**APPENDIX: The Impact of Positive Resection Margins on Survival and Recurrence Following Resection and Adjuvant Chemotherapy for Pancreatic Ductal Adenocarcinoma.**

**Specialists Contributing to the Treatment of Patients in the ESPAC-3 Trial.**

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SUPPL. Figure 1: CONSORT

**1151** Patients with histological proven Ductal

Adenocarcinoma of the Pancreas (PDAC) who had undergone ‘curative’ resection.

**ALLOCATION**

**551**

Assigned to 5FU/FA

Ineligible: n=2

Reasons:

 Liver metastasis

 Prior pulmonary malignancy

Received 5FU/FA:

n = 486 (median 6 cycles)

Didn’t receive allocated treatment:

n= 65

Reasons:

 Patient Decision (26)

 Patient ill heath (8)

 Disease Progression (6)

 Unknown (21)

 Ineligible (2)

 Death (2)

Analysed: n = 551

Excluded from analysis: n= 0

**62**

Assigned to Observation

RANDOMISED

Ineligible: n=2

Reasons:

 Previous malignant

melanoma

 Metastatic disease

Received Gemcitabine:

n = 479 (median 6 cycles)

Didn’t receive allocated treatment:

n= 59

Reasons:

 Patient Decision (30)

 Patient ill heath (5)

 Disease Progression (4)

 Unknown (17)

 Ineligible (2)

 Death (1)

Analysed: n = 538

Excluded from analysis: n= 0

**538**

Assigned to Gemcitabine

Analysed: n = 62

Excluded from analysis: n= 0

Observation arm dropped 20th June 2003

Lost to follow-up: n = 28 Reasons:

 Unknown (25)

 Patient moved (2)

 PI Retirement (1)

Discontinued trial

intervention:

n = 30

Reasons:

 Patient decision (30)

Lost to follow-up: n =5 Reasons:

 Unknown (3)

 Patient moved (2)

Discontinued trial

intervention:

n = 3

Reasons:

 Patient given Adjuvant

therapy (2)

 Patient decision (1)

Lost to follow-up: n = 24

Reasons:

 Unknown (22)

 Patient moved (1)

 PI Retirement (1)

Discontinued trial

intervention:

n = 22

Reasons:

 Patient decision (22)

**FOLLOW-UP**

**ANALYSIS**

**SUPPL. Figure 2:** a) Overall survival and b) Recurrence free survival based on a single involved margin only

**a)**

**b)**

**SUPPL. Figure 3**: a) Overall and b) recurrence free survival by R0, R1<1mm and R1-direct status for the anterior surface.

**a)**

**b)**

**SUPPL. Figure 4**: a) Overall and b) recurrence free survival by R0, R1<1mm and R1-direct status for the pancreatic transection margin.

**a)**

**b)**

**SUPPL. Figure 5**: a) Overall survival and b) Recurrence free survival by R0, R1<1mm and R1-direct status for the medial margin.

**a)**

**b)**

**~~SUPPL. Figure 6:~~** ~~Competing Risks analyses for local distant and other recurrence and death.~~

**Supplementary Tables**

**SUPPL. Table 1**: Patient demographics

|  |  |  |  |
| --- | --- | --- | --- |
| Category |  | Resection Margins | Total |
| None | Within 1mm | Direct |  |
| Total | All | 646 (56.1%) | 146 (12.7%) | 359 (31.2%) | 1151 |
| Sex | Female | 295 (46%) | 63 (43%) | 153 (43%) | 511 (44%) |
| Male | 351 (54%) | 83 (57%) | 206 (57%) | 640 (56%) |
| Age | Years (IQR) | 62 (56, 69)  | 66 (58, 70) |  62 (55, 69.5) | 63 (56, 69)  |
| Arm | 5FU/FA | 308 (48%) | 77 (53%) | 166 (46%) | 551 (48%) |
| Gemcitabine | 309 (48%) | 65 (45%) | 164 (46%) | 538 (47%) |
| Observation | 29 (4%) | 4 (3%) | 29 (8%) | 62 (5%) |
| Lymph nodes | pN0 | 212 (33%) | 29 (20%) | 87 (24%) | 328 (28%) |
| pN1 | 432 (67%) | 116 (79%) | 272 (76%) | 820 (71%) |
| Stage | 1 | 89 (14%) | 7 (5%) | 17 (5%) | 113 (10%) |
| 2 | 186 (29%) | 40 (27%) | 86 (24%) | 312 (27%) |
| 3 | 335 (52%) | 92 (63%) | 235 (65%) | 662 (58%) |
| 4 | 23 (4%) | 5 (3%) | 14 (4%) | 42 (4%) |
| WHO performance status | 0 | 228 (35%) | 48 (33%) | 116 (32%) | 392 (34%) |
| 1 | 343 (53%) | 81 (55%) | 202 (56%) | 626 (54%) |
| 2 | 74 (11%) | 17 (12%) | 41 (11%) | 132 (11%) |
| Tumor Differentiation | Well | 96 (15%) | 18 (12%) | 38 (11%) | 152 (13%) |
| Moderate | 395 (61%) | 93 (64%) | 220 (61%) | 708 (62%) |
| Poor | 144 (22%) | 31 (21%) | 97 (27%) | 272 (24%) |
| Weight | kg (IQR) | 67.4 (58.65, 76) | 68 (58.1, 75.7) | 67.9 (59.275, 77) | 67.8 (58.625, 76) |
| Smoke | Never | 253 (39%) | 41 (28%) | 123 (34%) | 417 (36%) |
| Past | 215 (33%) | 68 (47%) | 141 (39%) | 424 (37%) |
| Present | 101 (16%) | 23 (16%) | 58 (16%) | 182 (16%) |
| Concurrent medical condition | No | 325 (50%) | 68 (47%) | 135 (38%) | 528 (46%) |
| Yes | 280 (43%) | 71 (49%) | 205 (57%) | 556 (48%) |
| Diabetes | IDDM | 74 (11%) | 23 (16%) | 54 (15%) | 151 (13%) |
| NIDDM | 67 (10%) | 13 (9%) | 33 (9%) | 113 (10%) |
| No | 461 (71%) | 103 (71%) | 250 (70%) | 814 (71%) |
| Morbidity | No | 463 (72%) | 103 (71%) | 256 (71%) | 822 (71%) |
| Yes | 145 (22%) | 38 (26%) | 82 (23%) | 265 (23%) |
| Postoperative CA19-9 | KU/L (IQR) | 20 (9, 54) | 24 (11, 75) | 26.5 (10, 75.25) | 23.5 (10, 63) |
| Operation | Standard PPD | 337 (52%) | 94 (64%) | 200 (56%) | 631 (55%) |
| PP-PPD | 198 (31%) | 33 (23%) | 103 (29%) | 334 (29%) |
| Distal Panc. | 58 (9%) | 5 (3%) | 20 (6%) | 83 (7%) |
| Total Panc. | 15 (2%) | 10 (7%) | 19 (5%) | 44 (4%) |
| Maximun tumour size | mm (IQR) | 30 (20, 40) | 30 (25, 36.5) | 30 (25, 40) | 30 (22.75, 40) |

IDDM = Insulin-dependent diabetes mellitus; NIDDM = non insulin-dependent diabetes mellitus; PPD= partial pancreato duodenectomy; PP = pylorus preserving; Panc. = pancreatectomy

**SUPPL. Table 2**: Multivariable regression of factors associated with positive R1 resection margins including both R1-direct and R1<1mm margins.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|   |   | est (se) | OR (95% CI) | P |
| Intercept |   | -1.22 (0.46) | 0.29 (0.119, 0.724) | 0.008 |
| Lymph Nodes | Negative |   |   |   |
| Positive | 0.42 (0.144) | 1.53 (1.153, 2.026) | 0.003 |
| Maximum Tumour Size |   | 0.24 (0.133) | 1.27 (0.979, 1.648) | 0.072 |
| Type of Surgery | Standard PPD  |   |   |   |
| Pylorus preserving PPD | -0.27 (0.142) | 0.76 (0.576, 1.006) | 0.055 |
| Distal Pancreatectomy | -0.68 (0.259) | 0.51 (0.307, 0.845) | 0.009 |
| Total Pancreatectomy | 1.05 (0.357) | 2.85 (1.418, 5.739) | 0.003 |

PPD = partial pancreato- duodenectomy

**SUPPL. Table 3**: Multivariable Cox model for overall and recurrence free survival.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  |   | Overall Survival |   | Recurrence Free Survival |
|   |   | est (se) | Hazard Ratio (95% CI) | P |   | est (se) | Hazard Ratio (95% CI) | P |
| Resection Margins | R0  |  |  |  |   |  |  |   |
| R1<1mm | -0.05 (0.149) | 0.95 (0.709, 1.268) | 0.719 |  | 0.04 (0.14) | 1.04 (0.791, 1.368) | 0.779 |
| R1-Direct | 0.27 (0.092) | 1.31 (1.093, 1.566) | 0.003 |  | 0.29 (0.089) | 1.34 (1.122, 1.592) | 0.001 |
| Tumor Differentiation | Well |  |  |  |  |  |  |  |
| Moderate | 0.15 (0.11) | 1.16 (0.933, 1.434) | 0.184 |  | 0.09 (0.105) | 1.1 (0.893, 1.349) | 0.376 |
| Poor | 0.45 (0.121) | 1.57 (1.239, 1.995) | <0.001 |  | 0.35 (0.117) | 1.42 (1.129, 1.786) | 0.003 |
| Lymph Nodes | Negative |  |  |  |  |  |  |  |
| Positive | 0.58 (0.083) | 1.79 (1.52, 2.105) | <0.001 |  | 0.55 (0.079) | 1.74 (1.491, 2.032) | <0.001 |
| WHO Performance status | 0 |  |  |  |  |  |  |  |
| 1 | 0.19 (0.076) | 1.21 (1.047, 1.41) | 0.011 |  | 0.15 (0.074) | 1.16 (1.006, 1.342) | 0.041 |
| 2 | 0.31 (0.12) | 1.36 (1.075, 1.721) | 0.01 |  | 0.29 (0.116) | 1.33 (1.062, 1.671) | 0.013 |
| Maximum Tumor Size | Log (Maximum Tumor Size + 1)) | 0.19 (0.069) | 1.21 (1.059, 1.386) | 0.005 |  | 0.2 (0.065) | 1.22 (1.078, 1.39) | 0.002 |
| Posterior Resection Margin | R0  |  |  |  |  |  |  |  |
| R1<1mm | 0.13 (0.159) | 1.13 (0.832, 1.548) | 0.426 |  | 0.02 (0.151) | 1.02 (0.76, 1.377) | 0.88 |
| R1-Direct | 0.29 (0.125) | 1.34 (1.047, 1.71) | 0.02 |  | 0.24 (0.122) | 1.28 (1.004, 1.622) | 0.047 |
| R1-Lymph Node | 0.27 (0.456) | 1.31 (0.536, 3.199) | 0.554 |  | 0.27 (0.456) | 1.3 (0.534, 3.187) | 0.56 |
| Unknown | 0.15 (0.082) | 1.16 (0.992, 1.367) | 0.063 |  | 0.13 (0.079) | 1.14 (0.978, 1.333) | 0.093 |