financial conflict of interest.

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