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Regret affects the choice between neoadjuvant therapy and upfront surgery for potentially resectable pancreatic cancer

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ABSTRACT

Background: When treating potentially resectable pancreatic adenocarcinoma, therapeutic decisions are left to the sensibility of treating clinicians who, faced with a decision that post hoc can be proven wrong, may feel a sense of regret that they want to avoid. A regret-based decision model was applied to evaluate attitudes toward neoadjuvant therapy versus upfront surgery for potentially resectable pancreatic adenocarcinoma.

Methods: Three clinical scenarios describing high-, intermediate-, and low-risk disease-specific mortality after upfront surgery were presented to 60 respondents (20 oncologists, 20 gastroenterologists, and 20 surgeons). Respondents were asked to report their regret of omission and commission regarding neoadjuvant chemotherapy on a scale between 0 (no regret) and 100 (maximum regret). The threshold model and a multilevel mixed regression were applied to analyze respondents' attitudes toward neoadjuvant therapy.

Results: The lowest regret of omission was elicited in the low-risk scenario, and the highest regret in the high-risk scenario ($P < .001$). The regret of the commission was diametrically opposite to the regret of omission ($P \leq .001$). The disease-specific threshold mortality at which upfront surgery is favored over the neoadjuvant therapy progressively decreased from the low-risk to the high-risk scenarios ($P \leq .001$). The nonsurgeons working in or with lower surgical volume centers ($P = .010$) and surgeons ($P = .018$) accepted higher disease-specific mortality after upfront surgery, which resulted in the lower likelihood of adopting neoadjuvant therapy.

Conclusion: Regret drives decision making in the management of pancreatic adenocarcinoma. Being a surgeon or a specialist working in surgical centers with lower patient volumes reduces the likelihood of recommending neoadjuvant therapy.

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Introduction

Surgical resection currently represents the only hope for significant improvement in survival in patients with localized pancreatic ductal adenocarcinoma (PDAC). The standard of care for resectable PDAC consists of upfront surgical resection followed by adjuvant chemotherapy. Unfortunately, adjuvant chemotherapy is often delayed by surgical complications or slow postsurgical recovery. Adopting preoperative (neoadjuvant) treatment with chemotherapy or chemoradiation has potential advantages over an "upfront approach," including higher preoperative compliance and delivery rates, improved pathological outcomes, and control of micro-metastatic disease—the cause of early tumor relapse after pancreatic resection. Although data suggest that neoadjuvant chemotherapy likely prolongs survival compared to upfront surgery,[1,2] high-quality evidence that convincingly supports its use in resectable patients is limited.[3,4] Additionally, PDAC can progress during neoadjuvant chemotherapy, making unresectable initially radiologically assessed resectable cancer. In this context, the result of neoadjuvant treatment can be interpreted as the loss of a surgical opportunity, as well as the avoidance of a procedure that would have been futile due to biological aggressiveness that would have resulted in early tumor relapse.

The choice of the optimal approach is consequently fraught with uncertainty. Faced with expected benefit and harms of these 2 therapeutic strategies, oncologists and surgeons adopt one of these management options based on their perceived probability of increasing the patient's life expectancy. However, under this uncertainty, it is possible to make a wrong decision, that is, to choose the strategy that, in retrospect, proves to be the least effective. This knowledge can impart to clinicians a sense of loss or regret.[5–7] Regret theory postulates that the anticipation of regret can influence people's choices and that certain decisions can be associated with high regret that they would like to minimize or eventually avoid. To minimize anticipated regret, the optimal choice would be the one associated with the least amount of regret. This approach has already been investigated and validated in end-life settings, treatment of primary liver cancer, and the decision to perform pancreatic surgery.[5–8] Regret theory is particularly applicable to single-point, nonrepeatable decisions, such as a decision about whether to administer neoadjuvant therapy to patients with resectable PDAC.

The present study aimed to apply regret theory to the choice between neoadjuvant chemotherapy followed by surgery versus upfront surgery when treating potentially resectable PDAC. The ultimate goal was to provide evidence about modifiers of clinical decisions in the surgical management of PDAC.

Methods

The present study relied on the estimation of benefits and harms of the following strategies for patients with localized, potentially resectable PDAC: (1) neoadjuvant chemotherapy followed by surgery and subsequent adjuvant chemotherapy versus (2) upfront surgery followed by adjuvant chemotherapy. Based on personal knowledge and experience, physicians can value differently the regret due to the loss of surgical opportunity if the disease progressed during neoadjuvant therapy versus regret arising from performing immediate surgery that could have resulted in longer survival with the administration of neoadjuvant chemotherapy.[9,10] These regrets were elicited here through a regret modeling approach, which had the disease-specific mortality as the event of interest. The study followed the COREQ standards for reporting qualitative research.[11] Ethical approval was not sought for the present study because of its survey nature.

Regret model

Regret can be a consequence of the omission of potentially beneficial therapy and the commission of treatment in the case that it was subsequently proved to be more harmful than beneficial. The *regret of omission* here refers to the regret felt by the physician who withheld neoadjuvant therapy from a patient who otherwise may have benefited from this treatment. The *regret of commission* refers to the regret felt by the physician who decided to start neoadjuvant therapy resulting in the loss of performing upfront surgery. Both regrets were assessed from physicians based on their holistic individual expertise and knowledge about upfront surgery and neoadjuvant therapy.

Regret of omission was elicited using the following question (Supplementary Figure S1): "How would you rate the level of your regret, on a scale of 0 to 100 (0 = no regret, 100 = maximum regret) if you decided NOT to start neoadjuvant therapy and the patient died after upfront surgery due to early tumor relapse?" Regret is here the consequence of the missed opportunity to control the tumor biology, so that the patient was upfront resected and eventually died after tumor recurrence.

Regret of the commission was similarly elicited using the following question: "How would you rate the level of your regret, on a scale of 0 to 100 (0 = no regret, 100 = maximum regret) if you started neoadjuvant therapy but the patient's disease ultimately became unresectable and he/she died because of cancer?" Regret is here the consequence of the decision to administer neoadjuvant chemotherapy, which ultimately prevented undertaking a theoretically life-prolonging surgery.

The elicited regret of omission or commission was related to the disease-specific mortality (M). If the regret of omission is larger than the regret of commission, physicians give more weight to failure to give neoadjuvant chemotherapy. The regret model assumes that there must be some probability at which regret of omission equals the regret of commission. According to the regret model,[12] the relation between M and regret of omission and commission is defined by the following equation (Supplementary Figures S2 and S3 and Figure 1)[4,13]:

$$Mt = (1 / [1 + (\text{regret of omission} / \text{regret of commission})]) \times 100$$

Where Mt is threshold mortality at which we are indifferent between 2 management strategies. The equation indicates that as the regret of omission becomes greater than the regret of commission, mortality due to pancreatic cancer above which we should administer neoadjuvant chemotherapy progressively decreases. That is, if the "expected mortality" (M) is above this "threshold mortality," a patient should be given neoadjuvant treatment if our goal is minimization of regret, whereas below the threshold we should refrain from administering neoadjuvant chemotherapy if we desire to minimize regret.[13]

Survey and expected mortality

Regret of omission and commission were elicited using an online survey. Three hypothetical clinical cases, at high, intermediate, and low risk for tumor recurrence after upfront surgery (Supplementary Table S1), were sent for consultation to a purposeful sample formed by 20 surgeons, 20 oncologists, and 20 gastroenterologists with at least 10 years of clinical experience in this setting. Respondents were informed that the 2 therapeutic strategies were neoadjuvant chemotherapy followed by surgery and subsequent adjuvant chemotherapy versus upfront surgery followed by adjuvant chemotherapy. No data about expected mortality after upfront surgery, the receipt of adjuvant therapy, or

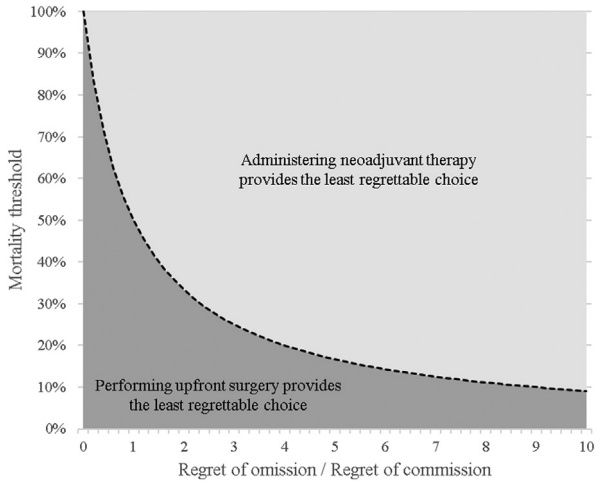

Figure 1. Relationship between regret of omission and commission of administering neoadjuvant therapy. Coordinates identify the mortality threshold. If expected mortality due to pancreatic cancer with upfront surgery is lower than the threshold, the regret of administering neoadjuvant treatment (commission) will be larger than the regret of not administering it (omission); hence, we should not administer neoadjuvant treatment. Conversely, if expected mortality is above the threshold, the regret of not administering neoadjuvant treatment (omission) will be larger than the regret of administering it (commission); hence we should administer neoadjuvant treatment to minimize regret. Regret of omission is the consequence of the missed opportunity to control the tumor spread, so that the patient who had upfront surgical resection eventually died after early tumor progression. Regret of commission is a consequence of the decision to administer neoadjuvant chemotherapy, which delay and ultimately prevents undertaking a theoretically life-prolonging surgery. As an example, if a physician feels that omission of neoadjuvant chemotherapy in favor of upfront surgery would lead to a regret of 60 (on the scale 0 = minimum regret, 100 = highest regret) and feels that committing to neoadjuvant treatment would lead to a regret of 30, the corresponding mortality threshold is 33%. If the expected mortality after upfront surgery is above this threshold, neoadjuvant treatment should be pursued to minimize regret.

the response rates with neoadjuvant therapy were provided to respondents during the survey. The intent was to elicit regret by relying entirely on respondents' experience and knowledge. This approach was chosen to avoid the so-called value-induced bias.[14]

Responses were anonymized, and only the principal investigator had full access to all data. Participants were also informed that by completing the task, they approved the use of their data. The study was not externally funded, and respondents were given no remuneration.

Expected mortalities after upfront surgery were extracted from the MD Anderson prognostic calculator for each of 3 hypothetical clinical cases.[15] This score was selected from all available[16] because it was the only one based on preoperative variables rather than intraoperative or postoperative findings not known at the time when the therapeutic decision is made. The expected disease-specific mortality of these clinical cases ranged between 11.2 and 37.5 per 100 person-years.[15]

Statistical analysis

Descriptive statistics were reported as frequencies or as median and interquartile ranges. Differences among subgroups were assessed through the χ^2 test or Kruskal-Wallis rank test. Age of respondents, specialty, and surgical volume of the referral hospitals were tested as determinants of "threshold mortality" applying a multilevel mixed-effects model, accounting for the survey nature of the study and the correlation in responses among the same participants. After multilevel regression, a power analysis was performed to assess whether the sample size was sufficient to exclude the null hypothesis of no difference, assuming a power of 80% and an alpha of .05. Statistical analyses were performed with Stata (Stata Statistical Software: Release 15, StataCorp, LLC, College Station, TX).

Results

Respondents were mostly male (49/60; 81.7%) with a median age of 52 years (IQR: 45, 58). Twenty-seven (45.0%) worked in hospitals with surgical referral units performing <50 pancreatic resections/year (low-medium volume). Eighteen (30.0%) worked in or with surgical units performing 50 to 100 pancreatic resections/year (high volume), and 15 respondents (25.0%) worked in or with surgical units performing ≥100 pancreatic resections/year (very high volume). In addition, most respondents declared that patients were always discussed during regular multidisciplinary team meetings (83.3%). In contrast, the remaining proportion of physicians declared that if the patient was evidently fit for surgery, multidisciplinary team was avoided.

Elicitation of regret

Regret of omission from the neoadjuvant strategy was highest in the high-risk recurrence scenario. It decreased through the intermediate-risk and the low-risk scenarios (P value for trend <.001, Table I and Figure 2, *A*). On the other hand, regret of commission to neoadjuvant chemotherapy was the lowest in the high-risk recurrence scenario. It increased through the intermediate-risk and the low-risk scenarios (P value for trend < .001). In simple terms, the higher the expected risk of recurrence after upfront surgery, the higher the regret from omitting neoadjuvant; additionally, the higher the recurrence risk, the lower the regret deriving from starting neoadjuvant if the tumor progresses during chemotherapy.

Threshold mortality

Table I and Figure 2, *B* also show threshold mortality, at which disease-specific mortality with upfront surgery equals that of neoadjuvant strategy. It can be seen that threshold mortality was lowest in the high-risk recurrence scenario and highest in the low-risk scenario. In the high-risk recurrence scenario the median value of the threshold mortality was 32.0%, in the intermediate-risk scenario it was 44.2%, and in the low-risk scenario it was up to 65.2% (P value for trend < .001).

This means that to minimize regret in the case of the wrong decision, respondents accept lower disease-specific mortality after upfront surgery in the high-risk scenario, and higher disease-specific mortality after upfront surgery in the low-risk scenario. However, if expected mortality after upfront surgery is higher than this threshold, neoadjuvant strategy would represent the least regrettable strategy to adopt. Thus, applying expected mortalities extracted from the literature, it was observed that neoadjuvant therapy represented the least regrettable choice in 60.0% of respondents in the high-risk scenario, 18.3% in the intermediate-risk scenario, and only 3.3% in the low-risk scenario (P value for trend < .001).

Specialists' effect

No differences were observed among specialists when faced with the high-risk clinical vignette (Table II). This means that the specialists uniformly adhered to the least regrettable choice in worst-case scenarios.

In the intermediate-risk scenario, surgeons had the lowest regret of omission related to neoadjuvant therapy ($P = .005$). Still, they experienced the highest regret of commission ($P = .013$),

Table I
Survey results reporting the elicited regret, on a scale from 0 (no regret at all) to 100 (maximum regret), from the 60 respondents over 3 clinical vignettes at different risks of tumor recurrence after upfront surgery

Item	High-risk scenario	Intermediate-risk scenario	Low-risk scenario	P value for trend
Regret of omission	74 (58–100)	51 (46–69)	37 (25–50)	< .001
Regret of commission	36 (20–50)	45 (31–55)	73 (54–92)	< .001
Threshold mortality	32.0% (21.4–43.6)	44.4% (31.1–57.1)	65.2% (50.4–76.8)	< .001
Neoadjuvant as least regrettable*	36/60 (60.0%)	11/60 (18.3%)	2/60 (3.3%)	< .001

Data are reported in median and interquartile range (25th and 75th). Threshold mortality = 1/1 + (omission/commission), as reported in Figure 1, and depicts the mortality after upfront surgery below which the regret is minimized. Above this value, neoadjuvant chemotherapy represents the least regrettable choice. Neoadjuvant is the least regrettable choice when expected mortality is above the threshold mortality. The following mortality rates were adopted from the literature: high risk = 37.5 per 100 person-years; intermediate risk = 27.9 per 100 person-years; low-risk = 11.2 per 100 person-years.
* Proportion of respondents.

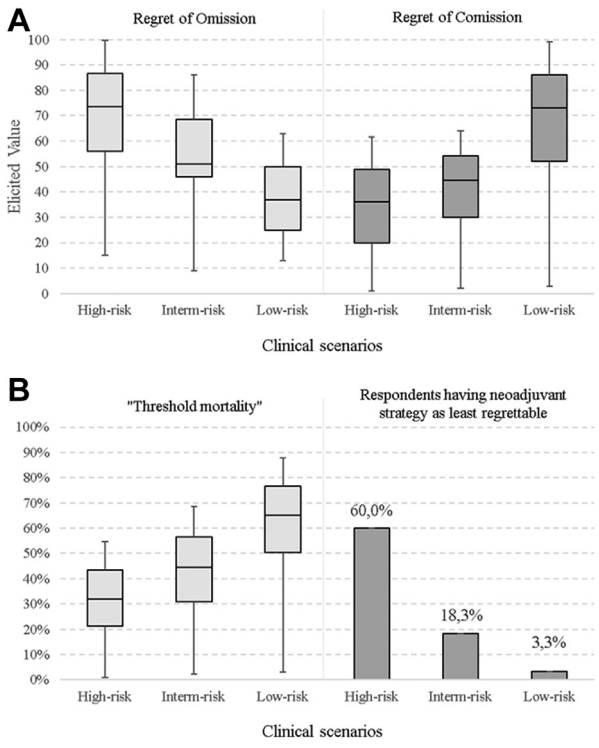

Figure 2. (A) Box plot reporting regret of omission and of commission in each of the 3 clinical vignettes presented to the 60 respondents. (B) Box plot presenting threshold mortality = 1 / (1+ [regret of omission/regret of commission]) and columns reporting the percentage of respondents in which the expected mortality after upfront surgery extracted from the literature is above their threshold mortality, indicating that neoadjuvant would be the least regrettable choice. The following mortality rates were adopted from the literature: high risk = 37.5 per 100 person-years; intermediate risk = 27.9 per 100 person-years; low risk = 11.2 per 100 person-years.

giving more weight to potential harms from neoadjuvant therapy versus potential benefits of surgery than other specialists. This resulted in significant differences in the threshold mortality among 3 groups of specialists ($P = .007$); neoadjuvant therapy represented the least regrettable choice in 35.5% of oncologists versus 15.0% of gastroenterologists versus 5.0% of surgeons ($P = .044$).

In the case of the low-risk clinical vignette, no differences were observed among specialists. This also means that, in best-case scenarios, specialists uniformly adhered to the least regrettable choice.

Surgical volume of the referral hospital effect

In the high-risk recurrence scenario, the surgical volume of the referral hospital had no impact on the regret of omission or commission ($P > .10$ in both cases), meaning that oncologists, gastroenterologists, and surgeons uniformly adhered to the least regrettable choice (Table II).

In the intermediate-risk scenario, respondents working in the low/medium surgical volumes settings had slightly higher regret of commission versus respondents working in high/very high surgical volumes settings ($P = .054$). This translated into the highest threshold mortality with upfront surgery in respondents working in the low/medium surgical volumes settings ($P = .035$). Neoadjuvant therapy represented the least regrettable choice in 30.3% of respondents practicing in high/very high surgical volumes environments versus 3.7% of respondents working in low/medium surgical volumes institutions ($P = .008$).

In the low-risk recurrence scenario, respondents from low/medium surgical volume settings showed higher regret of commission than those working in high/very high-volume facilities ($P = .013$). This translated into the highest threshold mortality with upfront surgery ($P = .008$), which, in turn, determined that neoadjuvant therapy was the least regrettable in 0% of respondents working in the low-medium surgical volumes facilities and 6.1% of respondents practicing in the high-very high surgical volume settings.

Regression analysis

Overall, we observed a decrease in the effect on the threshold mortality ($P = .010$) for physicians working in hospitals with high/very high surgical volume units. This means that these physicians would be more prone to avoid upfront surgery, deciding more frequently for neoadjuvant strategy, compared to physicians working in hospitals with lower surgical volumes (Table III). Finally, when surgeons were compared to oncologists, an incremental effect ($P = .018$) on the threshold mortality was observed, meaning that surgeons would accept higher mortality of upfront surgery with lower propensity to opt for neoadjuvant strategy. Power analysis confirmed that the sample was sufficient to prove these relationships (Table III).

Discussion

Both emotions and deliberation characterize clinical decision-making[17]; this makes regret theory particularly suitable for application to clinical situations similar to those described in this work. According to regret theory, optimal medical decisions are associated with regret-averse decision processes and outcomes.[10,18] In the present study, we analyzed how regret can drive medical decisions related to the administration of neoadjuvant therapy to patients with localized and potentially resectable PDAC. Previous studies showed the applicability of the regret model in other settings,[7,8]

Table II
Survey results reporting the elicited regret, on a scale from 0 (no regret at all) to 100 (maximum regret), from the 60 respondents over 3 clinical vignettes at different risks of tumor recurrence after upfront surgery, stratified by respondent specialty and the volume of the referral surgical unit

	Specialty			
	Oncologists ($n = 20$)	Gastroenterologists ($n = 20$)	Surgeons ($n = 20$)	*P* value
High-risk scenario				
Regret of omission	74 (61–97)	73 (54–88)	78 (65–100)	.486
Regret of commission	33 (24–41)	44 (29–66)	36 (17–50)	.126
Threshold mortality	32.0% (21.9–39.8)	40.7% (25.1–51.5)	27.3% (14.9–40.5)	.188
Neoadjuvant as least regrettable*	14/20 (70%)	9/20 (45%)	13/20 (65.0%)	.233
Intermediate-risk scenario				
Regret of omission	55 (50–64)	64 (50–74)	47 (32–51)	.005
Regret of commission	39 (16–48)	47 (34–62)	53 (43–79)	.013
Threshold mortality	36.4% (23.1–49.7)	42.6% (31.8–54.2)	57.1% (42.4–67.1)	.007
Neoadjuvant as least regrettable*	7/20 (35.0%)	3/20 (15.0%)	1/20 (5.0%)	.044
Low-risk scenario				
Regret of omission	38 (31–51)	34 (25–51)	29 (23–46)	.505
Regret of commission	59 (42–77)	78 (61–97)	77 (61–100)	.074
Threshold mortality	61.5% (47.5–69.2)	66.9% (54.0–79.2)	67.8% (52.6–78.7)	.330
Neoadjuvant as least regrettable*	1/20 (5.0%)	1/20 (5.0%)	0/20 (0.0%)	.596

	The surgical volume of the referral hospital		
	Low-medium ($n = 27$)	High-very high ($n = 33$)	
High-risk scenario			
Regret of omission	80 (56–97)	72 (64–100)	.940
Regret of commission	38 (28–67)	32 (20–43)	.186
Threshold mortality	35.0% (22.4–43.2)	29.8% (20.0–44.0)	.435
Neoadjuvant as least regrettable*	16/27 (59.3%)	20/33 (60.6%)	.916
Intermediate-risk scenario			
Regret of omission	50 (37–58)	59 (48–71)	.093
Regret of commission	51 (36–71)	42 (21–48)	.054
Threshold mortality	50.0% (34.8–62.5)	40.6% (23.4–50.5)	.035
Neoadjuvant as least regrettable*	1/27 (3.7%)	10/33 (30.3%)	.008
Low-risk scenario			
Regret of omission	31 (22–44)	42 (29–52)	.078
Regret of commission	78 (65–100)	62 (49–83)	.013
Threshold mortality	71.8% (62.5–80.0)	59.6% (45.5–69.6)	.008
Neoadjuvant as least regrettable*	0/27 (0.0%)	2/33 (6.1%)	.193

Data are reported in median and interquartile range (25th and 75th). Threshold mortality = 1/1 + (omission/commission), as reported in Figure 1, and depicts the mortality after upfront surgery below which the regret is minimized. Above this value, neoadjuvant chemotherapy represents the least regrettable choice. Neoadjuvant is the least regrettable choice when "expected mortality" is above the threshold mortality. The following mortality rates were considered from the literature: high risk = 37.5 per 100 person-years; intermediate risk = 27.9 per 100 person-years; low risk = 11.2 per 100 person-years.

* Proportion of respondents.

and we now corroborate the validity of the regret threshold model in the surgical oncological setting.

According to the US National Comprehensive Cancer Network and the European Society of Medical Oncology guidelines, upfront surgery is recommended for resectable disease except in cases with preoperative high-risk features.[19,20] The latter include highly elevated CA19-9, large primary tumors, positive regional lymph nodes, excessive weight loss, and severe pain. The present high-risk clinical scenario fulfilled these characteristics, for which a disease-specific mortality around 50% to 60% after 1 year from upfront surgery is predictable.[15,21] Facing such a high probability of unfavorable prognosis, practically all respondents would opt for a neoadjuvant strategy, justifiable based on the regret model.

The intermediate-risk case provided interesting findings. Subgroup analyses revealed a large gap among different specialists and in relationship with the surgical volume of their referral hospitals. First, surgeons were more prone to experience higher regret of commission related to neoadjuvant therapy and lower regret if they omitted it (Table II). However, this clinical vignette had a sort of a trap for them, since it was designed to tempt them to go for an "easy" distal pancreatectomy, usually associated with lower risk of severe complications. That is, surgeons can lose sight of the potential oncological benefit deriving from neoadjuvant treatment by focusing only on technical feasibility, as in this scenario when they felt that benefits from neoadjuvant therapy were low. The oncologists stand on the opposite side of the regret spectrum as they would focus mainly on the systematic treatment of the cancer, losing sight of the fact that the tumor could have been easily removed if time was not lost on neoadjuvant chemotherapy. Compared to the other 2 vignettes, where a pancreatoduodenectomy was required, the present clinical case clearly represents the cognitive bias that clinicians display on a daily basis in their decision making on PDAC. Second, respondents working in low/medium volume surgical hospitals deemed higher mortality acceptable when recommending upfront surgery; thus, they were less prone to propose neoadjuvant treatment. Multivariable analysis showed that these features were independently related to mortality cutoffs, meaning that surgeons working in low/middle surgical units were more inclined to adopt upfront surgery rather than neoadjuvant therapy.

Surgical volume also affected threshold mortality with upfront surgery in the low-risk clinical scenario, with respondents working in a low/middle surgical volumes setting showing a higher tendency to opt for upfront surgery (Table II). It is already known that patients treated in low/medium hospitals undergo neoadjuvant therapy less frequently.[22,23] However, this is commonly viewed as the consequence of the fact that more complex cases are referred to high-volume hospitals because of the perceived need for neoadjuvant chemotherapy. The present results highlight that when patients are evidently not at high risk for recurrence, physicians working in low/middle surgical volumes settings give less value to

Table III
Multilevel mixed-effects regression evaluating the effect of respondent age, specialty, and surgical volume of the referral hospital on the threshold mortality

Variable	Coef. (95% CI)	*P* value
Age (per year of increase)	0.001 (-0.004, 0.004)	.921
High/very high surgical volume (versus low/medium)	-0.091 (-0.160, -0.021)	.010
Specialty		
Oncologists	Ref.	-
Gastroenterologists	0.078 (-0.007, 0.162)	.071
Surgeons	0.102 (0.018, 0.187)	.018

Positive coefficients mean that the variable increases the threshold mortality; negative coefficients mean that the variable decreases the threshold mortality.
The r-squared was 0.488, and, assuming a power of 80% and an alpha of .05, the estimated sample necessary to exclude the null hypothesis was 16 patients, thus lower than the sample for each specialty considered, confirming sufficient power.

mortality after upfront surgery. As a consequence, the patients with potentially resectable PDAC will not be referred even if they may benefit from it. Considering that centralization of services can result in outcomes with higher life-expectancy,[22,23] the present results suggest referral to hospitals with high/very high patient volumes even in cases not at evidently high biological risk for tumor progression.

The current study has some limitations. First, we considered only physician preferences and not patient preferences. However, the clinical decision about surgical resection and neoadjuvant treatment is quite complex to be fully understood by patients, and although the patient has to consent to the procedure, the final responsibility for the recommended treatment rests with the physician(s).[6] The second limitation refers to the fact that each respondent elicited their own regret on the basis of their own experience, which did not necessarily reflect adequate and updated knowledge of biology of tumor.[24] In addition, we acknowledge that respondents were selected through a purposeful-sample approach and that the present sample may not fully represent all clinicians treating patients with PDAC. However, all participants were deemed to be experienced clinicians, expected to know the latest evidence on the topic, and, of paramount importance, are people, who, in fact, make these very same decisions in actual clinical settings on daily basis. Third, it is conceivable that a larger sample size could detect statistically smaller, yet meaningful, effects; however, the observed large effects confirm the important role of regret in clinical decision-making of pancreatic cancer akin to similar effects seen in other clinical settings.[5,7,8] Educating physicians to reflectively think about their regret has the potential to improve medical decision-making. Fourth, the expected mortality data used here were extracted from the MD Anderson model[15]; thus, the change in the model can modify the interpretation of the results. Nevertheless, data about expected mortality after upfront surgery of each clinical vignette were not provided to respondents during the survey, indicating that elicitation of regret was not affected.

In conclusion, the present study demonstrates that different physicians working in different hospitals will likely make similar decisions for PDAC patients with high-risk features but can decide differently on the same patient who presents with intermediate or low biological risk. This particularly affects surgeons working in low/medium volume surgical units, who are more prone to opt for upfront surgery. Given these differences, it would be preferable to make decisions in multidisciplinary teams working, preferably, in high-volume hospitals to ensure that more consistent elicitation of preferences can be achieved.

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Conflict of interest/Disclosure

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Supplementary materials

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