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Permalink

https://escholarship.org/uc/item/4xb742jq

Journal

Journal of the American College of Surgeons, 233(1)

ISSN

1072-7515

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Publication Date

2021-07-01

DOI

10.1016/j.jamcollsurg.2021.02.014

Peer reviewed

Is Improved Survival in Early-Stage Pancreatic Cancer Worth the Extra Cost at High-Volume Centers?

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Abstract

BACKGROUND: Volume of operative cases may be an important factor associated with improved survival for early-stage pancreatic cancer. Most high-volume pancreatic centers are also academic institutions, which have been associated with additional healthcare costs. We hypothesized that at high-volume centers, the value of the extra survival outweighs the extra cost.

STUDY DESIGN: This retrospective cohort study used data from the California Cancer Registry linked to the Office of Statewide Health Planning and Development database from January 1, 2004 through December 31, 2012. Stage I-II pancreatic cancer patients who underwent resection were included. Multivariable analyses estimated overall survival and 30-day costs at low- vs high-volume pancreatic surgery centers. The incremental cost-effectiveness ratio (ICER) and incremental net benefit (INB) were estimated, and statistical uncertainty was characterized using net benefit regression.

RESULTS: Of 2,786 patients, 46.5% were treated at high-volume centers and 53.5% at low-volume centers. There was a 0.45-year (5.4 months) survival benefit (95% CI 0.21–0.69) and a

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$7,884 extra cost associated with receiving surgery at high-volume centers (95% CI $4,074–$11,694). The ICER was $17,529 for an additional year of survival (95% CI $7,997–$40,616). For decision-makers willing to pay more than $20,000 for an additional year of life, high-volume centers appear cost-effective.

CONCLUSIONS: Although healthcare costs were greater at high-volume centers, patients undergoing pancreatic surgery at high-volume centers experienced a survival benefit (5.4 months). The extra cost of $17,529 per additional year is quite modest for improved survival and is economically attractive by many oncology standards.

Cost-effectiveness analyses in surgery have become increasingly popular, especially given the exorbitant healthcare expenditures in the United States compared with all other countries in the Organization for Economic Cooperation and Development.[1,2] Although the United States devoted 17.7% of its economy to healthcare in 2018, this spending does not necessarily result in improvements in care.[2–7] For this reason, discussing value in healthcare has become essential. Cost-effectiveness analysis provides a framework for considering value by describing an intervention using the ratio of extra costs in relation to extra health outcome.[8] The incremental cost-effectiveness ratio (ICER) estimates the ratio of the extra cost to the extra effect ($\Delta C/\Delta E$) and helps quantify the trade-off between resources used and outcomes gained.[9]

Pancreatic cancer surgery is important to study because of its complex care and poor overall survival. In 2020, an estimated 57,600 new cases were diagnosed in the United States, and 47,050 people died from the disease.[10,11] Currently, pancreatic cancer is the fourth leading cause of cancer-related deaths in the United States; by the year 2030, it is projected to become the second leading cause.[12] The high morbidity and mortality associated with pancreatic cancer create a prime opportunity to study clinical outcomes and their associated costs.

Numerous studies have demonstrated a strong and well-established association between high surgical volume and improved perioperative outcomes.[13–23] Although some follow-up studies have examined the impact of high-volume on costs and value for pancreatic cancer, no cost-effectiveness analyses comparing survival at high- and low-volume centers have been reported.[24–26] Considering that the 5-year survival rate for all pancreatic cancer is 10%, measures that improve survival, such as care at high-volume centers, are important to patients.[10] However, this survival benefit may have an associated cost. In general, cancer and surgical care in the United States is very expensive; predictive models projected that aggregate cancer care would reach $158 billion dollars in 2020 and that aggregate noncancer and cancer-related surgical expenditures will grow to $912 billion by the year 2025.[27,28] Furthermore, the direct costs of resectable locoregional pancreatic cancer are at least $134,700 per patient, with an estimated $51,000 tied to surgical expenditures.[29] In light of these findings, we performed a cost-effectiveness analysis examining the extra costs of improved survival at high- vs low-volume centers performing pancreatic cancer surgery. We hypothesized that the value of the extra survival would outweigh the extra costs.

METHODS

This retrospective cohort study used data from the California Cancer Registry linked to the Office of Statewide Health Planning and Development (OSHPD) database for patients diagnosed with pancreatic adenocarcinoma between January 1, 2004 and December 31, 2012, with associated 5-year survival follow-up (ie, patient follow-up through December 2016). The research protocol was approved by the institutional review board of the University of California, Davis, and the California Health and Human Services Agency Committee for the Protection of Human Subjects with a waiver of consent granted for use of deidentified data.

A total of 8,723 patients with stages I to II pancreatic adenocarcinoma were identified based on the *International Classification of Diseases for Oncology, Third Revision*, codes for site and histology. Patients who did not undergo a pancreatic resection (n = 5,207) or with missing costs data (n = 730) were excluded. The final cohort consisted of 2,786 patients with stages I to II pancreatic cancer, who underwent resection across 157 licensed hospitals in California.

Information regarding patient age, sex, race, tumor grade, tumor and node categories, composite American Joint Committee on Cancer stage (seventh edition), chemotherapy, and radiotherapy were abstracted from the California Cancer Registry. Pancreatic surgical resections were identified from the linked OSHPD files based on *International Classification of Diseases, Ninth Revision* (ICD-9) codes.[26] The Elixhauser comorbidity index was used to measure risk associated with comorbid health conditions and created using ICD-9 codes. This validated method for creating a weighted index score to represent the severity of comorbidity burden ranges from −11 to 62, with higher scores indicating greater comorbidities.[30–33] Perioperative complications were derived from ICD-9 codes for the index hospitalization and readmissions within 30 days of discharge, and included standard complications (pulmonary failure, pneumonia, myocardial infarction, cardiac arrest, pulmonary embolism, deep vein thrombosis, gastrointestinal tract hemorrhage, surgical site and organ space infections, systemic shock, acute kidney injury, delayed gastric emptying, gastrointestinal or enterocutaneous fistula, and bile leak).[25] Pancreatic fistula was not included as the ICD-9 lacks a specific code for this complication.

High-volume pancreatic surgery centers were defined as centers that performed at least 20 pancreatic resections annually based on previous research showing improved mortality at this cutoff.[34–36] Of 157 hospitals, 8 met the criteria for high-volume centers. Costs were estimated from charges for the index surgical hospitalization and hospital readmissions within 30 days of discharge. As previously described, charges were multiplied by the ratio of hospital-specific cost to charge, adjusted for geographic variation using the wage index, and adjusted for inflation using the Health Care Price Index.[26,37] Survival time was defined as months alive from the date of the pancreatic cancer diagnosis until death or the end of the study period, whichever arrived first. Of 2,786 patients, 464 (16.7%) were alive or presumed alive.

Statistical analysis

Multivariable linear regression analyses estimated overall survival and 30-day costs for patients receiving care at low- vs high-volume pancreatic surgery centers, while controlling for demographic and clinicopathologic differences. The incremental cost-effectiveness ratio (ICER) was then estimated from the results using the coefficient estimate on the high-volume indicator variable. Confidence intervals for the ICER estimate were computed using Fieller's Theorem. The ICER estimate and 95% CI were then verified visually by inspecting Figure 1.[38,39]

Incremental net benefit (INB) regression estimates were computed using different willingness-to-pay (WTP) values to assess the cost-effectiveness of high-volume centers compared to low-volume centers.[9,39] Multiple net benefit regression results produced estimates of the INB adjusted for the same variables as the cost and effectiveness equations: age, sex, race, socioeconomic status, Elixhauser comorbidity index score, grade, T-category, N-category, stage, chemotherapy, radiotherapy, pancreatic resection type, 30-day complications, 30-day readmissions, and hospital type. INB estimates greater than zero were evidence of high-volume centers' extra benefit, outweighing their extra cost compared with low-volume centers. WTP describes the amount that a decision-maker for health policy or insurance coverage is willing to pay for a benefit; these values were varied from $0 per year of life up to $50,000 per year of life. The INB estimate and its 95% confidence interval were plotted on an INB by WTP graph (Fig. 1). The uncertainty results were summarized in a cost-effectiveness acceptability curve (CEAC) using net benefit regression.[40]

Additionally, 2 subgroup analyses were performed to assess the robustness of our findings by accounting for characteristics that could be strong confounders. The first subgroup analysis excluded 114 patients who died within 30 days of surgery to account for potential confounding related to the management of severe postoperative complications that could influence cost and survival. The second subgroup analysis stratified patients into Stage IA/IB/IIA or Stage IIB disease to examine possible confounding by nodal involvement. A total of 7 patients had regional lymph nodes that could not be evaluated (NX) and were excluded from this analysis. Of the remaining 2,779 patients, 1,053 (37.9%) were classified as Stage IA/IB/IIA and 1,726 (62.1%) as Stage IIB. Each of the subgroup analyses used multivariable linear regression models to estimate overall survival and 30-day costs for patients receiving care at low- vs high-volume pancreatic surgery centers; the ICER was then estimated from the results. The regression models were adjusted for the same confounding variables as the original model; however, for the analysis stratified by nodal involvement, tumor and nodal stage were removed as covariates due to collinearity. All analyses were performed using Stata, version 15.1 (StataCorp).[38]

RESULTS

Demographic and clinicopathologic characteristics for patients treated with surgical resection for stage I-II pancreatic cancer are shown in Table 1. Of 2,786 patients, the mean age was 67 (±10.7) years, 1,395 (50%) were male, and 2,308 (82.8%) were White. The mean Elixhauser comorbidity index score was 13.9 (±8.9), with possible ranges from −11 to 62. Most patients presented with moderately differentiated (1,373 [49.3%]) and larger

tumors (T3 = 2,147 [77.1%]), with presence of nodal disease (1,725 [61.9%]). Receipt of postoperative chemotherapy was most common (1,238 [44.4%]) and the majority of patients did not receive radiotherapy (874 [31.4%]). Pancreaticoduodenectomy (2,207 [79.2%]) was the type of surgical resection most frequently performed. Development of at least 1 complication within 30 days of discharge was common (1,037 [37.2%]), as were hospital readmissions within 30 days (565 [20.3%]). The median hospital length of stay was 12 days (interquartile range [IQR] 9–18 days) after the index procedure. The majority of patients were treated at low-volume pancreatic surgery centers (1,489 [53.4%]), while 1,297 (46.6%) were treated at 1 of the 8 high-volume pancreatic surgery centers. Additionally, 1,127 patients (40.5%) received care at a National Cancer Institute-designated cancer center and 1,428 (51.3%) were treated at a teaching hospital.

Data that reflect or impact costs are reported as the arithmetic mean despite skewed distributions, because other measures (such as median) do not provide an accurate estimate of total cost.[41,42] Mean surgical hospitalization costs for the index procedure and any readmissions within 30 days of discharge were $60,939 (±$56,779). The mean 30-day costs at low- and high-volume centers were $59,525 (±$54,993) and $62,561 (±$58,742), respectively. The overall mean survival was 2.3 years (±2.1 years), with a mean survival time at low- and high-volume centers of 2.2 years (±2.1 years) and 2.5 years (±2.2 years), respectively. By the end of the study period, the majority of patients had died due to pancreatic cancer (2,020 [72.5%]), while 247 (9.0%) died from other causes, 55 (2.0%) died from unknown causes, and 464 (16.7%) were alive or presumed alive.

Table 2 shows the results of the unadjusted and adjusted multivariable model estimates for costs, survival time, and the ICER when comparing low- to high-volume pancreatic surgery hospitals. Without adjustment for potentially cofounding variables, the cost differential for receiving treatment at a high-volume surgery center was $3,036 (95% CI −$1,211–$7,283) with a survival benefit of 0.33 years (95% CI 0.18–0.49) or 4 months. The unadjusted ICER describing the cost of this survival benefit was $9,082 per life-year (95% CI cost saving −$28,887). After multivariate adjustment for demographic, clinicopathologic, and facility differences between patients, the cost differential for care at high-volume centers was $7,884 (95% CI $4,074–$11,694), and the survival benefit was 0.45 years (95% CI 0.21–0.69) or 5.4 months. The adjusted ICER for the cost of this survival benefit was $17,529 per life-year (95% CI $7,997–$40,616).

Multivariable estimation of the INB for different WTP values is shown in Table 3. When a decision-maker's WTP is $0, the INB estimate is −$7,884 (95% CI −$11,694–$4,074). Given that the INB estimate is less than 0, the survival benefit does not outweigh the extra costs when a decision-maker is willing to spend $0 for this additional health outcome. As illustrated in Figure 1, once the WTP surpasses $20,000, the INB estimates are greater than zero, indicating that the extra survival benefit outweighs the extra costs. The cost-effectiveness acceptability curve (CEAC) shown in Figure 2 summarizes the probability that high-volume pancreatic surgery centers are cost-effective for different WTP values. These WTP values are a range of dollar amounts that decision-makers who decide health policy or insurance coverage may be willing to spend for improved survival. At WTP of $20,000, the probability of cost-effectiveness is approximately 60%. As WTP increases to $30,000, the

probability of cost-effectiveness increases to greater than 80% and nears 100% at WTP > $50,000. Given the probability of 100% cost-effectiveness beyond $50,000, additional WTP values were unnecessary.

For the subgroup analysis excluding patients who died in the immediate postoperative period (n = 114), the extra cost estimate for high-volume care was $7,538, which is unchanged from the original model. The new survival benefit estimate was 0.41 years (4.9 months), compared with the original regression estimate of 0.45 years (5.4 months). The ICER estimate for improved survival at high-volume centers after the exclusion of early deaths was $19,229 compared with the original estimate of $17,529.

Additional subgroup analysis stratifying Stage IA/IB/IIA (n = 1,053) and Stage IIB (n = 1,726) disease demonstrated that Stage IA/IB/IIA patients had a survival benefit of 0.48 year (5.8 months) by receiving care at high-volume centers, with an associated extra cost of $7,571 and an ICER estimate of $15,744. Stage IIB patients had a survival benefit of 0.35 years (4.1 months) when receiving care at high-volume centers. The associated extra cost was $8,435 for this survival benefit, and the ICER estimate was $24,795 per life-year.

DISCUSSION

In this cost-effectiveness analysis evaluating patients with early-stage disease in California, the 5.4-month survival benefit at high- vs low-volume centers was associated with an additional cost of $7,884. The ICER quantifies the extra cost for an additional year of life at $17,529. Additional analysis demonstrated that when decision-makers are willing to spend $20,000 or more, the survival benefit from receiving care at a high-volume center appears cost-effective. When excluding patients who died within 30 days of surgery, the ICER estimate was $19,229 per life-year, which is similar to the original estimate including all patients. This finding suggests that deaths in the immediate postoperative period do not greatly influence the cost-effectiveness of receiving care at high-volume surgery centers for pancreatic cancer. Additionally, when stratifying patients by nodal involvement, the ICER estimate for survival at high-volume centers was $15,744 per life-year for Stage IA/IB/IIA and $24,795 per life-year for Stage IIB. These stratified ICER estimates only slightly bracket the original estimate, with modest increased cost-effectiveness for patients with Stage IA/IB/IIA cancer.

For cost-effectiveness analyses to guide healthcare decisions and policy, one must also consider the willingness-to-pay (WTP) in terms of life expectancy, or the amount that a decision-maker would pay to extend life. The empirical value varies widely depending on the type of intervention and the particular disease. For many cost-effectiveness experts, interventions within the realm of $50,000 per life-year are reasonable for payers, while very low C/ E ratios of less than $20,000 are considered cost-effective, which is where our analysis for pancreatic cancer landed.[1,8,43] More specifically, Lakdawalla and colleagues[44] studied a patient's WTP for an additional year of life for certain cancers. For pancreatic cancer, patients themselves were willing to pay $40,644 annually for survival gains, which is among the largest values calculated in this study. However, some patients with pancreatic cancer were willing to pay nearly 80% of their full income for survival gains, despite the

average survival improvement of less than 1 year. The rationale for a very high WTP for pancreatic cancer may be attributed to the unusually high value placed upon incremental survival gains by terminally ill patients.[45]

It is critical to contextualize our claims of cost-effectiveness against other observations in cancer. Aguiar and associates[46] modeled the cost-effectiveness of osimertinib as a first-line therapy for patients with locally advanced or metastatic non-small cell lung cancer with EFGR mutations. The resulting ICER estimates for osimertinib vs erlotinib, gefitinib, and afatinib were all greater than $200,000 in the United States. When considering a high WTP threshold of $180,000 (which is much higher than what we used for interpretation), osimertinib was found not to be a cost-effective first-line therapy. By contrast, the ICER estimates for erlotinib, gefitinib, and afatinib as first-line therapies were all less than $140,000 and below the $180,000 WTP threshold. Additionally, Edwards and coworkers[47] performed a cost-effectiveness analysis of patients with advanced or metastatic renal cell carcinoma, who were previously treated with VEGF-targeted therapy. The authors estimated the ICER of everolimus vs best supportive care to be £45,000 (approx. $61,000 in 2018 USD) per quality-adjusted life-year (QALY), which is considered cost-effective at the British threshold of £50,000. Other treatments for second-line treatment of renal cell carcinoma such as axitinib, nivolumab, and cabozantinib were deemed ineffective or prohibitively expensive compared to everolimus, and therefore, were not cost-effective therapies. Furthermore, Huxley and coauthors[48] studied the cost-effectiveness of the EFGR-specific therapies cetuximab and panitumumab as first-line treatments for patients with RAS WT untreated metastatic colorectal cancer. When comparing the addition of each of these targeted therapies to FOLFOX vs FOLFOX alone, the ICER estimate for cetuximab was £104,205 (approx. $134,000 in 2017 USD) per QALY and £204,103 (approx. $263,000 in 2017 USD) per QALY for panitumumab. Although clinically beneficial, use of these therapies as first-line agents was deemed to be a poor value and not cost-effective at even very high WTP thresholds exceeding £100,000. All of the preceding studies are relevant and recent examples that illustrate the high costs and high WTP values for advanced cancers. The high costs of oncologic care are especially apparent when considering the use of novel therapies as first-line treatment for locally advanced or metastatic disease. By contrast, the ICER estimate of $17,529 presented in our work is extremely modest and cost-effective, even at very conservative WTP values. Contextualizing the costs of oncology care helps to demonstrate that our ICER estimate for improved survival for patients with stage I-II pancreatic cancer treated at high- vs low-volume centers is very economically attractive.

Our study expands on previous research demonstrating strong and consistent associations between high-volume surgical centers and improved perioperative outcomes.[13–23] However, when considering marginal improvements in diseases with substantial morbidity and mortality, it is important to consider the cost and value of those improvements. Using Surveillance, Epidemiology, and End Results-Medicare data, Nathan and colleagues[24] studied the relationship between hospital volume and cost for several cancer operations, including pancreatic resections. The authors found improved perioperative outcomes with higher volume, but no association between hospital volume and costs. Instead, increased complication rates were greatly associated with higher costs. Their findings are corroborated by Bateni and associates,[25] who used the University HealthSystems Consortium database

(aka Vizient) and found significant improvements in adverse events when comparing high- and low-volume pancreatic cancer surgery centers, without a significant difference in mean costs. Similarly, the authors state that complications significantly influence total costs and there was a small magnitude of difference in the complication rates in their study cohort. Each of these previous studies demonstrates that the improved perioperative outcomes at high-volume centers are not necessarily more costly. However, lack of a significant cost differential between high- and low-volume centers does not necessary mean that high-volume care is more valuable. In fact, a recent study using the California Cancer Registry, found that high-volume hospitals performing pancreatic resections were, indeed, not associated with greater value.[26]

Our study supports the need to further examine cost within the context of an outcome so that the relative value of healthcare interventions can be quantified. Cost-effectiveness analyses are essential to drive priorities in healthcare delivery by providing evidence to inform health policy decisions. Although there has been significant emphasis to direct patients to high-volume centers for optimal outcomes, it remains critical that the high-volume centers continue to examine how to achieve optimal outcomes in a cost-efficient manner.

Limitations

This study does have some important limitations inherent to the analysis of administrative data. First, the allocated study data are limited to the years 2004 to 2012, with 5 years of patient follow-up. Analysis of this timeframe does not include more recent data, which may reflect changes in practice patterns, including increased healthcare costs and modern chemotherapy regimens such as FOLFIRINOX and nab-paclitaxel/gemcitabine.[49–51] We expect that newer chemotherapy regimens would increase survival times, which is an important component of ICER in this analysis. However, aggregate healthcare costs have also increased in recent times, which would likely make the slight survival benefit of modern chemotherapy regimens negligible when calculating ICER. If anything, we would expect an updated ICER estimate to be greater than our estimate of $17,529 per life-year, owing to increased costs. Additional analysis with recent data is necessary to test this hypothesis. Another notable limitation is that patients were not randomized to treatment approaches. Despite multivariate analyses, our results may have been influenced by unmeasured confounders related to selection bias, as nuanced clinical, pathologic, or sociodemographic features may have affected patient or physician treatment decisions. Additionally, we were provided with only the total costs of each hospitalization from OSHPD, and we were unable to perform an analysis comparing itemized costs at high- vs low-volume centers such as operations, nursing care, medications, imaging, and laboratory studies. Regarding our patient population, OSHPD does not report data from Kaiser Permanente facilities; therefore, a significant portion of California patients could be excluded from our analysis. Furthermore, our analysis includes a small amount of censored data, which were unlikely to have affected the findings from our analysis.

CONCLUSIONS

In this retrospective study of early-stage pancreatic cancer patients in California undergoing resection, we examined the cost-effectiveness of improved survival at high-volume surgery centers. High-volume centers had a 5.4-month survival benefit that was associated with an additional cost of $7,884. The ICER for improved survival at high-volume centers was $17,529 per additional life-year, which is cost-effective for decision-makers willing to spend at least $20,000 for an extra year of life. Beyond WTP values of $50,000, the probability that high-volume centers are cost-effective is very high. When considering the poor overall survival for pancreatic cancer patients, an intervention that prolongs survival with an ICER estimate less than $20,000 is extremely economically attractive. Therefore, receipt of surgical care at high-volume centers for pancreatic cancer appears valuable and worth the extra cost. Future research should confirm the results and study the reasons for this finding.

Acknowledgments

Abbreviations and Acronyms

ICER	incremental cost-effectiveness ratio
INB	incremental net benefit
OSHPD	Office of Statewide Health Planning and Development
QALY	quality-adjusted life year
WTP	willingness to pay

REFERENCES

1. Finlayson SRG, Birkmeyer JD. Cost-effectiveness analysis in surgery. Surgery 1998;123:151–156. [PubMed: 9481400]

2. Anderson GF, Frogner BK. Health spending in OECD countries: obtaining value per dollar. Health Aff 2008;27:1718–1727.

3. Historical. Available at: https://www.cms.gov/Research-Statistics-Data-and-Systems/Statistics-Trends-and-Reports/NationalHealthExpendData/NationalHealthAccountsHistorical. Accessed October 15, 2020.

4. Obama B. United States Health Care Reform: Progress to Date and Next Steps. JAMA 2016;316:525–532. [PubMed: 27400401]

5. McGlynn EA, Asch SM, Adams J, et al. The quality of health care delivered to adults in the United States. N Engl J Med 2003;348:2635–2645. [PubMed: 12826639]

6. Fisher ES, Wennberg DE, Stukel TA, et al. The implications of regional variations in Medicare spending. Part 2: health outcomes and satisfaction with care. Ann Intern Med 2003;138:288–298. [PubMed: 12585826]

7. Explaining high health care spending in the United States: an international comparison of supply, utilization, prices, and quality. Available at: https://www.commonwealthfund.org/publications/issue-briefs/2012/may/explaining-high-health-care-spending-united-states-international. Accessed October 15, 2020.

8. Garber AM, Phelps CE. Economic foundations of cost-effectiveness analysis. J Health Econ 1997;16:1–31. [PubMed: 10167341]

9. Hoch JS. Improving efficiency and value in palliative care with net benefit regression: an introduction to a simple method for cost-effectiveness analysis with person-level data. J Pain Symptom Manage 2009;38:54–61. [PubMed: 19615627]

10. Cancer of the Pancreas - Cancer Stat Facts. Available at: https://seer.cancer.gov/statfacts/html/pancreas.html. Accessed October 15, 2020.

11. Cancer Facts & Figures 2020. Available at: https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/annual-cancer-facts-and-figures/2020/cancer-facts-and-figures-2020.pdf. Accessed March 6, 2021.

12. Rahib L, Smith BD, Aizenberg R, et al. Projecting cancer incidence and deaths to 2030: the unexpected burden of thyroid, liver, and pancreas cancers in the United States. Cancer Res 2014;74:2913–2921. [PubMed: 24840647]

13. Gordon TA, Burleyson GP, Tielsch JM, Cameron JL. The effects of regionalization on cost and outcome for one general high-risk surgical procedure. Ann Surg 1995;221:43–49. [PubMed: 7826160]

14. Lieberman MD, Kilburn H, Lindsey M, Brennan MF. Relation of perioperative deaths to hospital volume among patients undergoing pancreatic resection for malignancy. Ann Surg 1995;222:638–645. [PubMed: 7487211]

15. Rosemurgy AS, Bloomston M, Serafini FM, et al. Frequency with which surgeons undertake pancreaticoduodenectomy determines length of stay, hospital charges, and in-hospital mortality. J Gastrointest Surg 2001;5:21–26. [PubMed: 11309644]

16. Birkmeyer JD, Siewers AE, Finlayson EVA, et al. Hospital volume and surgical mortality in the United States. N Engl J Med 2002;346:1128–1137. [PubMed: 11948273]

17. Birkmeyer JD, Stukel TA, Siewers AE, et al. Surgeon volume and operative mortality in the United States. N Engl J Med 2003;349:2117–2127. [PubMed: 14645640]

18. Chowdhury MM, Dagash H, Pierro A. A systematic review of the impact of volume of surgery and specialization on patient outcome. Br J Surg 2007;94:145–161. [PubMed: 17256810]

19. Teh SH, Diggs BS, Deveney CW, Sheppard BC. Patient and hospital characteristics on the variance of perioperative outcomes for pancreatic resection in the United States: a plea for outcome-based and not volume-based referral guidelines. Arch Surg 2009;144:713–721. [PubMed: 19687374]

20. Allareddy V, Ward MM, Allareddy V, Konety BR. Effect of meeting Leapfrog volume thresholds on complication rates following complex surgical procedures. Ann Surg 2010;251:377–383. [PubMed: 20054271]

21. Finks JF, Osborne NH, Birkmeyer JD. Trends in hospital volume and operative mortality for high-risk surgery. N Engl J Med 2011;364:2128–2137. [PubMed: 21631325]

22. Avritscher EBC, Cooksley CD, Rolston KV, et al. Serious postoperative infections following resection of common solid tumors: Outcomes, costs, and impact of hospital surgical volume. Support Care Cancer 2014;22:527–535. [PubMed: 24141699]

23. Hata T, Motoi F, Ishida M, et al. Effect of hospital volume on surgical outcomes after pancreaticoduodenectomy. Ann Surg 2016;263:664–666. [PubMed: 26636243]

24. Nathan H, Atoria CL, Bach PB, Elkin EB. Hospital volume, complications, and cost of cancer surgery in the elderly. J Clin Oncol 2015;33:107–114. [PubMed: 25422483]

25. Bateni SB, Olson JL, Hoch JS, et al. Drivers of cost for pancreatic surgery: it's not about hospital volume. Ann Surg Oncol 2018;25:3804–3811. [PubMed: 30218244]

26. Bateni SB, Gingrich AA, Hoch JS, et al. Defining value for pancreatic surgery in early-stage pancreatic cancer. JAMA Surg 2019;154:e193019. [PubMed: 31433465]

27. Mariotto AB, Yabroff KR, Shao Y, et al. Projections of the cost of cancer care in the United States: 2010–2020. J Natl Cancer Inst 2011;103:117–128. [PubMed: 21228314]

28. Muñoz E, Muñoz WI, Wise L. National and surgical health care expenditures, 2005–2025. Ann Surg 2010;251:195. [PubMed: 20054269]

29. O'Neill CB, Atoria CL, O'Reilly EM, et al. Costs and trends in pancreatic cancer treatment. Cancer 2012;118:5132–5139. [PubMed: 22415469]

30. Elixhauser A, Steiner C, Harris DR, Coffey RM. Comorbidity measures for use with administrative data. Med Care 1998;36:8–27. [PubMed: 9431328]

31. van Walraven C, Austin PC, Jennings A, et al. A modification of the Elixhauser comorbidity measures into a point system for hospital death using administrative data. Med Care 2009;47:626–633. [PubMed: 19433995]

32. Gutacker N, Bloor K, Cookson R. Comparing the performance of the Charlson/Deyo and Elixhauser comorbidity measures across five European countries and three conditions. Eur J Public Health 2015;25[Suppl 1]:15–20.

33. Moore BJ, White S, Washington R, et al. Identifying increased risk of readmission and in-hospital mortality using hospital administrative data: The AHRQ Elixhauser Comorbidity Index. Med Care 2017;55:698–705. [PubMed: 28498196]

34. de Wilde RF, Besselink MGH, van der Tweel I, et al. Impact of nationwide centralization of pancreaticoduodenectomy on hospital mortality. Br J Surg 2012;99:404–410. [PubMed: 22237731]

35. Swan RZ, Niemeyer DJ, Seshadri RM, et al. The impact of regionalization of pancreaticoduodenectomy for pancreatic Cancer in North Carolina since 2004. Am Surg 2014;80:561–566. [PubMed: 24887793]

36. Gooiker GA, Lemmens VEPP, Besselink MG, et al. Impact of centralization of pancreatic cancer surgery on resection rates and survival. Br J Surg 2014;101:1000–1005. [PubMed: 24844590]

37. Dunn A, Grosse SD, Zuvekas SH. Adjusting health expenditures for inflation: a review of measures for health services research in the United States. Health Serv Res 2018;53:175–196. [PubMed: 27873305]

38. StataCorp L. Stata statistical software: Release 15. College Station, TX: StataCorp LP; 2017.

39. Hoch JS, Briggs AH, Willan AR. Something old, something new, something borrowed, something blue: a framework for the marriage of health econometrics and cost-effectiveness analysis. Health Econ 2002;11:415–430. [PubMed: 12112491]

40. Hoch JS, Rockx MA, Krahn AD. Using the net benefit regression framework to construct cost-effectiveness acceptability curves: an example using data from a trial of external loop recorders versus Holter monitoring for ambulatory monitoring of "community acquired" syncope. BMC Health Serv Res 2006;6:68. [PubMed: 16756680]

41. Barber JA, Thompson SG. Analysis and interpretation of cost data in randomised controlled trials: review of published studies. BMJ 1998;31:1195–2000.

42. Ramsey SD, Willke RJ, Glick H, et al. Cost-effectiveness analysis alongside clinical trials IIdAn ISPOR Good Research Practices Task Force Report. Value Health 2015;18:161–172. [PubMed: 25773551]

43. Grosse SD. Assessing cost-effectiveness in healthcare: history of the $50,000 per QALY threshold. Expert Rev Pharmacoecon Outcomes Res 2008;8:165–178. [PubMed: 20528406]

44. Lakdawalla DN, Sun EC, Jena AB, et al. An economic evaluation of the war on cancer. J Health Econ 2010;29:333–346. [PubMed: 20363520]

45. Becker G, Murphy K, Philipson T. The value of life near its end and terminal care (Working Paper Series). 2007. National Bureau of Economic Research; 2007. Available at:, http://www.nber.org/papers/w13333. Accessed March 6, 2021.

46. Aguiar PN Jr, Haaland B, Park W, et al. Cost-effectiveness of osimertinib in the first-line treatment of patients with EGFR-mutated advanced non-small cell lung cancer. JAMA Oncol 2018;4:1080–1084. [PubMed: 29852038]

47. Edwards SJ, Wakefield V, Cain P, et al. Axitinib, cabozantinib, everolimus, nivolumab, sunitinib and best supportive care in previously treated renal cell carcinoma: a systematic review and economic evaluation. Health Technol Assess 2018;22:1–278.

48. Huxley N, Crathorne L, Varley-Campbell J, et al. The clinical effectiveness and cost-effectiveness of cetuximab (review of technology appraisal no. 176) and panitumumab (partial review of technology appraisal no. 240) for previously untreated metastatic colorectal cancer: a systematic review and economic evaluation. Health Technol Assess 2017;21:1–294.

49. Conroy T, Desseigne F, Ychou M, et al. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. N Engl J Med 2011;364:1817–1825. [PubMed: 21561347]

50. Conroy T, Hammel P, Hebbar M, et al. FOLFIRINOX or gemcitabine as adjuvant therapy for pancreatic cancer. N Engl J Med 2018;379:2395–2406. [PubMed: 30575490]

51. Von Hoff DD, Ervin T, Arena FP, et al. Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. N Engl J Med 2013;369:1691–1703. [PubMed: 24131140]
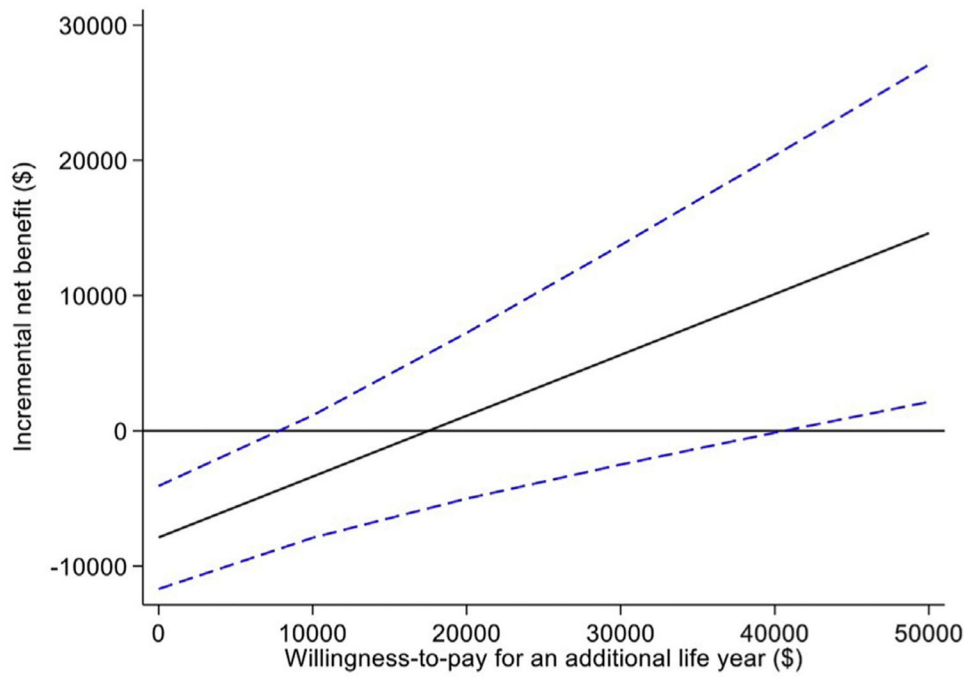
Figure 1.
Incremental net benefit by willingness-to-pay. The solid line represents the incremental net benefit estimate and the dashed lines represent the 95% CIs.
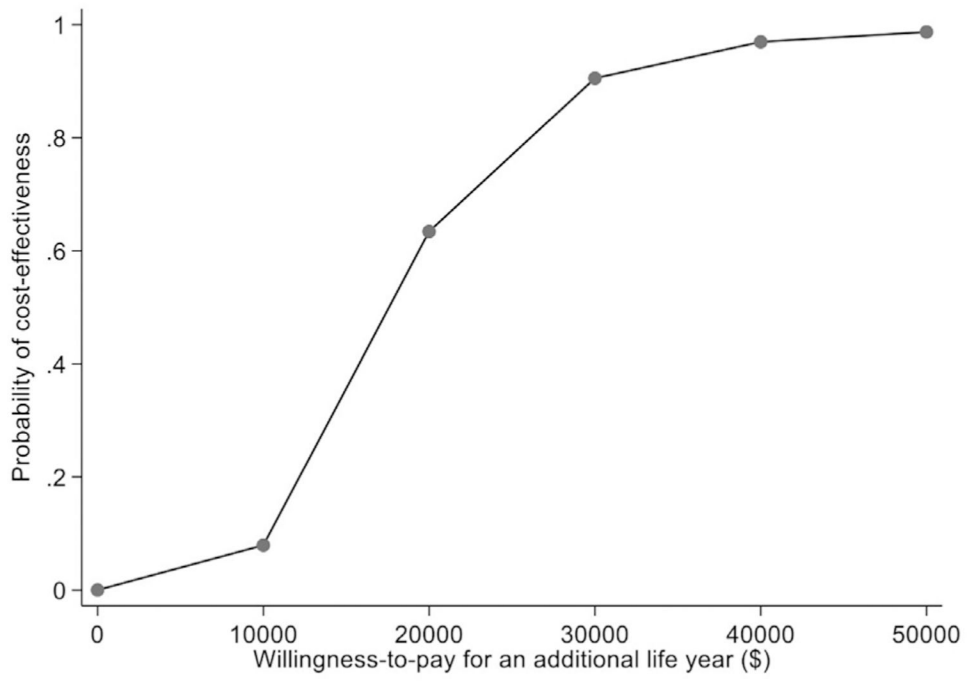
Figure 2.
Cost-effectiveness acceptability curve.

Table 1.

Demographic, Clinicopathologic, and Facility Characteristics for Patients with Stage I-II Pancreatic Cancer Who Underwent Resection

Characteristic	n = 2,786
Age, mean (SD)	67.0 (±10.7)
Sex, n (%)	
Male	1,395 (50.0)
Female	1,392 (50.0)
Race, n (%)	
White	2,308 (82.8)
Black	152 (5.5)
Asian/Pacific Islander	313 (11.2)
Other/unknown	13 (0.5)
Socioeconomic status, n (%)	
Lowest (first quintile)	531 (19.1)
Low to middle (second quintile)	527 (18.9)
Middle (third quintile)	545 (19.6)
Middle to high (fourth quintile)	545 (19.6)
Highest (fifth quintile)	638 (22.9)
Elixhauser comorbidity index score[*], mean (SD)	13.9 (±8.9)
Tumor grade, n (%)	
Well-differentiated	295 (10.6)
Moderately differentiated	1,373 (49.3)
Poorly differentiated or undifferentiated	949 (34.1)
Unknown	169 (6.1)
T category, n (%)	
T1	204 (7.3)
T2	435 (15.6)
T3	2,147 (77.1)
N category, n (%)	
N0	1,054 (37.8)
N1	1,725 (61.9)
NX[†]	7 (0.3)
Stage, n (%)	
I	399 (14.3)
II	2,387 (85.7)
Chemotherapy, n (%)	
None	1,070 (38.4)
Preoperative	89 (3.2)

Characteristic	n = 2,786
Postoperative	1,238 (44.4)
Preoperative and postoperative	50 (1.8)
Unknown	339 (12.2)
Radiotherapy	874 (31.4)
Pancreatic resection type, n (%)	
Pancreaticoduodenectomy	2,207 (79.2)
Distal pancreatectomy	387 (13.9)
Total pancreatectomy	98 (3.5)
Other	94 (3.4)
Complication within 30 d, n (%)	1,037 (37.2)
Readmission within 30 d, n (%)	565 (20.3)
Hospital length of stay, d, median (IQR)	12 (9–18)
Hospital pancreatic surgery volume[‡], n (%)	
Low	1,489 (53.4)
High	1,297 (46.6)
NCI-designated cancer center, n (%)	1,127 (40.5)
Teaching hospital, n (%)	1,428 (51.3)
Surgical hospitalization cost, $, mean (SD) [§]	60,939 (±56,779)
Low-volume	59,525 (±54,993)
High-volume	62,561 (±58,742)
Survival time, y, mean (SD)	2.3 (±2.1)
Low	2.2 (±2.1)
High	2.5 (±2.2)
Vital status, n (%)	
Death due to pancreatic cancer	2,020 (72.5)
Death due to other cause	247 (9.0)
Death due to unknown cause	55 (2.0)
Alive	464 (16.7)

[*] Elixhauser comorbidity index score: ranges from −11 to 62; higher scores indicate greater comorbidity.

[†] NX: regional lymph nodes could not be evaluated.

[‡] High-volume: 20 or more pancreatic cancer operations per year.

[§] Hospitalization cost includes index procedure, length of hospital stay, and readmission within 30 days.

IQR, interquartile range; NCI, National Cancer Institute

Table 2.

Unadjusted and Adjusted Multivariable Model Estimates for Cost, Survival Time, and Incremental Cost-Effectiveness Ratio When Comparing Low- with High-Volume Hospitals

Estimate	Unadjusted difference[*]	95% CI[†]	Adjusted difference[‡]	95% CI
Cost, $ (ΔC)	3,036	−1,211–7,283	7,884	4,074–11,694
Survival time, y (ΔE)	0.33	0.18–0.49	0.45	0.21–0.69
ICER[§] (cost/life-year, $)	9,082	Cost saving −28,887	17,529	7,997–40,616

[*] Difference between low- and high-volume center estimates.

[†] 95% CI for the incremental cost-effectiveness ratio (ICER) estimates were computed using Fieller's Theorem and then verified using the incremental net benefit by willingness to pay graph.

[‡] Difference between low- and high-volume center estimates after adjusting for demographic, clinicopathologic, and facility characteristics listed in Table 1.

[§] ICER = ΔC/ΔE

Table 3.

Multivariate Incremental Net Benefit Estimates for Varying Willingness-to-Pay Values When Comparing Low-with High-Volume Hospitals

Willingness-to-pay	INB estimate[*]	95% CI
0	−7,884	−11,694–4,074
10,000	−3,386	−7,909–1,137
20,000	1,111	−5,014–7,237
30,000	5,609	−2,498–13,715
40,000	10,106	−142–20,354
50,000	14,604	2,135–27,072

Data expressed as $

[*] Incremental net benefit (INB) = willingness-to-pay × E − C