The Role of Location of Tumor in the Prognosis of the Pancreatic Cancer

Mirang Lee †, Woobil Kwon †, Hongbeom Kim, Yoonhyeong Byun, Youngmin Han, Jae Seung Kang, Yoo Jin Choi and Jin-Young Jang *

Department of surgery, Seoul National University Hospital, Seoul 03080, Korea; rang5026@snu.ac.kr (M.L.); willdoc@snu.ac.kr (W.K.); surgoonkhb@snu.ac.kr (H.K.); yoonhyeong@snu.ac.kr (Y.B.); views@snu.ac.kr (Y.H.); 74398@snuh.org (J.S.K.); 74401@snuh.org (Y.J.C.)
* Correspondence: jangjy4@snu.ac.kr; Tel.: +822-2072-2194; Fax: +822-766-3975
† These authors contributed equally to this work as first authors.

Received: 9 June 2020; Accepted: 22 July 2020; Published: 24 July 2020

Abstract: Identification of prognostic factors is important to improve treatment outcomes in pancreatic cancer. This study aimed to investigate the effect of the location of pancreatic cancer on survival and to determine whether it was a significant prognostic factor. Altogether, 2483 patients diagnosed with pancreatic cancer were examined. Comparative analysis of clinicopathologic characteristics, survival analysis, and multivariate analysis were performed. Cancers of the pancreatic head or the uncinate process were present in 49.5% of patients. The head/uncinate cancers had more clinical T1/T2 tumors (59.4% vs. 35.5%, \( p < 0.001 \)) and a significantly higher 5-year survival rate (8.9% vs. 7.3%, \( p < 0.001 \)) than the body/tail cancers. The 5-year survival rate in patients with head/uncinate cancers was significantly lower in the resectable (\( p = 0.014 \)) and the locally advanced groups (\( p = 0.007 \)). In patients who underwent resection with curative intent, the 5-year survival rate was lower in the head/uncinate group (\( p = 0.046 \)). The overall outcome of the head/uncinate cancers was better than the body/tail cancers, due to the high proportion of resectable cases. In patients who underwent curative resection, the head/uncinate cancers had a higher number of T1/T2 tumors, but worse outcomes. In the multivariate analysis, tumor location was not an independent prognostic factor for pancreatic cancer.

Keywords: pancreatic neoplasm/analysis; pancreatic neoplasm/surgery; tumor location; survival; clinical staging

1. Introduction

Pancreatic cancer is one of the leading causes of cancer-related mortality in developed countries and one of the most lethal malignant neoplasms worldwide [1]. Its prognosis might be poor, and accurate prediction of the prognosis is important for patients as well as clinicians in the management of pancreatic cancer.

Surgical approach to pancreatic cancer and its prognosis greatly differ according to the tumor location [2–4]. Some authors have argued that pancreatic body and tail cancers have a worse prognosis due to delayed diagnosis. Others have reported that according to the tumor stage at diagnosis, pancreatic body and tail cancers showed superior survival than pancreatic head cancers, in localized and resectable tumors. Despite these differences, tumor location was never taken into consideration in any edition of the American Joint Committee on Cancer (AJCC) staging system, since the first edition in 1978. Thus, the effect of location on pancreatic cancer needs to be highlighted.

Several issues related to tumor location need to be scrutinized in depth. One of them is to clarify whether tumor location affects the prognosis of pancreatic cancer and if it does, the manner in which it affects the prognosis. Furthermore, it should be examined whether tumor location affects the prognosis.
to such an extent that it should be reflected in the staging system of pancreatic cancer. With these questions in mind, the present study aimed to compare the survival outcomes and clinicopathological features of pancreatic cancer, according to its location.

2. Results

2.1. Patient Demographics and Survival Outcomes

Altogether, 2483 patients were identified. Among these, 1228 patients (49.5%) had tumors in the pancreatic head or the uncinate process (PHU group) and 1255 patients (50.5%) had tumors in the pancreatic body or the tail (PBT group). Demographics and clinicopathological features are summarized in Table 1. The mean age was comparable between the PHU and the PBT groups (64.3 years and 64.0 years, respectively; $p = 0.468$). The sex ratio was also similar between the groups, showing male predominance (1:0.68 and 1:0.68, respectively; $p = 0.097$).

### Table 1. Demographics and clinicopathological features of overall patients.

| Variables                 | Total ($N = 2483$) | PHU ($N = 1228$) | PBT ($N = 1255$) | $p$-Value |
|---------------------------|--------------------|------------------|------------------|-----------|
| Age (years)               | 64.1 (23–94)       | 64.3 (28–94)     | 64.0 (23–93)     | 0.468     |
| Sex (Male:Female)         | 1:0.68             | 1:0.68           | 1:0.68           | 0.970     |
| Tumor size (cm)           | 3.8 (0.1–15.5)     | 3.4 (0.1–8.5)    | 4.3 (0.1–15.5)   | $<0.001$  |
| Clinical T stage          |                    |                  |                  |           |
| T1                        | 192 (7.7%)         | 113 (9.2%)       | 79 (6.3%)        |           |
| T2                        | 983 (39.6%)        | 616 (50.2%)      | 367 (29.2%)      | $<0.001$  |
| T3                        | 495 (19.9%)        | 152 (12.4%)      | 343 (27.3%)      |           |
| T4                        | 813 (32.7%)        | 347 (28.3%)      | 466 (37.1%)      |           |
| Resectability             |                    |                  |                  |           |
| Resectable                | 677 (27.3%)        | 449 (36.6%)      | 228 (18.2%)      |           |
| Borderline                | 124 (5.0%)         | 85 (6.9%)        | 39 (3.1%)        | $<0.001$  |
| Locally advanced          | 615 (24.8%)        | 313 (25.5%)      | 302 (24.1%)      |           |
| Distant metastasis        | 1067 (43.0%)       | 381 (31.0%)      | 686 (54.7%)      |           |
| Operation                 |                    |                  |                  |           |
| Non-resectable            | 1778 (71.6%)       | 766 (62.4%)      | 1012 (80.6%)     | $<0.001$  |
| Preemptive-resectable     | 705 (28.4%)        | 462 (37.6%)      | 243 (19.4%)      |           |

PHU—tumors in the pancreas head or uncinated process; PBT—tumors in the pancreas body and tail. Continuous variables were expressed as median (range). Statistical significance when $p$ value < 0.05.

Mean tumor size was significantly different between the PHU group and the PBT group (3.4 cm and 4.3 cm, respectively; $p < 0.001$). The proportion of clinical T stages was significantly different ($p < 0.001$). The PHU group had a higher proportion of cT2 (50.2% in PHU vs. 29.2% in PBT) tumors. The PBT group had a higher proportion of cT3 and cT4 tumors than the PHU group (cT3: 27.3% vs. 12.4% and cT4: 37.1% vs. 28.3%, respectively).

The proportion of tumors was significantly different in terms of classification according to resectability between the PHU and the PBT groups ($p < 0.001$). The PHU group had a higher proportion of resectable and borderline resectable pancreatic cancers (resectable—36.6% vs. 18.2% and borderline resectable: 6.9% vs. 3.1%, respectively) and a lower proportion of metastatic pancreatic cancer (31.0% vs. 54.7%, respectively) than the PBT group. The proportion of locally advanced pancreatic cancers was similar between the groups (25.5% and 24.1% in the PHU and the PBT groups, respectively).

The median survival in all patients was 11 months and the 5-year survival rate was 8.1%. The PHU group demonstrated significantly better survival than the PBT group (median survival—12 vs. 10 months, and 5-year survival—8.9% vs. 7.3%, respectively; $p < 0.001$) (Figure 1).
The proportion of tumors was significantly different in terms of classification according to resectability between the PHU and the PBT groups \((p < 0.001)\). The PHU group had a higher proportion of resectable and borderline resectable pancreatic cancers (resectable—36.6% vs. 18.2% and borderline resectable: 6.9% vs. 3.1%, respectively) and a lower proportion of metastatic pancreatic cancer (31.0% vs. 54.7%, respectively) than the PBT group. The proportion of locally advanced pancreatic cancers was similar between the groups (25.5% and 24.1% in the PHU and the PBT groups, respectively).

The median survival in all patients was 11 months and the 5-year survival rate was 8.1%. The PHU group demonstrated significantly better survival than the PBT group (median survival—12 vs. 10 months, and 5-year survival—8.9% vs. 7.3%, respectively; \(p < 0.001\)) (Figure 1).

Figure 1. The survival curves of pancreatic cancer in the head/uncinate region and body/tail regions in all patients are illustrated.

### 2.2. Demographics of the Patients Who Underwent Resection

Among 705 patients who were advised to undergo curative resection, 28 patients who underwent neoadjuvant treatment and 31 patients who ended up having non-curative surgery were excluded. Thus, 646 patients underwent curative resection. Altogether, 432 (66.9%) patients in the PHU group and 214 (33.1%) patients in the PBT group underwent curative resection. The PHU group had a significantly smaller tumor size, more angiolymphatic invasion and perineural invasion, a lower proportion of T3 and T4 tumors, a higher proportion of N2 and a lower proportion of N0 tumors, greater recurrence, and lower incidence of systemic recurrence, when compared to the PBT group. There were no differences in carcinoembryonic antigen and carbohydrate antigen (CA) 19-9 levels, lymph node (LN) metastasis rate, and the proportion of patients who received adjuvant therapy. Demographics and clinicopathological features are summarized in Table 2.

| Variables                  | Total \((N = 646)\) | PHU \((N = 432)\) | PBT \((N = 214)\) | \(p\)-Value |
|----------------------------|---------------------|-------------------|-------------------|-------------|
| Age (years)                | 64.6 (29–89)        | 63.7 (29–88)      | 66.4 (35–89)      | 0.001       |
| Sex (Male:Female)          | 1:0.7               | 1:0.67            | 1:0.75            | 0.552       |
| Preoperative CEA (ng/mL)   | 4.1 (0.5–179.1)     | 3.5 (0.5–63)      | 5.2 (0.5–179.1)   | 0.124       |
| Preoperative CA19-9 (U/mL) | 1040.7 (0.1–37800)  | 1109.2 (0.1–28700)| 901.7 (1–37800)   | 0.421       |
| Operation name             |                     |                   |                   |             |
| PPD                        | 251 (38.9%)         | 251 (58.1%)       | 0                 |             |
| Whipple’s operation        | 163 (25.2%)         | 163 (37.7%)       | 0                 |             |
| Distal pancreatectomy      | 190 (29.4%)         | 0                 | 190 (88.8%)       | <0.001      |
| Subtotal pancreatectomy    | 17 (2.6%)           | 0                 | 17 (7.9%)         |             |
| Total pancreatectomy       | 23 (3.6%)           | 17 (3.9%)         | 23 (3.6%)         |             |
| Central pancreatectomy     | 2 (0.3%)            | 1 (0.2%)          | 2 (0.3%)          |             |
### Table 2. Cont.

| Variables                      | Total (N = 646) | PHU (N = 432) | PBT (N = 214) | p-Value |
|--------------------------------|-----------------|---------------|---------------|---------|
| Complication                   |                 |               |               | <0.001  |
| Adjuvant therapy               |                 |               |               |         |
| Chemotherapy                   | 264 (40.9%)     | 199 (46.1%)   | 65 (30.4%)    |         |
| Radiotherapy                   | 516 (79.9%)     | 344 (79.6%)   | 172 (80.4%)   | 0.917   |
| Tumor size(cm)                 | 3.3 (0.2–12.2)  | 3.1 (0.2–8.0) | 3.5 (0.5–12.2)| 0.008   |
| Differentiation                |                 |               |               |         |
| Well Differentiated            | 43 (7.1%)       | 23 (5.6%)     | 20 (10.2%)    | 0.053   |
| Moderate Differentiated        | 488 (80.7%)     | 340 (83.1%)   | 148 (75.5%)   |         |
| Poorly Differentiated          | 74 (12.2%)      | 46 (11.2%)    | 28 (14.3%)    |         |
| Resection margin status        |                 |               |               |         |
| Tumor free                     | 549 (85.0%)     | 373 (86.3%)   | 176 (82.2%)   | 0.198   |
| Presence of tumor              | 97 (15.0%)      | 59 (13.7%)    | 38 (17.8%)    |         |
| Angiolymphatic invasion        |                 |               |               | <0.001  |
| Negative                       | 354 (55.0%)     | 213 (49.4%)   | 141 (66.2%)   |         |
| Positive                       | 290 (45.0%)     | 218 (50.6%)   | 72 (33.8%)    |         |
| Vascular invasion              |                 |               |               | 0.200   |
| Negative                       | 389 (60.3%)     | 252 (58.5%)   | 137 (64.0%)   |         |
| Positive                       | 256 (39.7%)     | 179 (41.5%)   | 77 (36.0%)    |         |
| Perineural invasion            |                 |               |               | 0.014   |
| Negative                       | 108 (16.7%)     | 61 (14.1%)    | 47 (22.0%)    |         |
| Positive                       | 538 (83.3%)     | 371 (85.9%)   | 167 (78.0%)   |         |
| T stage                        |                 |               |               |         |
| T1                             | 96 (14.9%)      | 62 (14.4%)    | 34 (15.9%)    | 0.041   |
| T2                             | 426 (65.9%)     | 299 (69.2%)   | 127 (59.3%)   |         |
| T3                             | 113 (17.5%)     | 66 (15.3%)    | 47 (22.0%)    |         |
| T4                             | 11 (1.7%)       | 5 (1.2%)      | 6 (2.8%)      |         |
| N stage                        |                 |               |               | 0.033   |
| N0                             | 252 (39.0%)     | 160 (37.0%)   | 92 (43.0%)    |         |
| N1                             | 270 (41.8%)     | 177 (41.0%)   | 93 (43.5%)    |         |
| N2                             | 124 (19.2%)     | 95 (22.0%)    | 29 (13.6%)    |         |
| Stage                          |                 |               |               |         |
| Ia                             | 65 (10.1%)      | 38 (8.8%)     | 27 (12.6%)    |         |
| Ib                             | 150 (23.2%)     | 101 (23.4%)   | 49 (22.9%)    | 0.171   |
| Iia                            | 34 (5.3%)       | 20 (4.6%)     | 14 (6.5%)     |         |
| Iib                            | 265 (41.0%)     | 175 (40.5%)   | 90 (42.1%)    |         |
| III                            | 132 (20.4%)     | 98 (22.7%)    | 34 (15.9%)    |         |
| Recurrence                     |                 |               |               | 0.006   |
| No                             | 211 (32.7%)     | 125 (29.0%)   | 86 (40.2%)    |         |
| Yes                            | 434 (67.3%)     | 306 (71.0%)   | 128 (59.8%)   |         |
| Recurrence type                |                 |               |               | 0.028   |
| Local                          | 66 (15.2%)      | 54 (17.7%)    | 12 (9.4%)     |         |
| Systemic                       | 367 (84.8%)     | 251 (82.3%)   | 116 (90.6%)   |         |

PHU—tumors in the pancreas head or uncinated process; PBT—tumors in the pancreas body and tail; PPPD—pylorus-preserving pancreatoduodenectomy. Continuous variables were expressed as median (range). Statistically significant when p value < 0.05.

### 2.3. Survival Analysis of the Patients Who Underwent Resection

The median survival duration was 25 months and the 5-year survival was 23.6%. For the PHU group, the median survival duration was 23 months and the 5-year survival was 20.8%. For the PBT group, the median survival duration was 30 months and the 5-year survival was 29.7%. Thus, the survival outcome in the PBT group was significantly superior to that in the PHU group (p = 0.046) (Figure 2).
The median survival duration was 25 months and the 5-year survival was 23.6%. For the PHU group, the median survival duration was 23 months and the 5-year survival was 20.8%. For the PBT group, the median survival duration was 30 months and the 5-year survival was 29.7%. Thus, the survival outcome in the PBT group was significantly superior to that in the PHU group ($p = 0.046$) (Figure 2).

Figure 2. The survival curves of pancreatic cancer in the head/uncinate region and body/tail regions in resected patients are illustrated. Survival outcomes were compared according to the T category. For T1, T2, and T4 tumors, the PHU group had worse outcomes compared to the PBT group. The difference was not significant for the T1 (median survival 34 vs. 41 months, respectively; $p = 0.288$) and T4 tumors (median survival 6 vs. 8 months, respectively; $p = 0.067$). A significant difference was found in T2 tumors with a median survival of 22 months for the PHU group (5-year survival 19.4%) and a median survival of 34 months for the PHU group (5-year survival 34.8%) ($p = 0.005$, Figure 3).

Figure 3. The survival curves of pancreas head/uncinate cancer and pancreas body cancer according to the T categories.

According to the prognostic groups of the AJCC cancer staging system (edition 8), there were no differences in survival outcomes between the PHU and the PBT groups, in all stages from stage Ia to stage III (Figure S1).

2.4. Prognostic Factors of Pancreatic Cancer

Tumor location, histological grade, margin status, angiolymphatic invasion, venous invasion, perineural invasion, T category, N category, adjuvant chemotherapy, adjuvant radiotherapy, and preoperative CA 19-9 were significantly associated with survival. In the multivariate analysis, tumor location did not reach statistical significance (vs. PBT: hazard ratio [HR] 1.174, confidence interval [CI] 0.932–1.478, $p = 0.173$). Histological grade, margin status, angiolymphatic invasion, venous invasion, T4 stage, lymph node metastasis, adjuvant chemotherapy, adjuvant radiotherapy, and preoperative CA 19-9 were independent prognostic factors (Table 3).

Table 3. Univariate and multivariate analysis comparing the 5-year survival rates in resected patients.

| Variables            | Univariate | Multivariate |
|----------------------|------------|--------------|
| Sex                  |            |              |
| Male                 | 0.269      |              |
| Female               | 0.273      |              |
| Age (years)          |            |              |
| <65                  | 0.070      | 0.049        |
| ≥65                  | 1.095      | 0.881–1.362  |
| Site of tumor        |            |              |
| Head                 | 0.046      | 1.174        |
| Body, tail           | 0.297      | 0.932–1.478  |
| Complication         |            |              |
| N                    | 0.005      |              |
| P                    | 0.067      |              |
| Sex                  |            |              |
| Male                 | 0.173      |              |
| Female               | 0.194      |              |
In node-negative disease, the PHU group had worse median survival than the PBT group, but the difference was not significant (33 vs. 39 months, respectively; \( p = 0.454 \)). Similarly, in the node-positive disease, the PHU group had worse outcomes than the PBT group, but the difference lacked statistical significance (19 vs. 25 months, respectively; \( p = 0.112 \)).

According to the prognostic groups of the AJCC cancer staging system (edition 8), there were no differences in survival outcomes between the PHU and the PBT groups, in all stages from stage Ia to stage III (Figure S1).

### 2.4. Prognostic Factors of Pancreatic Cancer

Tumor location, histological grade, margin status, angiolymphatic invasion, venous invasion, perineural invasion, T category, N category, adjuvant chemotherapy, adjuvant radiotherapy, and preoperative CA 19-9 were significantly associated with survival. In the multivariate analysis, tumor location did not reach statistical significance (vs. PBT: hazard ratio [HR] 1.174, confidence interval [CI] 0.932–1.478, \( p = 0.173 \)). Histological grade, margin status, angiolymphatic invasion, venous invasion, T4 stage, lymph node metastasis, adjuvant chemotherapy, adjuvant radiotherapy, and preoperative CA 19-9 were independent prognostic factors (Table 3).

### Table 3. Univariate and multivariate analysis comparing the 5-year survival rates in resected patients.

| Variables             | Univariate | Multivariate |
|-----------------------|------------|--------------|
|                       | \( n \)    | 5 YSR, %     | \( p \) Value | HR     | 95% CI       | \( p \) Value |
| Sex                   |            |              |              |        |              |              |
| Male                  | 380        | 21.2         |              |        |              |              |
| Female                | 266        | 27.3         | 0.269        |        |              |              |
| Age(years)            |            |              |              |        |              |              |
| <65                   | 301        | 24.0         |              |        |              |              |
| ≥65                   | 345        | 23.6         | 0.070        | 1.095  | 0.881–1.362  | 0.414        |
| Site of tumor         |            |              |              |        |              |              |
| Head                  | 432        | 20.8         |              |        |              |              |
| Body, tail            | 214        | 29.7         |              |        |              |              |
| Complication          |            |              |              |        |              |              |
| No                    | 382        | 22.7         |              |        |              |              |
| Yes                   | 264        | 24.9         | 0.986        |        |              |              |
| Histologic grade      |            |              | \(<0.001\)   | \(<0.001\) |              |              |
| Well differentiated    | 43         | 45.0         | \(<0.001\)   |        |              |              |
| Moderate differentiated| 488       | 21.9         | \(<0.001\)   | 2.092  | 1.306–3.351  | 0.002        |
| Poorly differentiated  | 74         | 11.2         | \(<0.001\)   | 3.133  | 1.834–5.354  | \(<0.001\)   |
| Margin                |            |              |              |        |              |              |
| Negative              | 549        | 26.5         | \(<0.001\)   | 1.471  | 1.126–1.923  | 0.005        |
| Positive              | 97         | 5.3          | \(<0.001\)   |        |              |              |
| Angiolymphatic invasion|           |              |              |        |              |              |
| Negative              | 354        | 31.0         | \(<0.001\)   | 1.473  | 1.191–1.823  | \(<0.001\)   |
| Positive              | 290        | 13.7         | \(<0.001\)   |        |              |              |
| Venous invasion       |            |              |              |        |              |              |
| Negative              | 389        | 30.1         |              |        |              |              |
| Positive              | 256        | 11.9         | \(<0.001\)   | 1.309  | 1.059–1.618  | 0.013        |
| Perineural invasion   |            |              |              |        |              |              |
| Negative              | 108        | 42.3         | \(<0.001\)   | 1.250  | 0.895–1.746  | 0.191        |
| Positive              | 538        | 19.7         | \(<0.001\)   |        |              |              |
Table 3. Cont.

| Variables                        | Univariate | Multivariate |
|---------------------------------|------------|--------------|
|                                 | n   | 5 YSR, % | p Value | HR  | 95%CI | p Value |
| T stage                         |     |         |         |     |      |         |
| T1                              | 96  | 37.9    | <0.001 | 1.143| 0.814–1.604 | 0.008   |
| T2                              | 426 | 23.7    | 0.001  | 1.278| 0.858–1.902 | 0.227   |
| T3                              | 113 | 15.0    | <0.001 | 4.874| 2.228–10.664| <0.001  |
| T4                              | 11  | 0.0     | <0.001 | 3.278| 0.858–1.902 | 0.227   |
| N stage                         |     |         |         |     |      |         |
| N0                              | 252 | 37.3    | <0.001 | 1.271| 1.002–1.613 | 0.048   |
| N1                              | 269 | 17.0    | <0.001 | 1.611| 1.207–2.150 | 0.001   |
| N2                              | 125 | 8.2     | <0.001 | 1.626| 1.206–2.193 | 0.001   |
| Adjuvant Chemotherapy           |     |         |         |     |      |         |
| Yes                             | 516 | 25.0    | <0.001 | 1.626| 1.206–2.193 | 0.001   |
| No                              | 130 | 18.4    | <0.001 | 1.417| 1.103–1.821 | 0.006   |
| Adjuvant Radiotherapy           |     |         |         |     |      |         |
| Yes                             | 343 | 27.3    | <0.001 | 1.417| 1.103–1.821 | 0.006   |
| No                              | 303 | 20.9    | <0.001 | 1.626| 1.206–2.193 | 0.001   |
| Preoperative CEA                |     |         |         |     |      |         |
| <5.0 ng/mL                      | 524 | 24.8    | <0.001 | 1.168| 0.884–1.544 | 0.274   |
| ≥5.0 ng/mL                      | 94  | 21.9    | 0.061  | 1.168| 0.884–1.544 | 0.274   |
| Preoperative CA19-9              |     |         |         |     |      |         |
| <37.0 U/mL                      | 187 | 38.9    | <0.001 | 1.600| 1.258–2.037 | <0.001  |
| ≥37.0 U/mL                      | 446 | 18.1    | <0.001 | 1.600| 1.258–2.037 | <0.001  |

YSR—year survival rate; HR—hazard ratio; CI—confidence interval. The variables with p-value less than 0.1 in univariate analysis were included in the multivariate analysis.

When analyzed separately for the PHU and the PBT groups, factors associated with survival in the univariate analysis were similar between the groups and similar to the factors associated with the overall patient population. For the PHU group, all associated categories were similar to those associated with the overall patient population. For the PBT group, T2 stage and preoperative CA 19-9 were not associated with survival, while age was associated with survival, when compared to the overall patient population.

Multivariate analysis showed that poorly differentiated histological grade, angiolymphatic invasion, perineural invasion, T4 stage, N2 stage, adjuvant chemotherapy, adjuvant radiotherapy, and preoperative CA 19-9 were significantly associated with survival in the PHU group. In the PBT group, histological grade, margin status, venous invasion, and adjuvant chemotherapy were significantly associated with survival (Table 4).
Table 4. Comparison of independent risk factors of pancreatic cancer in PHU and PBT.

| Variables              | PHU                                      |       | PBT                                      |       |
|------------------------|------------------------------------------|-------|------------------------------------------|-------|
|                        | Univariate                               | Multivariate | Univariate                               | Multivariate |
|                        | $n$ | 5YSR, % | $p$ Value | HR | 95%CI | $p$ Value | $n$ | 5YSR, % | $p$ Value | HR | 95%CI | $p$ Value |
| Sex                    |     |         |          |    |       |          |     |         |          |    |       |          |
| Male                   | 258 | 16.6    | 0.254    |    | 122   | 31.2     | 92  | 27.0    | 0.968     |
| Female                 | 174 | 26.9    |          |    | 92    |          | 92  | 27.0    |           |
| Age (years)            |     |         |          |    |       |          |     |         |          |    |       |          |
| <65                    | 220 | 19.3    | 0.272    |    | 81    | 39.0     | 133 | 24.3    | 0.020     | 1.135 | 0.740–1.740 | 0.561 |
| ≥65                    | 212 | 23.5    |          |    | 133   |           | 133 | 24.3    |           | 0.020 | 1.135 | 0.740–1.740 | 0.561 |
| Complication           |     |         |          |    |       |          |     |         |          |    |       |          |
| No                     | 233 | 18.8    | 0.645    |    | 149   | 28.7     | 65  | 33.1    | 0.883     |
| Yes                    | 199 | 22.8    |          |    | 65    |           | 65  | 33.1    |           |
| Histologic grade       |     |         |          |    |       |          |     |         |          |    |       |          |
| Well differentiated     | 23  | 27.7    | <0.001   | 0.001 | 20    | 69.1     | 65  | 33.1    | 0.883     |
| Moderate differentiated | 340 | 19.7    | 0.035    | 1.368 | 0.781–2.396 | 0.273 | 148 | 27.5    | 0.003     | 3.632 | 1.503–8.777 | 0.004 |
| Poorly differentiated   | 46  | 12.3    | <0.001   | 2.692 | 1.419–5.108 | 0.002 | 28  | 9.0     | <0.001    | 3.609 | 1.318–9.885 | 0.013 |
| Margin                 |     |         |          |    |       |          |     |         |          |    |       |          |
| Negative               | 373 | 22.5    | 0.006    | 1.165 | 0.823–1.649 | 0.388 | 38  | 4.4     | <0.001    | 2.431 | 1.580–3.743 | <0.001 |
| Positive               | 59  | 5.8     |          |    | 176   | 35.8     | 176 | 35.8    |           |
| Angiolymphatic invasion|     |         |          |    |       |          |     |         |          |    |       |          |
| Negative               | 213 | 29.0    | <0.001   | 1.393 | 1.079–1.799 | 0.011 | 72  | 18.5    | 0.002     | 1.412 | 0.952–2.095 | 0.087 |
| Positive               | 218 | 12.4    |          |    | 141   | 34.4     | 141 | 34.4    |           |
| Venous invasion        |     |         |          |    |       |          |     |         |          |    |       |          |
| Negative               | 252 | 26.5    | <0.001   | 1.239 | 0.966–1.590 | 0.092 | 77  | 14.3    | <0.001    | 1.523 | 1.014–2.288 | 0.042 |
| Positive               | 179 | 11.1    |          |    | 137   | 37.8     | 137 | 37.8    |           |
| Perineural invasion    |     |         |          |    |       |          |     |         |          |    |       |          |
| Negative               | 61  | 40.7    | <0.001   | 1.581 | 1.033–2.420 | 0.035 | 167 | 25.1    | 0.036     | 0.669 | 0.389–1.149 | 0.145 |
| Positive               | 371 | 17.4    |          |    | 47    | 45.2     | 47  | 45.2    |           |
| Variables                        | PHU                          | PBT                          | PHU                          | PBT                          |
|--------------------------------|------------------------------|------------------------------|------------------------------|------------------------------|
|                                | Univariate                   | Multivariate                 | Univariate                   | Multivariate                 |
|                                | Univariate                   | Multivariate                 | Univariate                   | Multivariate                 |
|                                | n                            | 5YSR, %                      | p Value                      | HR                           | 95%CI                        | p Value                      | n                            | 5YSR, %                      | p Value                      | HR                           | 95%CI                        | p Value                      |
| **T stage**                    |                              |                              |                              |                              |                              |                              |                              |                              |                              |                              |                              |                              |                              |
| T1                             | 62                           | 33.5                         | <0.001                       | 0.004                        | 34                           | 48.9                         | 0.001                        | 0.004                        | 34                           | 48.9                         | 0.001                        | 0.004                        |
| T2                             | 299                          | 19.4                         | 0.004                        | 1.303                        | 0.868–1.956                  | 0.201                        | 127                          | 34.8                         | 0.158                        | 0.827                        | 0.445–1.534                  | 0.546                        |
| T3                             | 66                           | 17.1                         | 0.034                        | 1.215                        | 0.734–2.012                  | 0.448                        | 47                           | 12.0                         | 0.001                        | 1.433                        | 0.749–2.742                  | 0.278                        |
| T4                             | 5                            | 0.0                          | <0.001                       | 13.539                       | 4.519–40.565                 | <0.001                       | 6                            | 0.0                          | <0.001                       | 2.336                        | 0.769–7.096                  | 0.134                        |
| **N stage**                    |                              |                              |                              |                              |                              |                              |                              |                              |                              |                              |                              |                              |                              |
| N0                             | 160                          | 33.2                         | <0.001                       | 0.037                        | 92                           | 45.3                         | 0.004                        | 0.180                        |                              |                              |                              |                              |
| N1                             | 177                          | 16.4                         | <0.001                       | 1.223                        | 0.920–1.627                  | 0.166                        | 92                           | 18.4                         | 0.005                        | 1.474                        | 0.936–2.319                  | 0.094                        |
| N2                             | 95                           | 7.3                          | <0.001                       | 1.571                        | 1.114–2.214                  | 0.010                        | 30                           | 12.2                         | 0.006                        | 1.554                        | 0.867–2.784                  | 0.139                        |
| **Adjuvant Chemotherapy**      |                              |                              |                              |                              |                              |                              |                              |                              |                              |                              |                              |                              |                              |
| Yes                            | 344                          | 22.5                         | <0.001                       | 0.018                        | 172                          | 30.6                         | 0.034                        | 2.466                        | 1.463–4.156                  | 0.001                        |                              |                              |
| No                             | 88                           | 14.1                         | <0.001                       | 1.511                        | 1.074–2.125                  | 0.018                        | 42                           | 26.2                         | 0.034                        | 2.466                        | 1.463–4.156                  | 0.001                        |
| **Adjuvant Radiotherapy**      |                              |                              |                              |                              |                              |                              |                              |                              |                              |                              |                              |                              |                              |
| Yes                            | 231                          | 25.1                         | <0.001                       | 1.482                        | 1.108–1.983                  | 0.008                        | 112                          | 32.1                         | 0.080                        | 1.279                        | 0.793–2.064                  | 0.313                        |
| No                             | 201                          | 17.0                         | <0.001                       | 1.827                        | 1.277                        | 0.917–1.778                  | 0.148                        | 34                           | 27.3                         | 0.459                        |                              |                              |
| **Preoperative CEA**           |                              |                              |                              |                              |                              |                              |                              |                              |                              |                              |                              |                              |                              |
| <5.0 ng/mL                     | 354                          | 22.1                         | <0.001                       | 1.482                        | 1.108–1.983                  | 0.008                        | 102                          | 29.2                         | 0.080                        | 1.279                        | 0.793–2.064                  | 0.313                        |
| ≥5.0 ng/mL                     | 60                           | 18.5                         | 0.053                        | 1.277                        | 0.917–1.778                  | 0.148                        | 34                           | 27.3                         | 0.459                        |                              |                              |                              |
| **Preoperative CA19-9**        |                              |                              |                              |                              |                              |                              |                              |                              |                              |                              |                              |                              |                              |
| <37.0 U/mL                     | 177                          | 39.9                         | <0.001                       | 1.621                        | 1.199–2.192                  | 0.002                        | 70                           | 35.6                         | 0.120                        |                              |                              |                              |
| ≥37.0 U/mL                     | 307                          | 14.2                         | <0.001                       | 1.621                        | 1.199–2.192                  | 0.002                        | 139                          | 26.8                         | 0.120                        |                              |                              |                              |

PHU—tumors in the pancreas head or uncinated process; PBT—tumors in the pancreas body and tail; 5YSR—year survival rate; HR—hazard ratio; CI—confidence interval; The variables which p-value was less than 0.1 in univariate analysis were included in the multivariate analysis.
3. Discussion

The AJCC staging system was revised for the eighth time since its first edition in 2018. Its validity was demonstrated in several studies [5–7]. The AJCC staging system always considered pancreatic cancers in terms of the whole pancreas, without dividing the pancreas according to the location, since pancreatic cancers in the head/uncinate process and those in the body/tail share the same prognosis and have comparable tumor biology. However, pancreatic cancer is usually treated according to the location. Many studies investigated pancreatic cancers separately according to the location [2,4,8–12]. Furthermore, many studies investigated whether the subjects underwent distal pancreatectomy or pancreatoduodenectomy, which is a reflection of the location of the tumor [13–16]. Pancreatic cancer is often not looked at somewhat differently. In this light, it must be clarified whether pancreatic head cancers and pancreatic body or tail cancers have comparable outcomes and oncological behaviors.

Traditionally, pancreatic cancers in the body/tail are believed to have a worse prognosis compared to pancreatic head cancers. This finding was supported by several studies [2,8–10,17] and it was also reproduced in the present study. The 5-year survival percentages and the median survival durations were significantly better for the PHU group than for the PBT group, in all pancreatic cancers, regardless of their resectability. The poor outcome of pancreatic cancers in the body/tail is usually explained by their late detection.

While a pancreatic head cancer might cause obstructive jaundice as the tumor progresses, patients with pancreatic body/tail cancers do not show symptoms until the tumor size increases sufficiently to cause abdominal pain and colon obstruction. In the present cohort, the tumor size measured on the cross-sectional images was significantly greater in the PBT group. Larger tumors reduce the possibility of resectability, which is also reflected in the results of the present study. In the present study, 36.6% of the pancreatic head cancers were deemed resectable, while only 18.2% of the pancreatic body/tail cancers were deemed resectable.

Late detection of the pancreatic body and tail tumors allows them to grow, reducing their resectability. It also increases the possibility of systemic involvement. Other studies that investigated pancreatic cancers according to their locations showed that pancreatic body and tail cancers often present with distant metastases at the time of diagnosis [2,11]. The present study also confirmed a higher proportion of systemic spread at presentation (54.7% in the body/tail cancers and 31.0% in the head/uncinate region cancers).

A completely opposite set of findings was observed when only the resected cases were considered. In the resected cases, pancreatic cancers in the head/uncinate region demonstrated significantly worse survival than those in the body/tail region. Many studies found similar results in resectable pancreatic cancers in the head/uncinate regions [11,12,18], while some studies failed to show worse results for the head region when compared to the body/tail region [9,10,13–16,19]. However, none of these studies showed significantly worse outcomes in pancreatic body/tail cancers [12].

Studies that demonstrated comparable outcomes between resectable pancreatic cancers in the head and those in the body/tail should be noted for their study population. Studies conducted by Sohn et al. [13], Wade et al. [14], and Brennan et al. [19] published in 2000, 1995, and 1996, respectively, are considered the historic ones. Their study populations were collected from as early as 1984 and up to 1999. During this period, safety and oncological feasibility of pancreatic cancer surgery was more of an issue. Furthermore, adjuvant treatment, which is currently an important part of pancreatic cancer treatment, was not established. The studies from the late 2000s and the 2010s had similar problems regarding patient populations as those associated with the patient populations from the 1980s and the 1990s, even though they included more recent cohorts [9,15,16].

Only one study that included 351 patients showed superior outcomes in the resected pancreatic head cancers, when compared with the resected body/tail cancers [4]. The median survivals of patients with pancreatic head cancers and of those with pancreatic body/tail cancers were 16 and 11 months, respectively. This rather poor survival outcome in patients with resected tumors limited the value of this study. All the other studies reported comparable or superior outcomes in resected pancreatic
body/tail cancers than in resected pancreatic head cancers. Therefore, based on the recent literature and the results of the present study, it could be safely concluded that resected pancreatic cancers in the body/tail region have better outcomes than those in the head region. As such is the case, resection of pancreatic body/tail cancers should not be discouraged because of the poor overall prognosis, but rather should be attempted, whenever deemed resectable.

When analyzed according to the T stages, significant difference was observed in survival between the groups for T2 tumors. The PHU group showed worse outcomes than the PBT group for T1 tumors, but the difference was not significant. This finding might perhaps be attributed to small-sized subgroups. Thus, earlier T categories (T1 and T2) demonstrated significantly worse median survival and 5-year survival (24 months and 21.8%) in the PHU group than in the PBT group (34 months and 37.2%) (p = 0.003). Meng et al. [12] also found that resected pancreatic head cancers had worse outcomes in the earlier T stages, but significant difference was observed only for the T1 stage.

When stratified according to the N stage and the prognostic groups, the survival rates were not significantly different. There was a tendency toward worse survival for pancreatic head/uncinate cancers in the N0 and LN metastasis groups. For the prognostic groups, pancreatic head/uncinate cancers in stages IB, IIB, and III tended to have worse survival. Re-evaluation using a larger cohort or meta-analysis might clarify the effect of cancer location in each stratified analysis.

There were varying results regarding whether the location of pancreatic cancer was an independent prognostic factor. The present study found that cancer location was not an independent risk factor (head vs. body/tail: HR 1.174, CI 0.932–1.478, p = 0.173). Similarly, Ruess et al. [16] and van Erning et al. [10] did not identify location as an independent risk factor. Several other studies suggested that location was a significant risk factor [2,4,9,11,12,18]. Therefore, the status of cancer location as an independent prognostic factor is still controversial and needs further high-level evidence.

The difference in survival outcomes between the locations might be due to plain anatomical differences causing symptoms at different time intervals. There might be additional differences in tumor biology and behavior. To investigate the differences in tumor biology and behavior, clinicopathological features of pancreatic cancers in the head/uncinate process and cancers in the body/tail region were analyzed and compared. Some differences were present, but common risk factors were also observed. Hence, the results are unclear and a definite conclusion cannot be obtained.

Additionally, differences on genetic and molecular levels should also be considered. The present study did not examine this aspect, but previous studies examined genetic profiles. Birnbaum et al. [20] found differences in 334-gene expression signature between tumors in the head and those in the body/tail. Dreyer et al. [8] reported that tumors might have different molecular pathology, according to their location and the body/tail tumors are enriched with gene programs involved in tumor invasion, epithelial-to-mesenchymal transition, and poor antitumor immune response. This is an important area of research, as the differences on genetic and molecular levels might open a new era of more tailored treatment approaches, according to the location.

The present study had some limitations. The study was retrospective in nature. In addition, the overall patient dataset was acquired through a clinical data warehouse. Hence, more specific variables could not be retrieved in detail. As the present study was performed at a tertiary hospital, many patients visited after being diagnosed at other primary or secondary hospitals, which might have resulted in bias regarding the date of diagnosis. The study population was insufficient for subgroup analyses after stratification.

4. Materials and Methods

4.1. Study Design

The study was approved by the ethical committee of the Institutional Review Board of Seoul National University Hospital (IRB No. H-1902-012-1006). Seoul National University Hospital’s Clinical
Data Warehouse was searched for patients who were diagnosed with pancreatic ductal adenocarcinoma between 2005 and 2016. A retrospective cohort study was performed.

This research was supported by the Collaborative Genome Program for Fostering New Post-Genome Industry of the National Research Foundation funded by the Ministry of Science and ICT (NRF-2017M3C9A5031591), and by a grant from the Korean Health Technology R and D Project, Ministry of Health and Welfare, Republic of Korea (HI14C2640).

4.2. Patient Selection

After the identification of patients with pancreatic cancer from the database, those with multiple tumors in both the head and the body/tail were excluded. Patients who had tumors across the junction of the head and the body were also excluded, as grouping according to the location was ambiguous in these tumors. Data regarding age, sex, tumor location, tumor size on radiological images, clinical feature (T) classification, and classification based on resectability were collected.

Further subgroup analysis was performed for patients who underwent resection with curative intent. Among all patients, 646 patients who underwent resection of pancreatic cancer with curative intent were examined. Patients who underwent only palliative operation including bypass or open biopsy were excluded. Since neoadjuvant treatment can alter the final pathological staging, patients who received neoadjuvant therapy were also excluded. Detailed information about the demographic and clinicopathological factors of these patients was obtained through a thorough review of their electronic medical records.

4.3. Determination of Tumor Location and Clinical T Staging

Computed tomography (CT) or magnetic resonance imaging (MRI) records of all patients were reviewed. An imaginary tangential line over the left border of the superior mesenteric vein or the portal vein was drawn on the CT image. The head/uncinate pancreatic cancer group (PHU) was defined as patients with tumors on the right side of this line. The body/tail pancreatic cancer group (PBT) was defined as patients with tumors on the left side of this line.

Clinical T staging was performed according to the AJCC staging system (edition 8) for pancreatic cancer. Tumor size was measured using CT and MRI.

4.4. Definition of Survival and Data Collection

Overall survival was used for the analysis. It was defined as the interval between the date of diagnosis and the date of death or the last follow-up. Survival status was acquired from the Ministry of Interior and Safety of Korea. Patients who were alive on 20 February 2019 were censored.

4.5. Statistical Analysis

Fisher’s exact test and chi-squared test were used to compare categorical variables and unpaired two-sided Student’s t-test was used to compare continuous variables between patients with tumors located in the head/uncinate process and patients with tumors in the body/tail. The Kaplan-Meier method with log-rank test was used for survival analysis. Cox regression test was used for the univariate and the multivariate analyses. A p-value < 0.050 was considered to be statistically significant. IBM SPSS statistics for Windows version 24 (IBM Corp., Armonk, NY, USA) was used for statistical analyses.

5. Conclusions

The prognosis of pancreatic cancers differed according to the location of the tumors. Pancreatic head cancers showed a better overall prognosis than pancreatic body/tail cancers, which might be related to a higher proportion of systemic involvement in the latter. On the contrary, resected pancreatic head cancers showed a worse prognosis than resected pancreatic body/tail cancers, especially in the earlier T stages. Tumor location was not an independent risk factor for pancreatic cancer.
Supplementary Materials: The following are available online at http://www.mdpi.com/2072-6694/12/8/2036/s1.

Figure S1: The survival curves of pancreas head/uncinate cancer and pancreas body cancer in terms of the prognostic group, according to the eighth edition of AJCC cancer staging system.

Author Contributions: Conceptualization, W.K. and J.-Y.J.; Data curation, M.L., W.K., H.K. and Y.H.; Formal analysis, M.L.; Funding acquisition, Y.H.; Investigation, M.L., J.S.K. and Y.J.C.; Methodology, Y.B.; Project administration, W.K., H.K. and J.-Y.J.; Resources, J.S.K. and Y.J.C.; Supervision, W.K.; Validation, W.K., H.K., Y.B., Y.H. and J.-Y.J.; Writing—original draft, M.L.; Writing—review & editing, M.L., W.K., Y.B. and J.-Y.J. All authors have read and agreed to the published version of the manuscript.

Funding: This study was supported by the Collaborative Genome Program for Fostering New Post-Genome Industry of the National Research Foundation, funded by the Ministry of Science and ICT (NRF-2017M3C9A5031591) and the Korean Health Technology R&D Project, Ministry of Health and Welfare (HI14C2640), Korea.

Conflicts of Interest: The authors declare no conflict of interest.

References
1. Ilic, M.; Ilic, I. Epidemiology of pancreatic cancer. World J. Gastroenterol. 2016, 22, 9694–9705. [CrossRef] [PubMed]
2. Lau, M.K.; Davila, J.A.; Shaib, Y.H. Incidence and survival of pancreatic head and body and tail cancers: A population-based study in the United States. Pancreas 2010, 39, 458–462. [CrossRef] [PubMed]
3. Sener, S.F.; Fremgen, A.; Menck, H.R.; Winchester, D.P. Pancreatic cancer: A report of treatment and survival trends for 100,313 patients diagnosed from 1985–1995, using the National Cancer Database. J. Am. Coll. Surg. 1999, 189, 1–7. [CrossRef]
4. Sheng, W.W.; Dong, M.; Wang, G.S.; Shi, X.Y.; Gao, W.; Wang, K.W.; Song, H.; Shi, G.; Tan, X.D. The diversity between curatively resected pancreatic head and body-tail cancers based on the 8th edition of AJCC staging system: A multicenter cohort study. BMC Cancer 2019, 19, 981. [CrossRef] [PubMed]
5. Van Roessel, S.; Kasumova, G.G.; Verheij, J.; Najarian, R.M.; Maggino, L.; de Pastena, M.; Malleo, G.; Marchegiani, G.; Salvia, R.; Ng, S.C.; et al. International Validation of the Eighth Edition of the American Joint Committee on Cancer (AJCC) TNM Staging System in Patients with Resected Pancreatic Cancer. JAMA Surg. 2018, 153, e183617. [CrossRef] [PubMed]
6. Allen, P.J.; Kuk, D.; Castillo, C.F.; Basturk, O.; Wolfgang, C.L.; Cameron, J.L.; Lillemoe, K.D.; Ferrone, C.R.; Morales-Oyarvide, V.; He, J.; et al. Multi-institutional Validation Study of the American Joint Commission on Cancer (8th Edition) Changes for T and N Staging in Patients with Pancreatic Adenocarcinoma. Ann. Surg. 2017, 265, 185–191. [CrossRef] [PubMed]
7. Kwon, W.; He, J.; Higuchi, R.; Son, D.; Lee, S.Y.; Kim, J.; Kim, H.; Kim, S.W.; Wolfgang, C.L.; Cameron, J.L.; et al. Multinational validation of the American Joint Committee on Cancer 8th edition pancreatic cancer staging system in a pancreas head cancer cohort. J. Hepatobiliary Pancreat. Sci. 2018, 25, 418–427. [CrossRef] [PubMed]
8. Dreyer, S.B.; Jamieson, N.B.; Upstill-Goddard, R.; Bailey, P.J.; McKay, C.J.; Australian Pancreatic Cancer Genome Initiative; Biankin, A.V.; Chang, D.K. Defining the molecular pathology of pancreatic body and tail adenocarcinoma. Br. J. Surg. 2018, 105, e183–e191. [CrossRef] [PubMed]
9. Artinyan, A.; Soriano, P.A.; Prendergast, C.; Low, T.; Ellenhorn, J.D.; Kim, J. The anatomic location of pancreatic cancer is a prognostic factor for survival. HPB (Oxford) 2008, 10, 371–376. [CrossRef] [PubMed]
10. van Erning, F.N.; Mackay, T.M.; van der Geest, L.G.M.; Groot Koerkamp, B.; van Laarhoven, H.W.M.; Bonsing, B.A.; Wilming, J.W.; van Santvoort, H.C.; de Vos-Geelen, J.; van Eijck, C.H.; et al. Association of the location of pancreatic ductal adenocarcinoma (head, body, tail) with tumor stage, treatment, and survival: A population-based analysis. Acta Oncol. 2018, 57, 1655–1662. [CrossRef] [PubMed]
11. Winer, L.K.; Dhar, V.K.; Wima, K.; Morris, M.C.; Lee, T.C.; Shah, S.A.; Ahmad, S.A.; Patel, S.H. The Impact of Tumor Location on Resection and Survival for Pancreatic Ductal Adenocarcinoma. J. Surg. Res. 2019, 239, 60–66. [CrossRef]
12. Meng, Z.; Cao, M.; Zhang, Y.; Liu, Z.; Wu, S.; Wu, H. Tumor location as an indicator of survival in T1 resectable pancreatic ductal adenocarcinoma: A propensity score-matched analysis. BMC Gastroenterol. 2019, 19, 59. [CrossRef]
13. Sohn, T.A.; Yeo, C.J.; Cameron, J.L.; Koniaris, L.; Kaushal, S.; Abrams, R.A.; Sauter, P.K.; Coleman, J.; Hruban, R.H.; Lillemoe, K.D. Resected adenocarcinoma of the pancreas-616 patients: Results, outcomes, and prognostic indicators. *J. Gastrointest. Surg.* 2000, 4, 567–579. [CrossRef]

14. Wade, T.P.; Virgo, K.S.; Johnson, F.E. Distal pancreatectomy for cancer: Results in U.S. Department of Veterans Affairs hospitals, 1987–1991. *Pancreas* 1995, 11, 341–344. [CrossRef]

15. Toomey, P.; Hernandez, J.; Golkar, F.; Ross, S.; Luberice, K.; Rosemurgy, A. Pancreatic adenocarcinoma: Complete tumor extirpation improves survival benefit despite larger tumors for patients who undergo distal pancreatectomy and splenectomy. *J. Gastrointest. Surg.* 2012, 16, 376–381. [CrossRef] [PubMed]

16. Ruess, D.A.; Makowiec, F.; Chikhladze, S.; Sick, O.; Riediger, H.; Hopt, U.T.; Wittel, U.A. The prognostic influence of intrapancreatic tumor location on survival after resection of pancreatic ductal adenocarcinoma. *BMC Surg.* 2015, 15, 123. [CrossRef] [PubMed]

17. Watanabe, I.; Sasaki, S.; Konishi, M.; Nakagohri, T.; Inoue, K.; Oda, T.; Kinoshita, T. Onset symptoms and tumor locations as prognostic factors of pancreatic cancer. *Pancreas* 2004, 28, 160–165. [CrossRef] [PubMed]

18. Zheng, Z.; Wang, M.; Tan, C.; Chen, Y.; Ping, J.; Wang, R.; Liu, X. Disparities in survival by stage after surgery between pancreatic head and body/tail in patients with nonmetastatic pancreatic cancer. *PLoS ONE* 2019, 14, e0226726. [CrossRef] [PubMed]

19. Brennan, M.F.; Moccia, R.D.; Klimstra, D. Management of adenocarcinoma of the body and tail of the pancreas. *Ann. Surg.* 1996, 223, 506–511. [CrossRef] [PubMed]

20. Birnbaum, D.J.; Bertucci, F.; Finetti, P.; Birnbaum, D.; Mamessier, E. Head and Body/Tail Pancreatic Carcinomas Are Not the Same Tumors. *Cancers* 2019, 11, 497. [CrossRef] [PubMed]

© 2020 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (http://creativecommons.org/licenses/by/4.0/).