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Impact of tumor size on survival outcome of pancreatic carcinoma following pancreatic resection: A systematic review and meta-analysis

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ABSTRACT

The aim of the study was to evaluate the influence of tumor size on long-term survival outcome of pancreatic tumors following pancreatic resection and the possibility of implementing another tumor size cut-off point in AJCC pancreatic tumor staging. Literature searches was conducted on electronic database to identify relevant studies on tumor size related survival outcome following pancreatic resection for pancreatic adenocarcinoma. Meta-analysis was done using the effect estimates and the use of 95% confidence intervals (CIs) was done to calculate the pooled risk estimates; heterogeneity among studies was examined using I^2 statistic. Total of 18 trials (13 retrospective and 5 prospective studies) including 6230 elderly patients was included in this study. The pooled HR of the tumor size with 2 cm cut-off was 1.43 with 95% CI of [1.27-1.62], $I^2 = 17\%$, $p < 0.00001$ and was statistically significant. Median survival for tumor size <2, >2, <3, >3, <4 and >4 were 41.02 months, 16.20 months, 19.41 months, 10.79 months, 24.2 months and 15.14 months respectively and the 1-, 3-, and 5-year survival rate decreased with increasing tumor diameter. Importantly, a total of four studies results indicated that 3-year survival rate and a total of five studies results indicated that 5-year survival rate had statistical significance with 3 cm cut-off. Tumor diameter of 2 cm seems to be a reasonable but relatively less comprehensive cut-off point. 3 cm cut-off maybe become a new potential tumor size cut-off point in addition to the current sole 2 cm cut-off point defining tumor stage.

Key words: Tumor size, Pancreatic cancer, Pancreaticoduodenectomy, Survival outcome

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INTRODUCTION

Pancreatic cancer is a highly fatal disease. It is regarded as one of the leading cause of cancer death accounting for 4.8% and 5.5% of cancer death in men and women respectively.[1,2] Prognosis in patient diagnosed with pancreatic cancer is very dismal and even after successful curative resection, the 5-year survival rate still remains as low as 5%-20% as reported by most of the literatures.[3-5] Tremendous development of surgical and vascular techniques and imaging technology, resection of pancreatic cancer has increased significantly in recent years. However, due to rapid local lymphatic spread, vascular invasion or metastasis, approximately 80% of the pancreatic cancer patients are not eligible for surgical resection.[6,7]

Several factors have been noted to influence the survival following surgical resection of pancreatic carcinoma. Lymph node status, peri-neural/vascular invasion, tumor staging (TNM status), tumor type, resectability, co-morbidity and patient age have all been reported to affect the outcome.[8-12] However, tumor size has been considered

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to be a key prognostic feature and certainly have a great impact on survival outcome after surgical resection. In fact, the American Joint Committee on Cancer (AJCC) staging system for pancreatic cancer has clearly defined the difference between a T1 and T2 tumor solely by the size of the tumor (≤ 2cm vs. > 2cm).[13] In AJCC TNM staging, tumor (T) staging is not relatively comprehensive as it is solely differentiated by tumor diameter with 2 cm cut-off. Tumor diameter with 3cm and 4 cm cut-offs are not specified in the staging and thus causing conflicts about selection of the tumor size cut-off in defining the tumor stage. Many studies have favored the AJCC tumor staging cut-off of 2 cm,[14-16] whereas there are studies[17-19] which reports the indication for reconsideration of the tumor stage cut-off, to provide more precise reference for staging and predicting survival outcome. Moreover, the impact of tumor size on survival outcome also remains controversial. Several studies[10,17,20] have reported no influence of tumor size on long-term survival, while others[9,14,21] have favored smaller tumor size to have better result than the larger tumors. An increased tumor mass could impact on the occurrence of metastatic lymph nodes, resection margins and finally, long-term survival.[14] Although previous literatures have analyzed heterogeneous array of patient and tumor factors, few have specifically examined the prognostic effect of the tumor size.[21] Therefore, the present study aimed to highlight following points: 1) to assess the influence of tumor size on survival outcome following pancreatic cancer, 2) to evaluate the accuracy and comprehensiveness of tumor size cut-off of 2 cm as suggested by current AJCC staging system, 3) to evaluate the possibility of implementing another tumor size cut-off using 3 cm or 4 cm so as to evaluate which accurate T stage does tumor with 3 cm and 4 cm diameter belong to, and to predict its prognosis following surgery, 4) to provide a pivotal reference for new AJCC stage system and treatment for pancreatic cancer.

MATERIAL AND METHODS

Search strategy and study identification

Electronic databases were searched for studies and literatures in the PubMed MEDLINE, Ovid MEDLINE, EMBASE and Cochrane library from January 2000 to December 2016. Searching terms were used as "(Whipple procedure or Whipple surgery or Whipple operation or pancreaticoduodenectomy or pancreatectomy) AND (pancreatic tumor or pancreatic carcinoma or pancreatic malignancy or pancreatic neoplasm) AND (survival outcome or prognosis) AND (tumor size)" with restriction of English language but not to article type. The titles of the articles were reviewed and a reference check was performed to determine whether the article met the inclusion criteria.

The flow diagram of searching strategy is shown in Figure 1. A total of 515 articles and abstracts were identified by initial searches, of which 460 articles were excluded by manual screening of the titles, abstracts and animal experiments. An additional 29 papers were excluded after reading the full text. A total of 4 manuscripts were further added after manual reference search, therefore, leaving 30 articles for full publication review. Of these, 30 appropriate manuscripts, we found survival outcome was not compared as per the tumor size cut-off in 3 studies,[22-24] tumor size was not differentiated in 5 studies[25-29] and outcomes of pancreatic adenocarcinoma was not differentiated with other pancreatic malignancies in 4 studies.[8,30-32] Finally, 18 articles were included after reading the full papers (Table 1).[4,15-19, 33-44]

Inclusion and exclusion criteria

Included studies should meet the following criteria: 1) Studies should be published in English language irrespective of research methods, 2) manuscripts containing data of pancreatic adenocarcinoma undergoing pancreatic resection, 3) manuscripts should contain major outcome determinants of long-term survival such as patient demographics, operative detail, tumor characteristics (tumor size, tumor differentiation), median survival rate, yearly survival rates, and/or effect estimates (HR) assessing the association of tumor size with its corresponding 95% CI.

Studies that were conducted on animals, and with insufficient data were all excluded. When two studies were reported including same patients totally or partly by the same institution, the publication with more sample size was included. Studies which did not differentiated the outcome data of other pancreatic malignancies like neuroendocrine

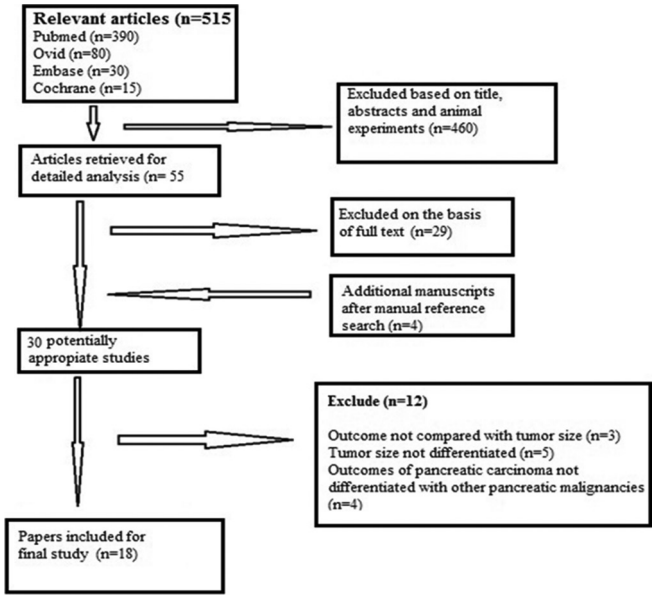

Figure 1: Flow chart of search identification process.

Table 1: Baseline characteristics of included studies (N-18)

Author	Year	Type of Study	M%	Sample Size (N)/(n)	Intervention	Country	Age (years) X/Y	Tumor size (cm)	Outcome comparison
*Sohn et al[19]	2000	Retrospective	54	593/616	PD-526 DP-52 TP-38	USA	64.3/66	<3 ≥3	a, c, d, e
Meyer et al[15]	2000	Retrospective	59	86/113	PD- 105 DP- 7 TP- 1	Germany	NA/64	≤2 >2	a, b, c, d
*Magistrelli et al[35]	2000	Retrospective	60	73/73	PD-45 DP-10 TP-18	Italy	60.9/62	<3 ≥3	b, c, e
*Benassai et al[18]	2000	Retrospective	67	67/75	PD-75	Italy	67/NA	<3 ≥3	c, d, e
*Kedra et al[16]	2001	Prospective	54	136/212	PD-98 PPPD- 50 TP- 35 PP-29	Poland	63.1/65	<2 ≥2	d, e
*Takai et al[41]	2003	Retrospective	53	90/94	PD-56 TP-13 DP-25	Japan	NA/64	<3 ≥3	a, b, c, d, e
Shoup et al[39]	2003	Prospective	47	57/57	DP	USA	NA/66	≤2 >2	d
*Lim et al[40]	2003	Retrospective	49	309/396	PD-351 PP-16 TP-29	USA	NA/72	≤2 >2	a, b, d, e
Connor et al[38]	2004	Prospective	59	56/59	PD	UK	NA/65	≤2 >2	d
Winter et al[4]	2006	Retrospective	54	NA/1175	PD-834 TP-79 vessel resection 47	USA	NA/66	<3 ≥3	a, c, d
Shimada et al[37]	2006	Retrospective	71	88/88	PD-76 Appleby operation-12	Japan	66/65	<4 ≥4	a, b, c, d
*Han et al[42]	2006	Retrospective	70	117/123	PD-98 TP-2 DP-22 Appleby operation-1	Korea	57.9/NA	≤3 >3	d, e
*Pawlik et al[44]	2007	Prospective	54	905/905	PD-260 PPPD- 645	USA	NA/66	2 cm cut-off	c, e
*Li et al[43]	2008	Retrospective	61	134/134	PD-105 PPPD-29	China	NA/57	≤2 >2	a, b, c, e
*Ueda et al[36]	2009	Retrospective	57	135/140	PD-54 DP-35 TP-6 PPPD-45	Japan	64.9/66	<3 ≥3	a, b, c, d, e
*De Jong et al[17]	2011	Prospective	53	1697/1697	PD-502 PPPD-1138 TP-57	USA	NA/67	≤2 >2	c, e
Chiang et al[34]	2012	Retrospective	62	206/230	PD	Taiwan	62.1/NA	<3 >3	a, b, d
*Rohan et al[33]	2013	Retrospective	81	32/43	DP	Taiwan	63.8/64.41	≤4 >4	a, b, d, e
Total			58	4781/6230	6045		63.39/65		

n- sample size undergoing intervention N- tumor size recorded sample size PD- Pancreaticoduodenectomy; DP- Distal pancreatectomy; TP- Total pancreatectomy; PP- Partial pancreatectomy; PPPD- Pylorus preserving pancreaticoduodenectomy X- mean age Y- median age a- 1-year survival; b- 3-year survival; c- 5-year survival; d- median survival; e- hazard ratio with 95% CI, (*)- Studies used for meta-analysis.

tumors, bile duct tumors and other ampullary carcinomas from the pancreatic adenocarcinoma were also excluded.

Data extraction

Two investigators (A.S. and A.B.) independently reviewed all the titles, abstracts, and manuscripts identified to determine if each study was eligible for inclusion in the study. Disagreement about eligibility were resolved by consensus with a third reviewer (L.F.Y.). All data were extracted using a standardized data extraction form. Relevant data were carefully extracted from each included studies which are as listed: first author, publication year, country, study design, sample size, intervention type, sex, age, recorded tumor size and comparable outcomes. Outcomes that were used to compare were median survival rate, 1-year survival rate, 3-year survival rate, 5-year survival rate and hazard ratio (HR) with its 95% CI.

The assessment of quality of all included studies for meta-analysis was performed based on the Newcastle-Ottawa

scale by determining the selection of participants, the comparability and the outcome (Table 2).[45]

Statistical analysis

In systematic review, qualitative data assessing 3-year and 5-year survival ratio and tumor size with 3 cm cut-off were analyzed using chi square test. Furthermore, meta-analysis was performed using Review manager 5.3 software (Cochrane Library) for all statistical analysis. P value ≤ 0.05 was considered statistically significant for all statistical analyses. Hazard ratio (HR) was considered as effect estimates and along with its corresponding 95% CI was used to perform meta-analysis. Heterogeneity among studies was examined by I^2 statistics. If chi-square test shows there is no significance of heterogeneity among the included studies (p>0.10), then fixed model was applied to calculate HR and its 95% CI. In contrary, if there is significant heterogeneity among the included studies (p≤0.10), then random effects model as described by DerSimonian and Laird was performed to calculate the HR and its respective 95% CI.

Publication bias was assessed using the visual inspection of funnel plots, the Begg's rank correlation method and the Eggar weighted regression method (P<0.05 was considered statistically significant publication bias). Fill and trim method were used if a publication bias existed.

RESULTS

The eighteen eligible manuscripts identified a total of 6230 patients in which pancreatic resection was performed for pancreatic adenocarcinoma with 4781 patients with recorded tumor size. These 4781 constitute the principal study population in this study. Included studies were mainly conducted in USA (6), Japan (3), Italy (2), Taiwan (2), UK (1), Poland (1), Germany (1), China (1) and Korea (1). Out of which thirteen retrospective and five prospective studies were included. The mean age in the 9 studies providing data on age was 63.3 years and the median age in the 15 studies providing data on age was 65 years. The median male % (M %) of the total study was 58 %. Table 1 shows the baseline characteristics of the final included studies. Finally, the quality assessment of the included studies for meta-analysis were done and shown in Table 2.

SECTION 1

Systematic review

Operation, intra-operative and post-operative data

Information on operative procedure was available for 6045 patients. Pancreaticoduodenectomy was carried out in 3504 (57.96%) with pylorus preserving pancreaticoduodenectomy in 1907 (31.54%) followed by total pancreatectomy in 278 (4.60%), distal pancreatectomy in 251 (4.15%), and partial pancreatectomy in 45 (0.74%). Appleby operation with other vessel resection was performed in 60 patients (0.99%). The median operating time for patient undergoing pancreatic resection for pancreatic adenocarcinoma was 6.3 hours as per 8 studies providing these data comprising of 4906 patients.[4,17-19,34-36,44] Peri-operative mortality or mortality within 30 days of the date of operation was found to be 2.12% (N=117) in 13 studies providing this data with total of 5512 patients.[4, 16-19, 33-36, 41-44]

Tumor size and survival

Comparison of median survival with different tumor sizes is being graphically showed in Figure 2.

Table 2: Assessment of quality of all included studies for meta-analysis

Studies	Selection		Comparability	Outcome	
	Were characteristics of subjects clearly described	Were subjects representative of the entire population	Was the study controlled for confounders adequate	Was the ascertainment of the outcome clearly described	Was the follow up long enough
Sohn 2000	Yes	Yes	Yes	Yes	Yes
Magistrelli 2000	Yes	Yes	Yes	Yes	Yes
Benassai 2000	Yes	Yes	Yes	Yes	Yes
Kedra 2001	Yes	Yes	Yes	Yes	Yes
Takai 2003	Yes	Yes	Yes	Yes	Yes
Lim 2003	Yes	Yes	Yes	Yes	No
Han 2006	Yes	Yes	Yes	Yes	Yes
Pawlik 2007	Yes	Yes	Yes	Yes	Yes
Li 2008	Yes	Yes	Yes	Yes	Yes
Ueda 2009	Yes	Yes	Yes	Yes	Yes
De Jong 2011	Yes	Yes	Yes	Yes	Yes
Rohan 2013	Yes	Yes	Yes	Yes	Yes

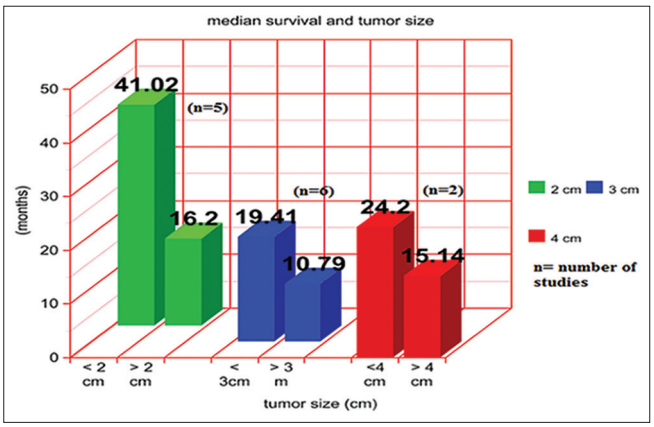

Figure 2: comparison of median survival month with (a) respective tumor size; (b) respective lymph node status, tumor grade and tumor resection margin.

Survival outcome <2 cm vs. >2 cm

6 studies[15,16,38-40,43] compared survival outcome between tumor size <2 cm and >2 cm. Out of which 5 studies[15,16,38-40] including 644 patients provided data on median survival. Median survival of 41.02 months was seen in tumor size <2 cm whereas, tumors >2 cm had median survival of 16.20 months. 3 studies[15,40,43] including 529 patients compared data on 1-year and 3-year survival rate. 1-year and 3-year survival rate of 79.36% and 49.38% was seen with tumor <2 cm respectively whereas, 1-year and 3-year survival rate of 56.40% and 24.89% was seen with tumors >2 cm respectively. Finally, 2 studies[15,43] including 220 patients provided data on 5-year survival rates. Tumors <2cm had 5-year survival rate of 41.68% whereas, tumors >2 cm had a low survival rate of 12.10%.

Survival outcome <3 cm vs. >3 cm

Seven studies[18,19,34-36,41,42] compared survival outcome between tumor size <3 cm and >3 cm. 6 studies[18,19,34,36,41,42] including 1208 patients provided data on median survival. Tumors <3 cm had a median survival of 19.41 months whereas, tumors >3 cm had a median survival of 10.79 months. Similarly, 4 studies[19,34,36,41] with a total of 1024 patients tallied data of 1-year survival rates. One year survival rate of 61.80% and 45.69% was seen with tumor size <3 cm and >3 cm respectively. Likewise, 4 studies[34-36,41] including 504 patients compared data of 3-year survival rates. Three year survival rate of 25.6% and 14.36% was seen with tumor size <3 cm and >3 cm respectively and the result being statistically significant (P<0.01) (Table 3). Finally, a total of 5 studies[18,19,35,36,41] with 958 patients provided data on 5-year survival rates. 5-year survival rate of 23.72% and 9.70% was seen with tumor size <3 cm and >3 cm respectively and the result being statistically significant (P<0.001) (Table 3).

Survival outcome <4 cm vs. >4 cm

Table 3: Studies showing 3-year/5-year survival rate and 3 cm tumor size cut-off

Studies	3-year Survival ratio (n/N)		P value
	< 3 cm	>3 cm	
Chiang et al	11/90	17/116	NS (P=0.613)
Ueda et al	19/49	9/86	P<0.001 (P=0.000)
Magistrelli et al	12/42	7/31	NS (P=0.564)
Takai et al	12/33	8/57	P<0.05 (P=0.014)
Total	54/214	41/290	P<0.01 (P=0.002)

Studies	5-year Survival ratio (n/N)		P value
	< 3 cm	>3 cm	
Benassai et al	11/33	3/34	P<0.05 (P=0.014)
Ueda et al	13/49	4/86	P<0.001 (P=0.000)
Sohn et al	59/268	39/325	P<0.01 (P=0.001)
Magistrelli et al	9/42	2/31	NS (P=0.021)
Takai et al	9/33	4/57	P<0.05 (P=0.021)
Total	101/425	52/533	P<0.001 (P=0.000)

n= total number of 5-year survivors
N= total number of patients
NS= not significant

Only 2 studies[33,37] compared survival outcome between tumor size <4 cm and >4 cm. These 2 studies comprising 120 patients provided data on median survival, 1-, and 3-year survival rates. Tumors <4 cm had a median survival of 24.2 months and tumors >4 cm had a median survival of 15.14 months. As per these 2 studies, 1- and 3-year survival rates of 81.50% and 40.90% was seen with tumor size <4 cm respectively. In contrast, 1- and 3-year survival of 63.77% and 21.74% was seen with tumor size >4cm respectively.

SECTION 2

Meta-analysis

Publication bias

The funnel plot of studies included in tumor size with 2 cm cut-off seemed symmetrical, and no significant evidence of publication bias was seen as indicated by Begg's test and Egger's test (Begg's Test P=0.086; Egger's Test P=0.057). However, for the studies included in the tumor size with 3 cm cut-off, significant publication bias was seen (Begg's Test P=0.024; Egger's Test P=0.013). The funnel plot showed asymmetry, so trim and fill method was used and the modified funnel plot after adding negative artificial data showed no asymmetry. The pooled result after the meta-trim method was summary HR= 1.352 with 95% CI of [0.860 -2.126].

Tumor size and survival outcome

2 cm cut-off point and survival outcome

The effect estimates along with its 95% CI of original studies were extracted and standard errors (SE) for

respective effect estimates were calculated for the meta-analysis. 5 studies[16, 17, 40, 43, 44] which provided the effect estimate assessing the tumor size with 2 cm cut-off point. The combined HR of the tumor size with 2 cm cut-off was 1.43 with 95% CI of [1.27-1.62], I^2= 17%, p<0.00001 and the result was statistically significant. As no heterogeneity among studies was seen (p=0.31), fixed effect was used. (Figure 3 a)

3 cm cut-off point and survival outcome

Similarly, 6 studies[18, 19, 35, 36, 41, 42] were reported to provide data on effect estimate assessing tumor size with 3 cm cut-off. The combined HR of the tumor size with 3 cm cut-off was 1.35 with 95% CI of [0.86-2.13], I^2= 85%, p=0.19 (p-value not significant). Random effect was applied, as heterogeneity among studies was seen (p<0.00001). (Figure 3 b)

4 cm cut-off point and survival outcome

Only one study[33] compared survival with tumor size cut-off point 4 cm. The tumor size more than 4 cm has HR of 2.96 with 95% CI of [1.28-6.82], p=0.01. As only one study was included, heterogeneity couldnot be calculated. (Figure 3 c)

Heterogeneity

Tumor size cut-off 2 cm had no heterogeneity among studies (I^2= 17%, p=0.31). However, for tumor size cut-off 3 cm, moderate heterogeneity existed among studies (I^2= 85%, p<0.00001). Therefore, a sensitivity analysis was done by omitting 1 study at a time and the pooled HR was calculated for the remaining studies to identify the potential source of heterogeneity between studies. Sensitivity analysis by omitting Sohn 2000[19], heterogeneity was partly attenuated with summary HR of 1.56 with a 95% CI of [1.00-2.45], I^2= 75%, p=0.003 but publication bias was still present.

Stratified analysis was also done to identify the potential sources of heterogeneity that existed among studies. Heterogeneity was completely eliminated when studies were stratified accordingly as studies conducted in Asia (I^2=0%, p=0.67), studies with no peri-operative mortality (I^2=0%, p=0.64) and studies conducted after the year 2000 (I^2=0%, p=0.67).

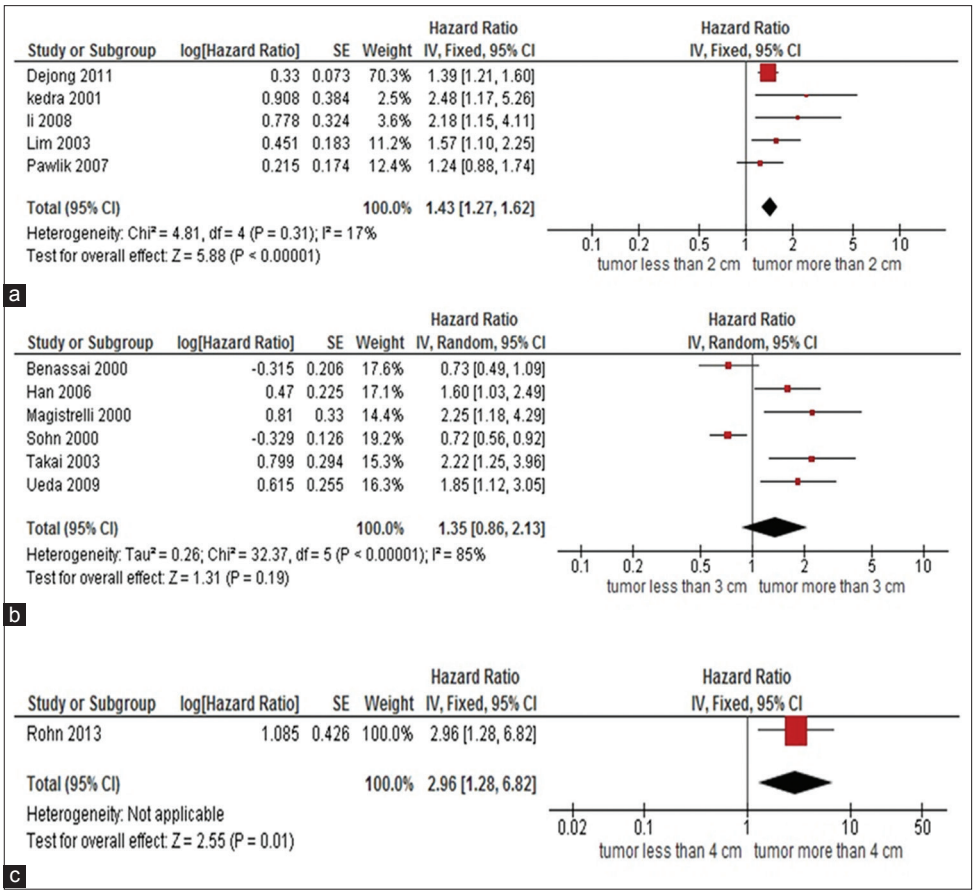

Figure 3: Meta-analysis of survival outcome and tumor size cut-off. Effect estimate (hazard ratio; 95% CI). Pooled HR is shown as diamond that spans the 95% CI. (a) Forest plot showing effect estimates of each study and the pooled hazard ratio comparing the 2 cm tumor size cut-off point. (b) Forest plot showing effect estimates of each study and the pooled hazard ratio comparing the 3 cm tumor size cut-off point. (c) Forest plot showing effect estimates of each study and the pooled hazard ratio comparing the 4 cm tumor size cut-off point.

DISCUSSION

American Joint Committee on Cancer (AJCC) staging system have been validated to predict the outcome of pancreatic cancer after pancreatic resection.[46] However, AJCC tumor (T) staging is not relatively comprehensive as it is solely differentiated by tumor size with 2 cm cut-off. Tumor size with 3cm and 4 cm cut-offs are not specified in the staging and thus causing conflicts about selection of the tumor size cut-off in defining the tumor stage.[17,47,48] Thus, many studies suggest that 2 cm as cut-off point is not relatively comprehensive and warrants further researches on re-defining or suggesting multiple cut-off points i: e 2 cm, 3cm or 4 cm in order to provide a more comprehensive guideline which accurately explains which tumor stage does tumors with 3 cm and 4 cm belong to and to plan treatment protocol in order to predict the survival outcome following surgery.[17,48-50] Tumor size is undoubtedly an important prognosticator for pancreatic tumor following pancreatic resection.[14,49] However, the topic of debate is in choosing the right cut-off point for tumor diameter and many studies have already assessed and the most reported size cut-offs ranged from 2cm to 3 cm.[10,17,51-54] In our present study, the greatest impact of tumor size was seen on tumors below and above 2 cm with median survival of 41.02 months vs. 16.20 months respectively. However, for the larger tumor size the results is found to be less appealing, may be due to lesser number of studies and trials as in the present study we were able to include only 2 studies reporting survival outcome of tumors less or more than 4 cm.[33,37]

Various published reports supported the fact that smaller tumors have comparatively better survival outcome than larger tumors and the cut-off points ranged from 2cm to 3cm.[17, 49, 51-53] Yeo et al.[9] reported a 5-year survival of 28% for tumor size less than 3 cm and 15% for tumor size more than 3 cm. Similarly, Petermann et al[14] reported a median survival of 40.8 months and 15.6 months for tumors less than 2 cm and more than 2 cm respectively, which was very similar to our result. Our systematic review analysis of tumor size and survival outcome, tumor size less than 2 cm had a median survival, 1-, 3-, and 5-year survival of 41.02 months, 79.36%, 49.38% and41.68% respectively. In contrast, tumor size more than 2 cm had a median survival, 1-, 3-, and 5-year survival of 16.20 months, 56.4%, 24.89% and 12.10% respectively. Similarly, tumor size less than 3cm had a median survival, 1-, 3-, and 5-year survival of 19.41 months, 61.8%, 25.6%, and 23.72% respectively. Whereas, tumor size more than 3 cm had a median survival, 1-, 3-, and 5-year survival of 10.79 months, 45.69%, 14.36% and 9.70% respectively. The 3-year and 5-year survival rate difference between tumor size < 3 cm and > 3 cm was statistically significant. Similar to our result, many studies[9, 26, 55, 56] reported that survival time have statistical significance with 3 cm cut-off, which indicate the 3 cm cut-off maybe become another new potential tumor size cut-off in the new T stage of pancreatic cancer in addition to the current sole 2 cm cut-off point defining tumor stage proposed by AJCC.

Subsequently, our meta-analysis showed that the combined HR of the tumor size with 2 cm cut-off was 1.43 with 95% CI of [1.27-1.62], I^2= 17%, and the result being statistically significant (p<0.00001). Similarly, the combined HR of the tumor size with 3 cm cut-off was 1.35 with 95% CI of [0.86-2.13], I^2= 85%, p=0.19. The combined pooled HR of tumor size with 3 cm cut-off did suggest that tumor size more than 3 cm have bad prognosis in comparison to tumor size less than 3 cm but the final result was not statistically significant and the study had moderate amount of heterogeneity. Stratified analysis was done to find the source of heterogeneity. Studies when stratified accordingly as studies conducted in Asia, studies with no peri-operative mortality and studies conducted after the year 2000 AD, all demonstrated statistically significant result with completely attenuated heterogeneity. Although the variables used for sub-group analysis have least clinical significance, but the result demonstrated were statistically significant. Therefore, concluding that further randomized controlled trials (RCTs) and retrospective studies with various tumor size cut-offs are required in future to obtain a clinically and statistically significant result. AJCC classification of tumor size via 2 cm cut-off point is supported by various studies[14, 23, 32, 46, 57, 58] but also debated by number of studies as the cut-off point being not relatively comprehensive.[17, 39, 47, 48] Currently, there are not adequate literatures that compares survival outcomes with respective tumor size cut-offs like 2 cm, 3 cm and 4 cm. If these sort of studies with more precise sub-division are available in the future than, the tumor stage classified by AJCC can be argued to be changed to a more feasible and effective point that can act as a pivotal reference to new AJCC staging system and thus help to decide in further planning the treatment protocol of the patient and predict survival outcome following surgery. However, for the time being, as per our study result the tumor size less than 2 cm seems to have a great impact on survival after pancreaticoduodenectomy.

Researches have reported that tumor size and prognosis are inversely proportionate.[9, 49, 50] Our study showed that patient with tumor size >2 cm had a reduced survival rate. There are many points that supports larger tumor size have negative impact on survival. Large tumors are believed to be more often associated with poor prognostic factors like micro-metastases, lymph vessel, perineural and loose connective tissue invasion due to their long term presence.[14, 17, 21] Likewise, larger tumor size was noted to

have longer operating times, more intra-operative blood loss, requirement of packed red blood cell transfusion and more importantly, larger tumor size are relatively harder to achieve microscopically negative tumor resection margin.[9, 17] Yamaguchi et al[21] reported that tumors measuring less than 2 cm were less likely to be associated with nodal metastasis and were better differentiated than larger tumors. Similarly, Petermann et al[14] reported that the risk for metastatic lymph nodes and positive resection margin was 40% and 7% respectively in the case of tumor size less than 2 cm compared with >80% and >30% for larger tumors respectively.

With tremendous development of imaging studies, it is now possible to detect smaller tumors early but the pancreatic carcinoma's long-term survival outcome in comparison to other abdominal malignancies is still far from satisfactory. This can be reasoned as many pancreatic cancer patients remain asymptomatic until late and CT or MRI findings of very small tumors are often understated and easily overlooked. [59] Thus, most of the patients are easily misdiagnosed and usually present late with the classical symptoms and larger tumor diameters. Therefore, a more practical and innovative approach towards early detection of pancreatic cancer is a necessity and may be the only approach to improve the current long term effectiveness of pancreatic carcinoma. In addition, radiological finding of early pancreatic cancer is not adequate to support for performing major surgery like PD, particularly if patient is asymptomatic. [60,61] Gangi et al[59] described the presence of pancreatic ductal dilation without any identifiable mass several months before final diagnosis of pancreatic cancer. Endoscopic ultrasound-guided FNA (EUS-FNA) is believed to provide cytological diagnosis with specificity of around 100%.[24,60,62] Therefore, usage of EUS-FNA whenever necessary can achieve early diagnosis and can act as a sound basis for prompt treatment and definitive management of pancreatic cancer, including PD. Other factor that is regarded highly in terms of survival outcome is tumor resection margin. [9,18] Larger tumors are relatively harder to achieve R0 resection. Preoperative use of neo-adjuvant therapy is being increasingly common. Mainly because neo-adjuvant therapy is believed to be able to downstage locally advanced tumors and achieve an enhanced resection rate.[63, 64] However studies do not support or advocate routine use of preoperative neo-adjuvant therapy for pancreatic cancer. [24]

Limitations

Present studies certainly have some limitation. First the tumor sizes provided by various studies have not stated if the tumor size is the post-operative pathological assessment or the pre-operative imaging assessment. However, the main purpose of the present study was to evaluate the impact of tumor size as predicted by AJCC. Another limitation of this study was the inclusion of pancreatic body or tail carcinoma due to limited number of studies performed exclusively on pancreatic adenocarcinoma of the head and uncinate process. However, the current study has solely included pancreatic adenocarcinoma only excluding all other neuroendocrine tumors and other pancreatic malignancies which have higher survival rates although with larger tumor diameters.

CONCLUSION

Surgical resection is the only possibility for chance of curative treatment available for pancreatic cancers. Improvement in imaging studies, surgical techniques as well as better understanding of its pathogenesis, availability of molecular markers and ability to perform biopsy of suspicious lesion with EUS-FNA safely all help to succeed in better and early diagnosis of the disease with better survival outcome.

Our study suggest tumor size less than 2 cm have significant impact on survival outcome and cancers with smaller tumor diameter is highly likely to be associated with negative lymph node metastasis and negative tumor resection margin. However, the 2 cm cut-off as suggested by AJCC is not relatively comprehensive and is thus debatable. Although our result supports the AJCC staging of pancreatic carcinoma, further evidence based trials, and further more studies discussing tumor with 3 cm and 4 cm cut-offs are required to provide the basis for formation of a comprehensive guideline which can settle the ongoing disputes regarding tumor staging suggested by AJCC and also to confirm that tumor size selection is one of the important prognostic factor that influence survival following pancreatic resection. Furthermore, the 3 cm cut-off maybe become another new potential tumor size cut-off point in new T stage of pancreatic cancer in addition to the current sole 2 cm cut-off point defining tumor stage.

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