

# The Clinical and Economic Impact of Alternative Staging Strategies for Adenocarcinoma of the Pancreas

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**OBJECTIVE:** Several innovative imaging modalities, including endoscopic ultrasound, have increased the number of available preoperative staging methods in patients with adenocarcinoma of the pancreas. Our goal was to estimate the clinical outcomes and cost-effectiveness of alternative staging strategies for pancreatic adenocarcinoma.

**METHODS:** Decision analysis was used to simulate alternative staging strategies. Cost inputs were based on Medicare reimbursements; clinical inputs were obtained from the available literature. Model endpoints of interest were cost per curative resection and appropriateness of treatment allocation based on pathological stage.

**RESULTS:** Endoscopic ultrasound followed by laparoscopy yielded the lowest cost per curative resection (\$37,600) and minimized the number of unnecessary surgical explorations (5.4 per 100 patients staged). Requiring angiographic confirmation when endoscopic ultrasound demonstrated an unresectable tumor yielded an intermediate cost-effectiveness ratio and virtually eliminated the risk of overstaging. Laparoscopy alone maximized the resection rate, but each additional resection would cost approximately \$2 million relative to a strategy employing both endoscopic ultrasound and angiography.

**CONCLUSIONS:** Staging strategies incorporating endoscopic ultrasound may improve treatment allocation and are cost-effective relative to angiography-based strategies. A staging protocol that does not incorporate an imaging modality to detect vascular invasion dramatically increases the cost per additional curative resection compared with more comprehensive staging protocols. (Am J Gastroenterol 2000;95:1708–1713. © 2000 by Am. Coll. of Gastroenterology)

## INTRODUCTION

Adenocarcinoma of the pancreas is the fifth leading cause of cancer death in the United States and approximately 27,000 new cases are diagnosed annually (1). Disease is usually advanced at the time of diagnosis and only 15% of patients have localized tumors amenable to attempted curative resection (2–7). The recent reports of 5-yr postresection survival rates of >20% and surgical mortality rates of <5% (8–11) have re-emphasized the need to consider surgical resection as a therapy with curative potential.

The prognosis for the 85% of patients with unresectable disease remains dismal. The median survival in this group is 6 months and the primary therapeutic goal is palliation (12, 13). Despite improvement in postoperative outcomes after curative resection, the operative mortality and morbidity for palliative surgery remains high (14, 15). Several randomized trials have demonstrated endoscopic biliary endoprosthesis placement to be equal in efficacy to surgical biliary bypass for relief of obstructive jaundice (16–19). In addition, endoscopic palliation is associated with significantly lower morbidity and mortality rates and may shorten the length of hospitalization relative to surgical interventions. Although surgical bypass remains the treatment of choice for duodenal obstruction, this is frequently a terminal event and fewer than 10% of patients will be candidates for duodenal bypass during the course of the disease (16). Therefore, the majority of patients with unresectable disease can be managed without surgery.

The emergence of nonsurgical means of palliation has underscored the importance of accurate preoperative staging and selection of patients for attempted curative resection. Candidates for attempts at curative surgery should have no evidence of distant metastatic disease, and the tumor should be amenable to complete extirpation based on a lack of invasion into major vascular structures. Computed tomography (CT) and, more recently, laparoscopy have become indispensable for detecting intraabdominal metastatic dis-

ease (20–25). Because CT is both noninvasive and a reliable means of documenting distant disease, it is the preferred initial procedure in any staging strategy. The detection of tumor invasion of the portal and mesenteric vasculature has traditionally relied on CT and mesenteric angiography (20, 22, 26–31). Endoscopic ultrasound (EUS) has emerged as an innovative pancreatic imaging modality with an accuracy of >90% in the local staging of pancreatic cancer (32–37). Although EUS is limited as a means of detecting distant disease, it compares favorably to angiography and CT for defining vascular invasion and tumor size (33, 38, 39).

There is currently no consensus on the optimal preoperative staging strategy for patients with adenocarcinoma of the pancreas. Furthermore, the impact of individual staging procedures on clinical and economic endpoints remains unclear. Using decision analysis, we investigated the effect of alternative staging strategies employed in clinical practice, incorporating EUS, angiography, and laparoscopy on the clinical outcomes and disease-specific costs in patients with pancreatic cancer.

## MATERIALS AND METHODS

Computer-based models simulating the staging and treatment of patients with adenocarcinoma of the pancreas were created with Decision Maker (Pratt Medical Group, Boston, MA). All patients entering the model were potential surgical candidates with no evidence of unresectable disease on dynamic CT. We chose dynamic as opposed to helical CT scanning because of its widespread availability in the community, its frequent use in screening examinations, and the ongoing debate regarding the magnitude of staging superiority that helical scanning provides (40). We evaluated seven alternative staging strategies representing popular clinical practices:

1. LAP: Patients proceeded directly to laparoscopy and if there was no evidence of intraabdominal dissemination, full surgical exploration was performed with the intent of undertaking a potentially curative resection.
2. ANG-LAP: Angiography was performed as the primary staging procedure, and patients with resectable tumors proceeded to laparoscopy followed by laparotomy for a potentially curative resection as outlined in the LAP strategy.
3. EUS-LAP: EUS was the primary staging procedure; if the tumor seemed resectable, laparoscopy followed by full surgical exploration was performed as in the LAP strategy.
4. LAP-EUS: Laparoscopy was performed as the initial procedure distinct from the planned laparotomy for possible curative resection. When laparoscopy revealed no intraabdominal dissemination, the patient proceeded to EUS and, if the tumor was deemed resectable, full surgical exploration was performed.
5. LAP-ANG: If the initial laparoscopy revealed no intra-

**Table 1.** Clinical Inputs

Clinical Variable	Probability	Range	References
Angiography sensitivity*	0.70	0.70–1.00	20, 22, 26–33
Angiography specificity*	0.91	0.70–1.00	
EUS sensitivity*	0.91	0.70–1.00	32–39
EUS specificity*	0.92	0.70–1.00	
Laparoscopy sensitivity†	0.85	0.85–1.00	21–25
Laparoscopy specificity†	1.00		
Tumor resectability	0.33		21–23
Obstructive jaundice	0.80		
Duodenal obstruction	0.10		

\* Detection of locally unresectable disease.

† Detection of intraabdominal dissemination (*e.g.*, peritoneal or hepatic metastasis).

EUS = endoscopic ultrasound.

abdominal dissemination, the patient proceeded to mesenteric angiography. If the tumor was resectable by angiographic criteria, full surgical exploration for a potentially curative resection was performed.

6. ANG-EUS-LAP: Angiography was performed as the primary staging procedure and EUS was performed as a confirmatory procedure only in patients with unresectable disease by angiography. If angiography or EUS demonstrated a resectable tumor, laparoscopy was performed followed by laparotomy when there was no evidence of intraabdominal metastasis.
7. EUS-ANG-LAP: EUS was performed as the primary staging procedure and angiography was performed as a confirmatory procedure only in patients with unresectable disease by EUS. If EUS or angiography demonstrated a resectable tumor, laparoscopy was performed followed by laparotomy when there was no evidence of intraabdominal metastasis. The last two strategies employed the confirmatory procedure as a means of minimizing overstaging and, hence, limiting the allocation of patients with resectable disease to palliative therapy.

Patients with unresectable disease determined by EUS, angiography, or laparoscopy were managed with endoscopic stenting for obstructive jaundice, CT-guided biopsy to confirm a histological diagnosis of adenocarcinoma, and gastrojejunostomy if the patient developed duodenal obstruction. Patients with unresectable disease at laparotomy were managed with surgical palliation, which included pancreatic biopsy, choledochojejunostomy in the setting of obstructive jaundice, and gastrojejunostomy when duodenal obstruction was present or anticipated.

### Clinical Inputs

All assumptions for clinical probabilities were derived from critical analysis of the literature. Performance characteristics for alternative staging procedures and disease natural history are outlined in Table 1.

### Cost Inputs

All cost estimates were based on Medicare reimbursements for our university-based hospital (Table 2). All staging procedures and nonsurgical palliative procedures were as-

**Table 2.** Cost Inputs

Procedure	Cost*	Range
Pancreaticoduodenectomy	\$23,800	
Choledochojejunostomy	\$16,720	
Gastrojejunostomy	\$16,160	
Laparoscopy with biopsy	\$ 2,880	
Angiography	\$ 1,720	\$600–2,000
ERCP with biliary stent	\$ 1,330	
CT-guided biopsy	\$ 760	
EUS	\$ 660	\$600–2,000

\* Medicare reimbursement.  
EUS = endoscopic ultrasound.

sumed to be outpatient procedures, as this is the current standard at the majority of centers. All hospital, professional, pharmaceutical, and pathology fees were included. Indirect costs (e.g., lost productivity) and nonmedical direct costs (e.g., travel, lodging) were not included.

**Analysis**

The model simulated the evaluation and initial treatment allocation of 100 patients with pancreatic adenocarcinoma limited to the head of the pancreas on dynamic CT. Favorable clinical outcomes measured included surgical resection for patients with resectable tumors and nonsurgical palliation for patients with unresectable disease. Missed opportunity for cure in patients with resectable disease and surgical exploration for unresectable disease were considered undesirable outcomes. Cost per curative resection was calculated for each of the staging strategies. When one strategy yielded a higher resection rate at an increased cost per curative resection, an incremental cost-effectiveness ratio (additional money spent per additional curative resection) was calculated. Sensitivity analysis examined the impact of varying the performance characteristics for staging techniques (Table 1) and procedural costs (Table 2) over a range of inputs.

**RESULTS**

**Treatment Allocation**

The distribution of patients into the desirable (e.g., resectable and explored, unresectable and not explored) and undesirable (e.g., resectable and not explored, unresectable

**Table 4.** Cost Outcomes

Strategy	Cost per Patient (\$)	Cost per Curative Resection (\$)
LAP	18,100	54,800
ANG-LAP	13,400	44,600
EUS-LAP	11,400	37,600
LAP-ANG	15,400	51,200
LAP-EUS	13,800	45,300
ANG-EUS-LAP	14,500	44,300
EUS-ANG-LAP	14,000	42,800

Abbreviations as in Table 3.

and explored) clinical categories is represented in Table 3. A strategy employing laparoscopy alone resulted in resection for *all* patients with resectable tumors, largely because of the requirement of pathological confirmation of distant disease to forestall resection. This level of precision, which eliminated missed opportunities for cure, came at a cost of nearly 40 surgical explorations in patients with unresectable disease per 100 patients staged.

Both ANG-LAP and LAP-ANG appropriately identified 91% (30 of 33) of individuals with resectable disease; however, 13.2% of patients staged underwent an unnecessary exploration. Strategies employing EUS followed by laparoscopy (EUS-LAP) or laparoscopy followed by EUS (LAP-EUS) similarly identified a slightly higher percentage (92%) of patients amenable for cure but resulted in the lowest rate of unnecessary surgical explorations (5.8% of patients staged), a greater than 2-fold reduction relative to angiography-based strategies and a 5-fold reduction relative to laparoscopy alone. The strategies employing a confirmatory procedure when the initial EUS or angiography predicted unresectable disease further increased the resection rate from 92% (30 of 33) to 99% (32 of 33); however, this intervention to reduce missed opportunity for cure increased the inappropriate exploration rate nearly 3-fold from 5.8% to 15.5%.

**Cost Analysis**

Since the goal of staging is the accurate allocation of patients to curative resection and palliative interventions, the economic analysis focused on the cost per curative resection (Table 4). This cost-effectiveness ratio was lowest for the

**Table 3.** Clinical Outcomes

Strategy	Optimal Treatment Allocation		Adverse Treatment Allocation	
	Resectable, Explored	Unresectable, Not Explored	Resectable, Not Explored	Unresectable, Explored
LAP	33.0%	27.4%	0.0%	39.6%
ANG-LAP	30.0%	53.8%	3.0%	13.2%
EUS-LAP	30.4%	61.2%	2.6%	5.8%
LAP-ANG	30.0%	53.8%	3.0%	13.2%
LAP-EUS	30.4%	61.2%	2.6%	5.8%
ANG-EUS-LAP	32.8%	51.5%	0.2%	15.5%
EUS-ANG-LAP	32.8%	51.5%	0.2%	15.5%

ANG = angiography; EUS = endoscopic ultrasound; LAP = laparoscopy. (For additional abbreviations, see Materials and Methods.)

EUS-LAP strategy at \$37,600. Reversing the order of staging procedures in the LAP-EUS strategy served only to increase the cost per patient by \$2,300 without altering the outcomes, yielding a cost per curative resection of \$45,300. The ANG-LAP strategy increased the cost per patient by \$2,000 relative to the EUS-LAP strategy, resulting in a cost per curative resection of \$44,600. Dissection of the expenditures within the model demonstrated that approximately 50% of this increased cost in the ANG-LAP strategy was attributable to differences in staging procedure costs and 50% was due to an increase in unnecessary surgical explorations. As with the EUS-based strategy, performing laparoscopy before angiography served only to increase the cost-effectiveness ratio to \$51,200 without altering outcomes. Laparoscopy alone was the least cost-effective strategy, resulting in a cost per curative resection of \$54,800, a 46% increase relative to the EUS-LAP strategy.

Both the EUS-ANG-LAP and ANG-EUS-LAP strategies were associated with increased total cost per patient because of added staging and surgical palliative costs, but the increase in curative resections resulted in intermediate cost-effectiveness ratios. The EUS-ANG-LAP strategy was cost-effective relative to the ANG-EUS-LAP strategy with a cost per curative resection of \$42,800.

Because the laparoscopy strategy yielded the highest rate of surgical resections yet required the greatest expenditures, an incremental cost analysis was performed. The additional resections realized in the LAP strategy came at an incremental cost of \$257,000 per additional curative resection relative to the EUS-LAP strategy and \$2,033,000 per additional curative resection relative to the EUS-ANG-LAP strategy. Similarly, the improved resection rate in the EUS-ANG-LAP strategy required \$108,000 per additional curative resection relative to the EUS-LAP strategy.

### **Sensitivity Analysis**

The EUS-LAP strategy remained the most cost-effective strategy when the cost of EUS and angiography were varied from \$400 to \$2000. The cost per curative resection was also insensitive to alterations of the sensitivity or specificity of EUS and angiography from 0.7 to 1.0.

## **DISCUSSION**

Pancreatic cancer is among the most lethal of malignancies, primarily because of the advanced stage at the time of diagnosis. The vast majority of patients have incurable disease, underscoring the importance of preoperative selection of patients for attempted resection. Patients with residual disease after resection have a median survival similar to patients treated with palliative therapy (8, 10, 15). Furthermore, several randomized trials have demonstrated the equivalent success and lower short-term mortality of non-surgical palliation of obstructive jaundice relative to surgical interventions (16–18). Therefore, the higher rate of early mortality and morbidity associated with surgical palliation

may be avoided in patients with advanced tumors if the preoperative staging strategy accurately identifies patients with unresectable disease. Similarly, to maximize clinical benefit, efforts to avoid unnecessary surgical interventions should not result in an excessive rate of overstaging, thereby denying patients with resectable disease the possibility of cure. Finally, there is also the concern that extensive preoperative imaging protocols increase expenditures without affecting management or outcomes.

Dynamic CT is a noninvasive means of detecting unresectable disease and should always be the initial imaging procedure when staging adenocarcinoma of the pancreas. Vascular invasion has traditionally been assessed with mesenteric angiography (41), but the emergence of other imaging modalities such as EUS has led to controversy regarding the optimal staging strategy for patients with pancreatic cancer. Recently, laparoscopy has been employed as a more sensitive means of detecting intraabdominal metastasis and is logically employed before a full laparotomy. However, some investigators have suggested laparoscopy as the initial staging procedure after CT as a means of avoiding other invasive imaging procedures such as angiography (23). Others have questioned the need for any specialized imaging procedure to evaluate for the presence of vascular invasion, instead employing CT and laparoscopy alone before surgical exploration. Our model represents the first systematic analysis of potential staging strategies incorporating these imaging procedures.

Because the goal of any staging procedure is to accurately allocate patients to appropriate treatment protocols based on pathological stage at the time of evaluation, our clinical endpoints of interest reflect this intention. The strategy employing EUS followed by laparoscopy (EUS-LAP) yielded the lowest rate of unnecessary surgical explorations and a 2.6% rate of overstaging. This low rate of overstaging translated into a surgical resection in 92% of patients with resectable tumors. Both strategies employing angiography as the sole method of detecting vascular invasion increased both undesirable outcomes relative to the EUS strategies. Because of the 100% specificity of laparoscopy with biopsy, the strategy employing laparoscopy alone maximized the number of resected patients. However, our model demonstrates the cost of this benefit as a 5-fold increase in the number of unnecessary surgical explorations in unresectable patients. Both strategies employing a confirmatory procedure produced a nearly perfect rate of identifying resectable tumors while reducing the number of unnecessary explorations by 61% relative to laparoscopy alone. Based on these estimated clinical outcomes, strategies incorporating EUS should be favored over strategies incorporating angiography as a means of detecting vascular invasion. Similarly, if minimizing missed opportunities for cure is prioritized, strategies with a confirmatory procedure to evaluate for vascular invasion (*e.g.*, EUS-ANG-LAP) are preferred to laparoscopy alone because of the significant reduction in unnecessary explorations.

In addition to projecting these clinical endpoints, our analysis provides an estimate of the relative cost-effectiveness of these staging protocols. The traditional strategy of angiography followed by laparoscopy (ANG-LAP) yielded a cost per curative resection of \$44,600. Substituting EUS for angiography yielded the most cost-effective strategy, lowering the cost per curative resection by \$7000 to \$37,600. Approximately one-half of this reduction was attributable to reduced staging costs, and one-half was due to a decrease in unnecessary explorations. Some have proposed laparoscopy as the initial staging procedure before specialized imaging procedures to define vascular invasion (23). In our analysis, both LAP-EUS and LAP-ANG increased the cost per curative resection without altering the clinical outcomes relative to the EUS-LAP and ANG-LAP, respectively. This increased cost is incurred because all patients are subjected up-front to the relatively costly procedure of laparoscopy. Similarly, the EUS-ANG-LAP strategy is preferred over the ANG-EUS-LAP strategy because of the lower cost of the former with identical clinical outcomes. The laparoscopy-alone (LAP) strategy proved to be the least cost-effective. Although this strategy yielded a slightly higher rate of curative resections, the incremental cost of this benefit was \$257,000 per additional curative resection relative to the EUS-LAP strategy and \$2,033,000 per additional curative resection relative to the EUS-ANG-LAP strategy. Therefore, although laparoscopy alone provides a marginal increase in the number of patients undergoing surgical resection, policy makers and clinicians need to consider the increased rate of unnecessary surgical explorations and incremental expenditures before adopting this strategy.

Our analysis cannot be used to select one strategy as the dominant strategy but, rather, provides a framework for physicians, policy makers, and payers to select appropriate staging algorithms given our current understanding of the individual components of staging. In addition, our model allows for the optimal design of future prospective studies designed to clarify the role of specific staging algorithms by avoiding strategies such as the angiography-based strategies, which are clearly deleterious from a clinical and cost perspective.

Our model has several limitations. All decision models contain a level of uncertainty inherent in the clinical and economic assumptions of the model. Sensitivity analysis provides a means of addressing this uncertainty by assigning a range of values to inputs prone to uncertainty. In our analysis we specifically address the importance and relative merits of specialized imaging procedures designed to detect vascular invasion. The cost per curative resection was insensitive to alterations in the cost and a wide range of performance characteristics of EUS and angiography. We examine the cost per curative resection as the primary economic outcome, inasmuch as accurate patient allocation is the primary goal of preoperative staging. It should be emphasized that our definition of curative resection is a patho-

logical cure at the time of resection. As the majority of these patients eventually succumb to recurrent disease, these cost estimates grossly underestimate the true cost per cure. An index such as cost per life-year gained would be more useful as a reference with other medical interventions such as the treatment of hypertension; however, our goal was to directly compare alternative staging strategies for pancreatic cancer. Furthermore, obtaining these parameters would require an estimate of survival attributable to accurate *versus* inaccurate staging, and these figures are currently not available.

Our analysis assumes the payer's perspective and, hence, only direct costs are included. We believe that this provides a conservative estimate of the relative cost-benefit analysis, and institutes a bias in favor of less aggressive staging strategies such as LAP, because the indirect costs are certainly higher for strategies with increased morbidity and mortality from unnecessary surgical explorations.

Finally, we have not included certain innovative imaging modalities such as helical CT, magnetic resonance imaging, and laparoscopic ultrasound, as high quality data on the performance characteristics for pancreatic cancer are still limited. Preliminary data from our institution (42) and others (43) supports the superiority of EUS relative to helical CT for defining locally unresectable disease, and when these results were incorporated into our model, strategies employing EUS remained cost-effective. These data support the strategy employing an initial cross-sectional imaging technique to determine the absence of metastatic disease, followed by a more sensitive technique such as EUS to determine local resectability. The adaptability of decision analysis will permit us to incorporate new information into the analysis as our knowledge of other imaging modalities and interventions for pancreatic cancer advances.

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