

Longitudinal quality of life data can provide insights on the impact of adjuvant treatment for pancreatic cancer—Subset analysis of the ESPAC-1 data

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The European Study Group for Pancreatic Cancer (ESPAC-1) study is the largest study of adjuvant treatment for pancreatic ductal adenocarcinoma to date and confirmed a survival advantage for adjuvant chemotherapy but not for chemoradiation. The importance of parallel evaluation of survival and quality of life (QoL) has been recognized as fundamental and the aim was to assess QoL and quality adjusted survival. A longitudinal QoL study on a subset of ESPAC-1 patients who prospectively completed the EORTC QLQ C-30 questionnaire during treatment and follow-up. An integrated quality-survival product method was used to adjust any treatment effect on survival by a function of measured QoL, calculated over a restricted 24-month-period (QALM-24). Three hundred and sixteen patients completed 1,201 questionnaires. There were no differences between treatment groups in dimension scores at baseline (randomization). For the chemotherapy group, the mean Quality Adjusted Life Months over 24 months (QALM-24) was 9.6 (95% CI: 8.7, 11.2) months compared with the mean QALM-24 of 8.6 (95% CI: 7.6, 10.5) months for the no chemotherapy group. For the chemoradiation group, the mean QALM-24 was 7.1 (95% CI: 6.0, 9.0) months compared with the mean QALM-24 of 8.1 (95% CI: 7.0, 10.0) months for the no chemoradiation group. The previously reported survival advantage supporting the use of adjuvant chemotherapy is maintained when adjusted using quality adjusted survival methodology. Chemotherapy provided on average an additional 1.0 quality-adjusted life months within a restricted 2-year time period from the time of resection.

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The results of the first trial of the European Study Group for Pancreatic Cancer (ESPAC-1) revealed a survival advantage for adjuvant chemotherapy but not chemoradiation and have been reported in detail elsewhere.^{1–3} The optimal chemotherapy regimen for use as adjuvant treatment is the subject of ongoing ESPAC studies. Although survival remains the primary outcome measure, there is increasing recognition that quality of life (QoL) assessment should receive higher priority⁴ in assessing the efficacy of treatment. This is particularly true in the treatment of tumors where recurrence is common or median survival is short; any survival advantage requires to be balanced against the potential effects of chemotherapy or chemotherapy associated toxicity on QoL.

Although QoL assessments have been employed successfully in descriptive and evaluative studies in surgical oncology, their use in cancer clinical trials has been compromised by the lack of sensitivity and disease specificity of generic health-related QoL models. At the time of study design, the European Organization for Research and Treatment of Cancer (EORTC) QoL questionnaire (EORTC QLQ-C30) was the most widely used and validated cancer specific instrument.

QoL assessments provide valuable dynamic endpoints, recording patient reported symptoms scoring and functional health, which may change over time, with alterations in treatment, disease progression or death. Previous longitudinal studies addressing QoL issues in patients with upper gastrointestinal cancer have encountered difficulties with accrual and fallout, leaving data incomplete.⁵ This may be addressed in part by providing a nurse led QoL service,⁶ but this may compromise data independence and may in itself influence the conception of received care.⁷

Standard longitudinal analysis for assessment of QoL often assumes that incomplete data points are missing at random. Clearly, in studies where death within the study time frame is a common occurrence, this assumption is invalid because data may be missing either due to death or illness. Within the current cohort, more than half of the patients died within the study period and any longitudinal analysis should account for dropout due to death as well as censored QoL estimates. As a result, we have utilized an integrated product of the survival and QoL functions,⁸ which is expressed as a Quality Adjusted Life Months (QALM-24). Either a measured reduction on QoL score or death within the study period would reduce the calculated QALM-24 product from a maximal score of 24. This methodology is described in detail elsewhere.⁸ The aim of this study was to report the longitudinal QoL data accrued using the EORTC QLQ-C30 core cancer module during the ESPAC-1 trial and the simultaneous assessment of QoL and survival. The primary objective was to compare QoL domain scores and quality adjusted survival in patients receiving adjuvant chemotherapy or chemoradiation with patients who did not.

Material and methods

The ESPAC-1 trial (Fig. 1) recruited a total of 550 patients (recruitment period: February 1994–April 2000).^{1–3} A total of 289 patients were recruited in the main factorial 2 × 2 design, the most efficient design for the study of 2 treatments, randomly assigning adjuvant chemo radiation (20 Gy in 10 daily fractions over 2 weeks with 500 mg/m² 5-Fluorouracil bolus on days 1–3,

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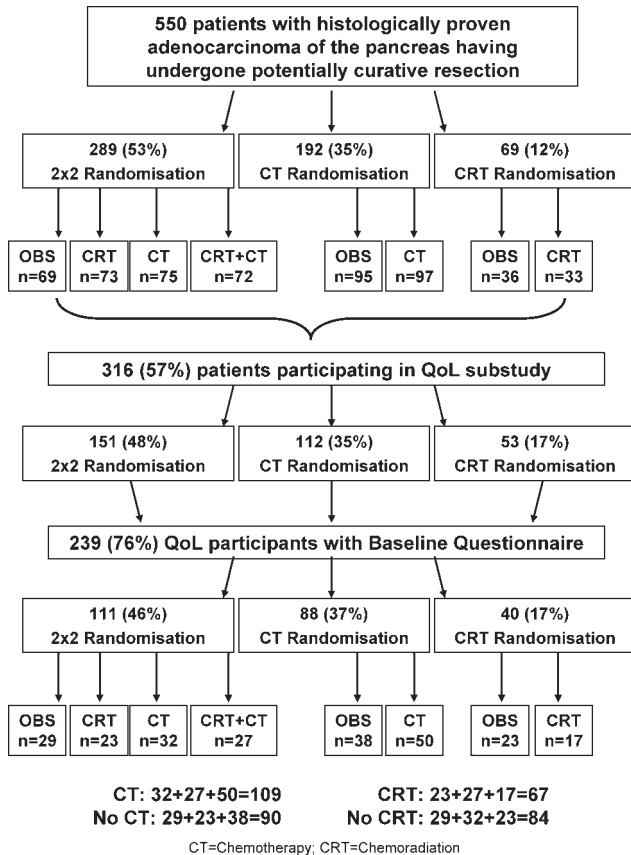


FIGURE 1 – QoL sub-study design.

repeated after 2 weeks) or adjuvant chemotherapy (bolus 5-Fluorouracil, 425 mg/m² days 1–5 with folinic acid, 20 mg/m², monthly for 6 months) to patients resulting in 4 randomization groups.² In addition, 261 patients were randomized for only one of the adjuvant treatments rather than both (192 chemotherapy *vs.* no chemotherapy, 69 chemoradiation *vs.* no chemoradiation) to provide supportive evidence. All the ESPAC-1 patients were requested to participate in the QoL sub-study but due to resource limitations, data capture was not universal.

Protocol violators were included in all analyses in their randomized treatment group on an intention-to-treat basis. Toxicity was assessed using the Common Toxicity Criteria⁹ with a clearly defined protocol for modifications and delays. The study required each centre to treat patients according to the radiotherapy quality assurance standards of that centre.

Quality of life assessment

The EORTC QLQ-C30¹⁰ is a validated questionnaire consisting of 30 questions, assessing 5 functional scales (physical, role, emotional, cognitive and social), 3 symptom scales (nausea and vomiting, fatigue and pain), 1 global health scale and 6 individual symptom items (dyspnea, insomnia, appetite loss, constipation, diarrhea and financial). EORTC QLQ-C30 forms were requested after surgery but before randomization (baseline) and at 3-month intervals thereafter. Symptom assessment at follow-up and QoL assessments were requested at identical times across the different treatment groups.

QoL scores were calculated according to the EORTC QLQ-C30 scoring manual.¹¹ The average of the items included in each scale was linearly transformed to produce a standardized score ranging from 0–100. The primary comparison was across treatment groups, as for the analysis of efficacy: (i) chemotherapy *versus* no chemotherapy and (ii) chemoradiation *versus* no chemoradiation.

Higher scores for the functional and global health scales indicated better QoL whereas higher scores for the symptom scales and items indicated poorer QoL.

Statistical considerations

The mean changes from baseline scores for all domains were calculated with confidence intervals over 24 months follow-up and compared using the Mann Whitney non-parametric test. This analysis however assesses specific time points individually and does not look at the time period as a whole and as such it introduces multiple testing. Standardized area under the curve (SAUC) methodology¹² was used to assess mean observed symptomatic and functional QoL over a clinically relevant symptomatic period of 12 months from baseline while minimising multiple testing. Linear interpolation was used to interpolate QoL scores throughout the 12-month period, with an area under the curve calculated on a per patient basis. Although SAUC analysis allows for analysis of a time period, it does not account for drop out because of death and as such SAUC analysis was most appropriate to explore symptomatic and functional QoL conditional on patients surviving to specific time points. SAUC analysis provided an average symptomatic or functional score per month, which was compared across treatments using the Mann Whitney non-parametric test.

The data may be affected if (i) the number and time of symptom assessments are different across patient groups, (ii) if there are different numbers of missing forms or missing items on forms across patients groups of (iii) the rates of death/progression occurring are different across patient groups. To account for drop out due to death and censored QoL estimates (due to patients remaining alive), quality adjusted survival methods were used as an alternative method for analysis of repeated QoL measures accounting for survival estimates.

Survival was calculated from the date of resection until the date of death from any cause or censored at the date last seen alive. Survival estimates were derived using the standard method of Kaplan and Meier and the log-rank test was used to assess differences between survival estimates of different groups. Quality adjusted survival analysis using the integrated quality-survival product method⁸ was used to directly combine longitudinal global QoL scores with survival data at a group level to deal with censored data appropriately. This analysis was most appropriate to explore global QoL. The integrated quality-survival product is the product of the survival and global QoL functions over a specific period of time. The primary comparison of survival in the main ESPAC trial was at 2-year follow-up and as such QALM in the 24 months following resection was clinically relevant, calculated as:

$$QALM(L) = \int_0^L Q(t)S(t)dt$$

where $L = 24$ months, $S(t)$ is the proportion of patients that survive to time t and $Q(t)$ is the global QoL of those survivors creating a quality adjusted survival estimate.

Linear interpolation was used to calculate global scores at the time of resection and at each specific death time within 24 months on per patient basis. The QoL function was derived by calculating the mean global QoL of survivors at a group level and connecting estimates at each death time using a step function, as with survival estimates, assuming the mean QoL remained constant between each specific death time:

$$\hat{Q}(t_j) = 1/n_j \sum_{i=1}^{n_j} q_i(t_j)$$

where $q_i(t_j)$ is the estimate of global QoL at time t_j calculated as the mean of all alive uncensored patients at time t_j using the actual timing of each individual patient QoL assessment.

The area under this curve up to 24 months gave the mean QALM for the group within 2 years of resection. As reference, a patient group with 100% survival and 100% QoL would yield a

QALM-24 score of 24 months. This QALM-24 score is downsized due to deaths and further downsized due to reduced QoL. The standard error and subsequent confidence interval for the mean QALM (*L*) for each treatment group was estimated using 500 bootstrap samples.¹³

Data manipulation and analysis was programmed using SAS and SAS macros (SAS and Marlow, UK). Two-sided *p*-values < 0.01 were considered to be statistically significant due to multiple testing.

TABLE I – PATIENT CHARACTERISTICS

	Main study		QoL study	
	N (550)	% (100%)	N (316)	% (100%)
Randomisation option				
2 × 2	289	53	151	48
RT only	69	12	53	17
CT only	192	35	112	35
Sex				
Male	327	59	184	58
Female	223	41	132	42
Age (years)				
Median	60		60	
IQR	53–67		54–67	
CT group				
CT	244	51	137	52
No CT	237	49	126	48
CRT group				
CRT	178	50	90	44
No CRT	180	50	114	56
Resection margins				
Negative	439	80	255	81
Positive	111	20	61	19
Tumor grade				
Well differentiated	110	21	62	20
Moderately differentiated	300	59	197	63
Poorly differentiated	102	20	53	17
Nodal status				
Negative	246	47	154	49
Positive	277	53	159	51
Max tumor Size (cm)				
<i>n</i>	497		299	
Median	3.0		3.0	
IQR	2.5–4.0		2.2–4.0	
Survival status				
Alive	115	21	59	19
Dead	435	79	257	81
Survival estimates				
Median survival (95% CI)	16.6 (15.4, 17.8)		17.7 (15.9, 20.7)	
12 and 24 months survival	65 and 35%		68 and 38%	

IQR, inter-quartile range.

Findings

A total of 1,201 questionnaires were completed by 316 (57%) of all 550 ESPAC-1 patients: 263 patients in the chemotherapy comparison (137 chemotherapy, 126 no chemotherapy) and 204 patients in the chemoradiation comparison (90 chemoradiation, 114 no chemoradiation) (Table I). The QoL subgroup of patients was representative of the main study group (Table I) with balanced treatment allocation across clinical and tumor characteristic groups. At each time point, incomplete data capture resulted from either death within the study period or non-returned forms (Fig. 2) including 77 (24%) patients failed to complete baseline forms and were not included in the statistical analysis. There were more patients with missing baseline forms in the group randomized to no chemotherapy [36 (29%) vs. 28 (20%)] and equal proportions in the chemoradiation and no chemoradiation groups [23 (26%) vs. 30 (26%)]. Further analyses are planned based on the multiple imputations of the missing baseline scores.

Quality of life in patients receiving adjuvant chemotherapy versus no chemotherapy

In the 90 patients randomized to no chemotherapy, there was a gradual improvement in physical, role and social functioning from baseline although not significantly so over all time points. Physical function was different at 12 months (*p* = 0.013), role function at 3 and 12 months (*p* = 0.006 and *p* = 0.003, respectively) and social function at 12 months (*p* = 0.004). The 109 patients randomized to receive chemotherapy maintained similar physical, role and social functioning from baseline. There were no significant differences between chemotherapy groups using SAUC analysis in the mean observed symptomatic and functional QoL scores within the 12 month duration from baseline (Table II).

Figure 3 shows the changes in global QoL scores from baseline by treatment group. Both groups in the chemotherapy comparison (Fig. 3a) appear to experience increased global QoL from baseline to 6 months, then the chemotherapy group appears to have lower

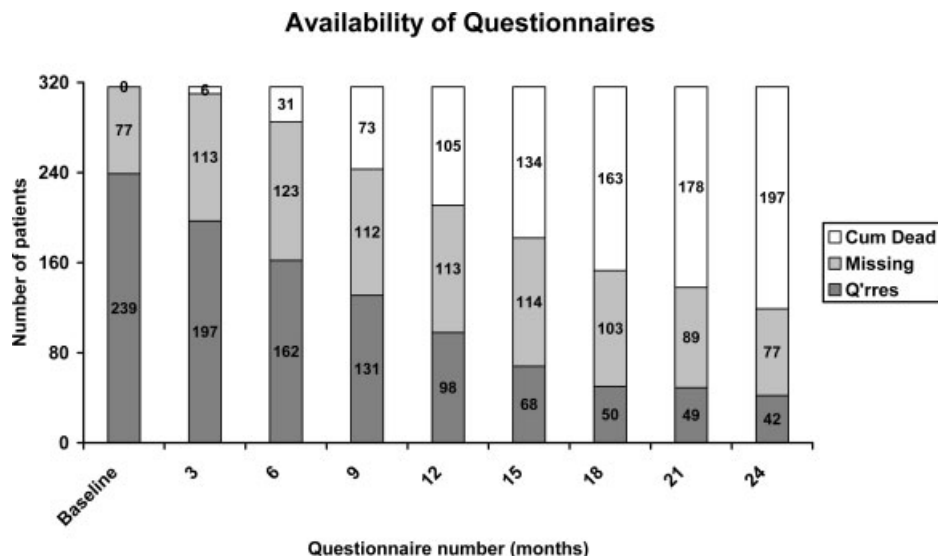


FIGURE 2 – Availability of clinical data and questionnaires.

TABLE II – STANDARDIZED AREA UNDER THE CURVE ANALYSIS OF THE MEAN OBSERVED SYMPTOMATIC AND FUNCTIONAL QUALITY OF LIFE SCORES

	Chemotherapy (CT) comparison Mean SAUC12 (SD)			Chemoradiation (CRT) comparison Mean SAUC12 (SD)		
	No CT	CT	Z, p-value	No CRT	CRT	Z, p-value
Physical function	68.3 (18.5)	69.9 (21.3)	-0.62, 0.53	67.7 (22.2)	69.5 (19.6)	-0.42, 0.67
Role function	65.8 (26.5)	60.5 (32.2)	0.78, 0.44	61.8 (30.8)	61.6 (29.5)	-0.14, 0.89
Emotional function	73.0 (18.5)	70.5 (20.3)	0.71, 0.48	71.4 (16.1)	71.4 (20.3)	-0.51, 0.61
Cognitive function	83.4 (16.3)	82.9 (15.6)	0.24, 0.81	83.0 (16.1)	83.2 (15.9)	0.01, 0.99
Social function	73.9 (19.8)	70.6 (24.2)	0.53, 0.60	73.0 (22.3)	70.2 (24.7)	0.54, 0.59
Fatigue	33.6 (20.2)	33.8 (19.9)	-0.16, 0.88	33.0 (19.3)	37.7 (21.4)	-1.21, 0.22
Nausea and vomiting	8.7 (11.8)	8.4 (10.1)	-0.40, 0.69	9.8 (11.4)	8.9 (9.7)	0.10, 0.92
Pain	20.8 (19.2)	20.5 (20.5)	0.44, 0.66	19.6 (19.1)	25.3 (21.3)	-1.65, 0.098
Dyspnea	13.1 (17.3)	9.1 (13.2)	1.10, 0.27	11.0 (16.5)	13.0 (16.8)	-0.99, 0.32
Sleep	24.5 (22.8)	24.2 (22.4)	0.01, 0.99	23.3 (21.2)	21.6 (20.7)	0.42, 0.67
Appetite	22.4 (21.1)	21.1 (20.0)	0.07, 0.94	23.1 (21.7)	20.1 (20.0)	0.52, 0.60
Constipation	6.9 (12.2)	8.1 (14.2)	-1.01, 0.31	7.4 (13.5)	10.6 (17.8)	-0.72, 0.47
Diarrhea	13.2 (16.7)	13.8 (17.3)	0.03, 0.97	12.2 (15.2)	18.1 (19.7)	-1.71, 0.087
Financial	15.1 (22.4)	12.3 (19.1)	0.49, 0.63	10.4 (18.9)	15.7 (21.7)	-1.32, 0.19

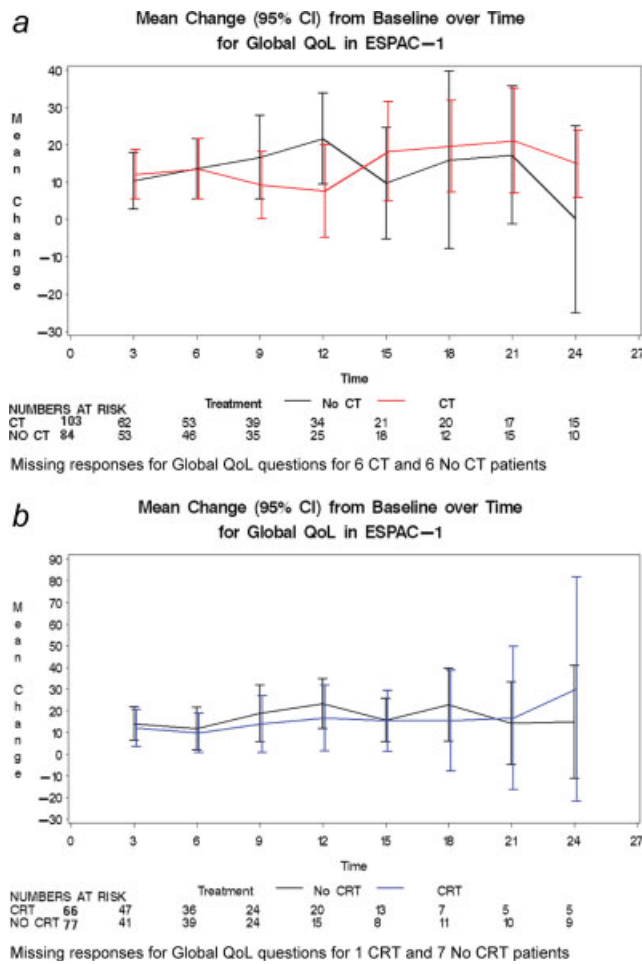


FIGURE 3 – Mean changes for global QoL, (a) chemotherapy (CT) comparison, (b) chemoradiation (CRT) comparison.

QoL (not significantly) from 6 to 12 months and then the groups again merge together. The simultaneous assessment of longitudinal global QoL scores and survival estimates is calculated as a quality-survival function $[QS(t)]$ by chemotherapy versus no chemotherapy (Fig. 4a) within the QoL subgroup of ESPAC patients. The mean life months within 24 months of resection (LM-24) excludes consideration of QoL and is estimated as 17.3

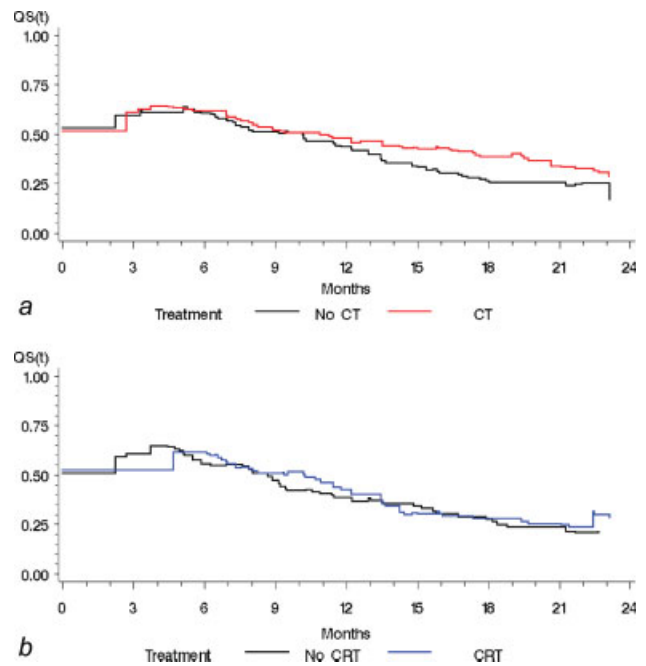


FIGURE 4 – Quality-survival product by (a) chemotherapy (CT) comparison, (b) chemoradiation (CRT) comparison.

(95% CI: 15.8, 18.8) months for the chemotherapy group, which reduced to a mean QALM within 24 months of resection (QALM-24) of 9.6 (95% CI: 8.7, 11.2) months when adjusted by global QoL scores (Table III, Fig. 4a). This compared with a mean LM-24 of 14.9 (95% CI: 13.4, 16.5) months and mean QALM-24 of 8.6 (95% CI: 7.6, 10.5) months for the no chemotherapy group. Chemotherapy provided this subgroup of patients on an average with an extra 2.4 life months of which 1.0 are quality-adjusted life months within a restricted 2 year time period from the time of resection.

Quality of life in patients receiving adjuvant chemoradiation versus no chemoradiation

The 84 patients randomized to no chemoradiation revealed improved cognitive functioning from baseline at 3 months ($p = 0.012$) but then both groups appear to maintain similar cognitive functioning to baseline over the remainder of the period. No significant differences were seen in the differences in QoL scores from baseline by 67 patients randomized to the chemoradiation

TABLE III – LIFE MONTHS AND QUALITY ADJUSTED LIFE MONTHS WITHIN 24 MONTHS OF RESECTION

	Chemotherapy (CT) comparison		Chemoradiation (CRT) comparison	
	No CT	CT	No CRT	CRT
LM (24) (95% CI)	14.9 (13.4, 16.5)	17.3 (15.8, 18.8)	14.6 (12.8, 16.3)	15.5 (13.8, 17.2)
QALM (24) (95% CI)	8.6 (7.6, 10.5)	9.6 (8.7, 11.2)	8.1 (7.0, 10.0)	7.1 (6.0, 9.0)

group in other domains. There were no significant differences between chemoradiation groups using SAUC analysis in the mean observed symptomatic and functional QoL scores within the 12-month duration from baseline (Table II).

Figure 3 shows the changes in global QoL scores from baseline by treatment group. Both groups in the chemoradiation comparison (Fig. 3b) appear to experience increased global QoL from baseline to 3 months. The simultaneous assessment of longitudinal global QoL scores and survival estimates is calculated as a quality-survival function [$QS(t)$] by chemoradiation *versus* no chemoradiation (Fig. 4b). The mean life months within 24 months of resection (LM-24) excludes consideration of QoL and is estimated as 15.5 (95% CI: 13.8, 17.2) months for the chemoradiation group, which reduced to a mean QALM within 24 months of resection (QALM-24) of 7.1 (95% CI: 6.0, 9.0) months when adjusted by global QoL scores (Table III, Fig. 4b). This compared with a mean LM-24 of 14.6 (95% CI: 12.8, 16.3) months and mean QALM-24 of 8.1 (95% CI: 7.0, 10.0) months for the no chemoradiation group. Chemoradiation provided this subgroup of patients on an average with an extra 0.9 life months but provided an average reduction of 1.0 quality-adjusted life months within a restricted 2 year time period from the time of resection.

Interpretation

The ESPAC-1 trial^{1,2} (Fig. 1) and subsequent meta-analysis³ have shown no overall survival benefit for adjuvant chemoradiation but have shown a significant survival benefit for adjuvant chemotherapy, which has since become the recognized standard of care for these patients. However, this change in standard is based on the improved survival rather than a combined assessment of survival and longitudinal QoL. This primary objective of the current study was to evaluate the balance between the potentially negative effects on QoL of adjuvant therapy taken in context with the previously reported improvements in survival.

The ESPAC-1 QoL subgroup (316 patients) includes patients randomized from both the 2×2 factorial study (289 patients) and those randomized in the supportive study (261 patients). The addition of chemoradiation in the ESPAC-1 QoL subgroup conferred a marginal non-significant increase in survival (15.5 *vs.* 14.6 life months). However, correction of the crude survival figures for therapy-associated alteration in QoL, revealed this to equate to a paradoxical reduction in quality-adjusted survival (7.1 *vs.* 8.1 QALM's) in those patients receiving it, highlighting the difficulty of using survival alone as a primary endpoint. Within the ESPAC-1 QoL subgroup, adjuvant chemotherapy increased survival by an average of 2.4 life months over the no chemotherapy group. Although significant, it was possible that this survival advantage following adjuvant chemotherapy for pancreatic adenocarcinoma be negated if adjuvant therapy was associated with a major reduction in QoL, when assessed by a global QoL adjusted survival product. This study, therefore, adds support to the conclusion of the main ESPAC-1 2×2 factorial trial, contrary to the effect of chemoradiation, that the survival advantage associated with adjuvant chemotherapy is maintained after adjustment for global QoL supporting the adoption of chemotherapy as a standard of care.

The baseline QoL at randomization should also not be equated with normality. The trial protocol stipulated randomization of patients within 12 weeks of pancreatoduodenectomy, at a time when QoL measurements may not have returned to pre-operative scores.¹⁴ The findings of a Dutch study¹⁴ of a temporary post-surgical decrease in physical function and subsequent return to pre-operative values was similar to that described in other longitudinal

studies in oesophageal and gastric cancer,^{15,16} and have been attributed to impairments caused by surgery. A degree of spontaneous improvement over baseline could therefore be expected within the first 3 months and this has been confirmed in this study. As this affects all groups equally, this should not alter the conclusions of the integrated quality-survival analysis.

In the management of pancreatic cancer, with high recurrence rates and low long-term survival, disease free/median survival assumes greater relevance than absolute or 5-year survival. Standard comparison of the mean changes from baseline scores in interval QoL assessment for all domains leads to the introduction of multiple testing across time points and to minimise this, SAUC methodology¹² was used to assess mean observed symptomatic and functional QoL over a clinically relevant symptomatic period of 12 months from baseline. This methodology did not however account for drop out due to death or censored QoL estimates during the study period and we have therefore employed an integrated quality-survival product method⁸ allowing simultaneous comparison of global QoL and survival in terms of QALM within 24 months of resection (QALM-24).

The limitation of health related QoL assessment as a treatment outcome measure has been well recognized and the relative importance of survival has been illustrated in studies on patients with tumors originating from other primary sites. In trials of adjuvant chemotherapy in breast cancer, health related QoL (HRQoL) measurement did not influence clinical decision making and within the palliative setting HRQoL outcomes provided little information beyond that obtained from traditional medical outcomes, including toxicity.¹⁷ It is only where clinical outcomes of treatment are equal, or approach equality, that HRQoL plays a significant role in clinical decision making over traditional outcome measures.

One disadvantage of the 2×2 factorial design employed in ESPAC-1 has been the relatively small numbers within the study that were randomized to no adjuvant therapy (Observation only $n = 69$). With incomplete QoL data accrual and fallout through death, there were insufficient data points to allow comparative analysis. With adjuvant therapy becoming a standard of care, the opportunity to compare an integrated quality-survival analysis of adjuvant treatment against observation alone, within the context of a randomized trial format may not be repeated. With mature data, there will be an opportunity to combine the observation group from this study with those patients recruited to the observation only arm ($n = 60$) within ESPAC-3 trial before the observation arm was closed.

The importance of parallel evaluation of survival and QoL has been recognized as fundamental in the comparison of treatments⁴; however, subjects are usually followed longitudinally over time, during which QoL is independently assessed on a number of occasions. Quality adjusted survival analysis⁸ is the most appropriate approach for simultaneous analysis of QoL and survival data. The quality adjusted survival analysis presented in our work confirms the benefit for adjuvant chemotherapy treatment is maintained, taking into account any negative effect of chemotherapy associated morbidity on QoL and reinforces adjuvant chemotherapy as the standard of care for suitable patients following pancreatoduodenectomy.

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