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Une analyse décisionelle de l'approche diagnostique optimale avant la cholécystectomie par voie laparoscopique

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Chez les patients en attente de cholécystectomie par voie laparoscopique, le moment et la façon d'intervenir pour exclure une cholédocholithiase asymptomatique concomitante sont incertains. Nous émettons l'hypothèse que, pour réduire les coûts hospitaliers, la stratégie optimale sera définie en fonction du risque pré-opératoire de cholédocholithiase.

Un arbre décisionnel a été construit pour comparer les coûts de 4 stratégies courantes: une conduite expectative, la cholangiographie rétrograde par voie endoscopique (CPRE), la cholangiographie intra-opératoire (CIO), et l'échographie endoscopique. Le modèle décisionnel a incorporé la précision diagnostique, le taux de complications, le taux d'examens échoués, et le coût relatif des procédures (et de leur complications). Le coût des 4 stratégies a été evalué en fonction du risque préopératoire de cholédocholithiase. Ce risque peut être estimé par le clinicien sur la base sur l'histoire clinique, de l'examen physique, du bilan biologique de base, et de l'échographie transcutanée de dépistage.

L'analyse de sensibilité à une variable ("1 way sensitivity analysis") variant seulement le risque de cholédocholithiase de 0 à 100% révèle que la stratégie la moins coûteuse semble changer en fonction du risque estimé de calculs. De 0 à 10% ("faible" risque), la conduite expectative est préférable, de 11% à 55% ("risque intermédiaire") l'échoendoscopie est

moins coûteuse, et de 56% à 100% la CPRE est la moins onéreuse. L'analyse de sensibilité à deux variables ("2 way sensitivity analysis") suggère que ces seuils sont le plus sensibles à des changements du risque de symptômes et de complications secondaires à une cholédocholithiase non-traitée, au coût relatif des trois procédures, et au niveau d'expertise de l'opérateur. La CIO est préférable à l'échoendoscopie seulement si son coût (en tant que procédure individuelle) est moins de 60-70% du coût de la CPRE et inférieur à celui de l'échoendoscopie. Les seuils sont relativement insensibles aux changements du risque et de la sévérité des complications dues à la CPRE.

Nous concluons que, dans le contexte des patients en attente de cholécystectomie par voie laparoscopique, l'analyse décisionelle suggère que la stratégie la moins coûteuse varie en fonction du risque pré-opératoire de cholédocholithiase. Des patients en attente de CVL peuvent être classés en trois groupes selon le risque estimé de cholédocholithiase: faible (<10%); intermédiaire (10-50%); et haut (>50%). Pour minimiser les coûts hospitaliers, la conduite expectative semble préférable pour des patients à faible risque, tandis que la CPRE est meilleure chez des patients à haut risque. Tout autre patient (i.e. ceux à risque intermédiaire) peut bénéficier d'une échoendoscopie ou d'une CIO, le moins cher des deux. Par contre, des procédures moins invasives

comme la CIO et l'échoendoscopie semblent réduire les coûts hospitaliers seulement si le risque de symptômes dus à une cholédocholithiase non-traitée est supérieur à environ 15%, si leur coût est moins de 60-70% de celui de la CPRE, et lorsque l'expertise de l'opérateur est suffisante pour assurer une précision diagnostique et un taux de réussite supérieurs à environ 90%.

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Liste des Sigles et Abbréviations

CPRE – cholangiopancréatogaphie retrograde endoscopique

CIO – cholangiographie intra-opératoire

CVL – cholécystectomie par voie laparoscopique

INTRODUCTION

L'histoire naturelle des calculs de la vésicule biliaire est bien connue. Il est généralement accepté que seulement des calculs *symptomatiques* méritent un traitement (médical ou chirurgical) pour prévenir des complications potentiellement graves comme, par exemple, une cholécystite aigue. Le mode de traitement reconnu est l'ablation chirurgicale de la vésicule biliaire; soit la cholécystectomie. On estime qu'environ 500 000 cholécystectomies sont pratiquées annuellement en Amerique du Nord.[1]

Auparavant, la cholécystectomie était pratiquée par l'approche "ouverte". Cette technique nécessite une incision de la peau et une section complète des muscles de la paroi abdominale au niveau de l'hypochondre droit; résultant en une morbidité post-opératoire non négligeable.

Dans les dix dernières années, l'approche *laparoscopique* a gagné en popularité. L'exérèse de la vésicule biliaire est pratiquée à l'aide d'instruments miniaturisés via quatres incisions abdominales de moins d'un centimètre chacune. Cette technique diminue la morbidité et la durée de la convalescence post-opératoire, en plus d'être esthétiquement préférable pour certains patients.[2,3] Malheureusement, la chirurgie par voie laparoscopique ne permet pas de palper les structures intra-abdominales. En conséquence, le chirurgien est incapable d'exclure la présence de calculs concomitants dans la voie biliaire principale (le

cholédoque) par la manipulation directe de cette structure; ce qui se faisait auparavant lors de la cholécystectomie ouverte.

Des calculs cholédociens asymptomatiques sont retrouvés chez dix à quinze pourcent des patients non-sélectionnés en attente de cholécystectomie[4], à cause des contractions vésiculaires qui expulsent occasionellement des calculs vers la voie biliaire principale. Ces calculs peuvent demeurer dans le cholédoque ou migrer vers la lumière intestinale. L'histoire naturelle des calculs *cholédociens* est moins bien étudiée que celle des calculs vésiculaires. Les calculs cholédociens peuvent demeurer asymptomatiques, mais peuvent également nuire au drainage biliaire ou pancréatique et causer des symptômes mineurs (e.g. douleur abdominale transitoire) ou des complications potentiellement mortelles (e.g. pancréatite aigue ou cholangite). La majorité des cliniciens ne tolèrent pas une conduite expectative face à la découverte d'une cholédocholithiase, symptomatique ou asymptomatique.[5] En conséquence, la proportion de calculs cholédociens ayant une évolution non-compliquée et la fréquence de complications *sévères* sont inconnues.

Plusieurs techniques sont utilisées pour le diagnostic des calculs cholédociens. Parmi celles-ci on retrouve: la cholangiopancréatographie rétrograde endoscopique (CPRE), la cholangiographie intra-opératoire (CIO), et l'échoendoscopie.[6-16] Chez les patients en attente de cholécystectomie par voie laparoscopique (CVL), la CPRE est la technique la plus fréquemment employée; car elle est disponible dans la

majorité des centres pratiquant la CVL, sa précision diagnostique est très élevée, et elle peut aussi servir de modalité thérapeutique. Par contre, elle est relativement coûteuse et nécessite un niveau d'expertise élevé. Elle peut aussi causer une pancréatite aigue chez environ 5% des patients.[17] La CIO et l'échoendoscopie ont également une haute précision diagnostique; mais sont moins coûteuses et ne causent pas de pancréatite. Cependant, ces procédures n'ont, à toute fin pratique, aucun potentiel thérapeutique.

Intuitivement, le coût et le risque de complications associées à la CPRE semblent difficiles à justifier chez des patients à faible risque de cholédocholithiase, puisque la majorité des examens seront normaux et les patients ne nécessiteront pas d'extraction endoscopique de calcul. Similairement, les alternatives non-thérapeutiques comme la CIO et l'échoendoscopie semblent moins appropriées lorsque le risque de calculs est élevé. Mais, exactement quel niveau de risque justifie quel niveau d'intervention?

Une revue exhaustive de la littérature a démontré qu'aucun auteur n'a abordé ce problème dans le but de préciser les seuils de risque nécessaires pour adéquatement classer les patients en attente de CVL. Plusieurs groupes ont étudié les prédicteurs cliniques de la cholédocholithiase.[14,18-25] Cependant, ces travaux aident à établir le niveau de risque de cholédocholithiase chez un patient individuel, sans

toutefois établir si ce niveau de risque justifie une intervention, ou quelle intervention est préférable.

Dans le climat économique actuel, une des façons de juger si une procédure diagnostique est "justifiée" et/ou "préférable" est de vérifier si son coût *total* est inférieur aux autres. Ce coût comprend non seulement le prix des procédures individuelles, mais également la consommation de ressources générée par des faux positifs, des faux négatifs, des échecs techniques, et des complications. Dans le contexte particulier de l'évaluation préopératoire des patients en attente de CVL, il est également important d'évaluer le coût d'une conduite expectative (i.e. l'option de ne pas intervenir pour diagnostiquer des calculs cholédociens), car plusieurs auteurs recommendent empiriquement cette stratégie pour des patients à faible risque.

Il serait difficile, sinon impossible, d'évaluer prospectivement le vrai coût de la conduite expectative, car il serait éthiquement injustifiable d'observer (i.e. de ne pas investiguer et/ou de ne pas traiter) des patients ayant une cholédocholithiase prouvée ou fortement suspectée; à cause du risque inconnu, mais non-négligeable, de complications sévères. Pour cette raison, une étude par analyse décisionelle est utile dans l'évaluation de la meilleure stratégie à adopter chez les patients en attente de CVL.

L'analyse décisionelle permet une étude rigoureuse et structurée d'un probleme dans des conditions d'incertitude.[26,27] Lorsqu'il s'agit d'une évaluation du meilleur choix entre des nouvelles technologies

diagnostiques, il faut d'abord construire un arbre décisionnel. Ce modèle décisionnel schématise une séquence logique et plausible des conséquences possibles de l'emploi de chaque modalité diagnostique considérée. Il est préférable d'inclure également l'option de ne pas tester. La construction de l'arbre décisionnel nous oblige à identifier et à mettre en relief les variables clefs du problème. Les valeurs des variables incertaines doivent être estimées, le plus souvent possible, à partir des données objectives disponibles. Finalement, il faut attribuer une valeur numérique à l'état clinique à la fin de chaque branche.

Notre hypothèse principale est que, chez les patients en attente de CVL, le test le moins coûteux pour diagnostiquer une cholédocholithiase varie en fonction du risque initial de cholédocholithiase. Cette variable a donc été choisie comme point de départ de l'arbre décisionnel. Ensuite, le modèle évalue le coût des 4 stratégies (une conduite expectative, la CPRE, la CIO, et l'échoendoscopie) en fonction du risque de cholédocholithiase, en considérant la précision diagnostique des tests ainsi que la fréquence de tests non-diagnostiques, et le risque et la sévérité des complications possibles. L'étude a donc commencé par une forme "étude de seuil" afin de déterminer s'il existe des seuils (exprimé en terme du risque de cholédocholithiase) auxquels la stratégie la moins coûteuse change.

Ensuite, une "analyse de sensibilité" a été effectuée pour vérifier si les seuils identifiés sont robustes et pour déterminer quelles variables

sont les plus susceptibles d'affecter ces seuils. Le but de cette étape de l'analyse est donc de déterminer quelles variables cliniques ont le plus grand impact sur le coût de l'investigation de la cholédocholithiase chez les patients en attente de CVL.

BILE DUCT STONES AND LAPAROSCOPIC CHOLECYSTECTOMY: A DECISION ANALYSIS TO ASSESS THE ROLES OF INTRA-OPERATIVE CHOLANGIOGRAPHY (IOC), ENDOSCOPIC ULTRASOUND (EUS), AND ENDOSCOPIC RETROGRADE CHOLANGIOPANCREATOGRAPHY (ERCP)

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ABSTRACT

BACKGROUND: The least costly management strategy for laparoscopic cholecystectomy (LC) patients is unclear. METHODS: A decision model incorporating cost ratios, test accuracy, complication, and failure rates was used to determine the costs of 4 peri-LC strategies: ERCP, intra-operative cholangiography (IOC), endoscopic ultrasound (EUS), and expectant management. RESULTS: The least costly strategy changes as the risk of choledocholithiasis increases: 0-10% ("low" risk) merits expectant management; 11%-55% ("intermediate" risk) merits EUS; and >55% ("high" risk) merits ERCP. Thresholds were most sensitive to changes in the risks (but not the severity) of symptoms and complications due to retained stones; and to procedural costs, sensitivity, and success rates. IOC is useful when EUS is unavailable and the risk of stones is between 17% and 34%. Neither IOC nor EUS reduce overall costs unless their accuracy and success rates are >85%-90% and their procedural cost is <60%-70% that of ERCP. When neither are available, ERCP is preferable when the risk of stones is >22%. Thresholds were relatively insensitive to changes in the risk and severity of ERCP-induced pancreatitis. CONCLUSIONS: The least costly strategy for LC patients depends primarily on the risk of stones and stone-related symptoms, but procedural costs and operator expertise are also critical.

INTRODUCTION

Laparoscopic cholecystectomy (LC) is currently the most popular means for treating symptoms attributable to stones in the gallbladder. However, a subgroup of patients awaiting LC will also have stones in the common bile duct.[1-5] It is generally accepted that common bile duct stones should be removed (even if asymptomatic), since they may be associated with severe complications such as pancreatitis and cholangitis. However, manipulation of the common bile duct during LC is not popular among most laparoscopic surgeons.[5,6] It is usually perceived to be technically difficult and time consuming and is currently unavailable in the majority of North American hospitals where LC is performed.

Endoscopic retrograde cholangiopancreatography (ERCP) is the most popular peri-LC common bile duct imaging method; since it is readily available, highly accurate, and has therapeutic potential. However, if ERCP is requested too liberally, its costs may outweigh its benefits; due to the small but significant risk of well-known complications. Clinical criteria may be used to group patients according to their risk of having common bile duct stones[7-15]. Presumably, patients with a "high risk" of harboring common bile duct stones benefit most from pre-operative ERCP -- since stones are likely to be found and their endoscopic removal can theoretically prevent the costs and morbidity associated with symptoms and/or complications related to choledocholithiasis.

In lower risk patients, many authors recommend safer but purely diagnostic tests like intraoperative cholangiography (IOC) and endoscopic ultrasound (EUS), or no intervention altogether (expectant management), as a means of cutting costs and

complications (which often go hand in hand). It is not known whether this strategy actually reduces costs and, if so, under which conditions. Important, yet unanswered questions include: 1) When selecting LC patients for testing, does the least costly strategy really change as the risk of stones increases?; 2) If so, what thresholds of risk for choledocholithiasis should be used to separate patients into "high", "moderate", and "low" risk subgroups?; and 3) Which variables are most likely to affect the overall costs of managing these patients?

To answer these questions, we used decision analysis, incorporating the costs, operating characteristics, complication, and failure rates of the various procedures; as well as the potential need for re-intervention due to retained common bile duct stones.

METHODS

Tree design and Model assumptions

Based on a consensus of expert local opinion, a decision tree was constructed using Data 2.6.7 computer software (TreeAge Software Inc.) to analyze 4 possible peri-LC management strategies: 1) ERCP, 2) EUS, 3) IOC, or 4) expectant management The tree was structured from the perspective of a clinician faced with an individual patient awaiting LC. The model required certain assumptions.

Prospective studies of IOC and EUS accuracy for detecting common bile duct stones were used to calculate weighted averages (based on the number of patients in each study).(**Tables 1 and 2**) The initial model inputs were therefore as follows: EUS sensitivity 92%; EUS specificity 97%; IOC sensitivity 90%; and IOC specificity 95%. To

maintain the overall superiority of ERCP as a diagnostic gold standard, it was attributed a sensitivity and specificity of 95% and 98% respectively. A range of 75% to 100% was used for sensitivity analysis.

The major difference between the three procedures is the risk of complications. EUS and IOC were assumed to have no associated complications -- based on information in the literature suggesting that the rate of complications requiring prolongation of hospitalization is < 0.1%.[16-20] Diagnostic ERCP can cause pancreatitis. For the purposes of this analysis, literature-based risk estimates were set initially at 3% (range 0-6%) for "mild" and 0.1% (range 0-1%) for "severe" pancreatitis.[21-24] No distinction was made between the risk of complications between diagnostic and therapeutic procedures (although the risk is generally higher with the latter).The definitions of mild and severe pancreatitis were adapted from those of Cotton et al.[22] Mild pancreatitis required 3 days (range 0-5 days) hospitalization in a regular ward and severe disease required 3 days (range 0-10 days) days in an intensive care unit, plus 7 days (range 0-20 days) in a regular ward.

Another potentially key variable is operator expertise. The model incorporated this as an independent variable by allowing each test to be either "positive", "negative" or "indeterminate" (e.g. due to failed cannulation at ERCP, inability to visualize the entire bile duct at EUS, inability to interpret images confidently due to lack of experience, etc.). Positive tests would require confirmatory ERCP (with endoscopic extraction of any stones identified), and negative tests would result in expectant management (with post-operative ERCP for symptoms only). Indeterminate tests could

be followed either by expectant management, by confirmatory ERCP (in the case of IOC and EUS), or by surgery with or without IOC (in the case of EUS and ERCP). In expert hands, it is reasonable to expect successful bile duct cannulation during ERCP in approximately 95% of cases. Therefore, the risk of indeterminate ERCP procedures was set at 5% initially; with a range [for sensitivity analysis] of 0% to 25%. Based on a review of the recent literature, weighted averages for the rates of indeterminate EUS and IOC were calculated and set at 3% and 9% respectively (range 0%-25%).(**Tables 1 and 2**) The value of IOC to prevent common bile duct injuries by delineating aberrant biliary anatomy is controversial[18,25-28], and was therefore not factored into the model.

Finally , the impetus for excluding choledocholithiasis in LC patients is the fear of stone-related symptoms -- mild and severe. If all, or a sufficiently high proportion of stones passed without incident, there would be little need to look for them. There is no literature specifically documenting: 1) the exact risk of retained stones producing *any* symptoms; nor 2) what proportion of any recurrent symptoms will take the form of a severe complication. A panel of 10 experts in the fields of laparoscopic biliary surgery and biliary endoscopy (see "Acknowledgements") was surveyed to determine if a crude "consensus" estimate of these risks could be obtained. The results were as follows: 1) for stones < 5mm: risk of *any* symptoms in a 10 year period = 27% (range: 1 to 60) and the proportion of recurrent symptoms presenting as a severe or "life-threatening" *complication* = 8% (range: 1 to 30); 2) for stones > 5mm: *any* symptoms = 62% (range: 25 to 97) and proportion of complicated symptoms = 23% (range: 5 to 90). The extremely wide ranges attests to the lack of adequate data required to answer these

questions. In fact, most respondents indicated spontaneously that they were very unsure and were basically guessing. We concluded that a true consensus of opinion could not be obtained.

Therefore, the model was designed to incorporate this uncertainty and to quantify its repercussions on the final outcome. This was accomplished by including the risk of *any* symptoms and the proportion of recurrent symptoms presenting as *complications* as separate and independent variables; and by allowing these risks to range from 0 to 100% in the sensitivity analysis. To maintain the conservative nature of the model, it was assumed initially that large stones would be missed as often as small stones, that the risk of symptoms and complications is independent of stone size, that the risk of any symptoms due to missed stones is 100% (i.e. all retained stones will produce symptoms), and that missed stones have a 50% risk of presenting as a severe complication (i.e. when retained stones become symptomatic, 50% will result in a severe complication).

*Un*complicated symptoms (e.g. biliary colic, jaundice without fever, etc.) incur only the costs of a therapeutic ERCP (with its associated risks); whereas complicated symptoms (e.g. life-threatening pancreatitis or cholangitis) incur the costs of therapeutic ERCP *plus* the costs of hospitalization (3 days in the ICU plus 7 days in a regular ward).

Cost estimates

Cost estimates were obtained from the perspective of the provider[29], and included direct as well as indirect costs for the following (as needed for each

endoscopic or surgical intervention): patient monitoring, intravenous kits and drugs, recovery time, physician time, operating room time, anesthesia, fluoroscopy, and all non-reusable endoscopic and operating room equipment.(**Table 3**) In our center, the following cost estimates were obtained: $786.00 for diagnostic ERCP, $338.00 for EUS, $448.00 for IOC (assuming that IOC adds the costs of 30 minutes of operating room time, anesthesia, and fluoroscopy to the cost of LC), $450.00 for one day of hospitalization in a regular ward, and $1250.00 for one day of hospitalization in an intensive care unit (ICU). For the purposes of sensitivity analysis, costs were varied between 0.5 and 5 times their initial estimates.

In order to facilitate the comprehension of sensitivity analysis involving cost data and to increase the int*er*- and int*ra*-institutional generalizability of our results, costs were incorporated into the model in the form of "relative cost *ratios*". This form of cost representation is based on the premise that, due to local factors, procedural costs may differ substantially in different institutions; whereas the cost *ratio* of competing technologies should remain relatively constant from one institution to another. In this case, the costs of EUS and IOC were expressed as fractions of the cost of a *diagnostic* ERCP (i.e. ERCP cost ratio = 1, EUS cost ratio = 0.43, and IOC cost ratio = 0.57).

The cost of *therapeutic* ERCP was calculated as the sum of the cost of *diagnostic* ERCP plus the product of the diagnostic ERCP cost multiplied by a factor (*f*) to adjust for the increased cost of therapeutic ERCP (i.e. therapeutic ERCP cost ratio = diagnostic ERCP cost ratio + [diagnostic ERCP cost ratio x *f*]. Based on the addition of

the costs of a sphincterotome, a guidewire, and a stone-retrieval balloon to the costs of diagnostic ERCP, *f* was initially set at 0.39 (range 0-2).(**Table 3**) The resulting therapeutic ERCP cost ratio was therefore = 1.39 -- meaning that therapeutic ERCP was initially assumed to cost 1.39 times that of diagnostic ERCP. Finally, the cost of a 1 day stay in ICU and the cost of a 1 day stay in a regular ward were also represented as a multiple of the cost of ERCP (ICU daily cost ratio = 1.59 (range 0.8-8), WARD daily cost ratio = 0.57 (range 0.29-2.85). The final cost of each decision tree branch was calculated as the sum of the costs of the procedures and of any required hospitalization for that branch. Conclusions were identical when dollar-value costs were re-substituted for cost ratios.

Clinical scenarios

The original tree incorporates the choice between 3 diagnostic modalities (ERCP, IOC, and EUS) and the option of expectant management with no imaging. While ERCP is currently available in most centers performing LC; this is not the case for IOC, and even less so for EUS. The decision tree was used to determine the optimal management strategy in "clinical scenarios" that reflected the availability (or lack thereof) of the initial 4 options. All possible combinations of the 4 options were therefore analyzed by removing one or more of the 4 major branches of the initial decision tree (except the options of ERCP and expectant management). In all scenarios, we assumed that *laparoscopic common bile duct exploration was unavailable* (since this is currently the situation in the great majority of north American hospitals where LC is performed).

Sensitivity analysis

For each scenario, 1 way sensitivity analysis was performed, plotting costs against the estimated risk of common bile duct stones, to determine the least costly strategy(ies) as a function of the risk of common bile duct stones (range 0-100%). This established thresholds (in terms of the risk of common bile duct stones) for expectant management or for testing (with ERCP, IOC, or EUS). Two way sensitivity analysis was then performed, plotting the risk of common bile duct stones (range 0-100%) versus changes in each of all the other variables (over the ranges specified above), to determine which variables have the most profound effect on the established threshold(s). *A "significant" change in any threshold was defined as any increase or decrease of ≥ 5% from the initial threshold determined by initial 1 way sensitivity analysis.*

RESULTS

Four clinical scenarios were investigated: 1) all 4 options available (ERCP vs IOC vs EUS vs expectant management); 2) EUS unavailable (ERCP vs IOC vs expectant management); 3) IOC unavailable (ERCP vs EUS vs expectant management); and 4) IOC and EUS unavailable (ERCP vs expectant management). Threshold values found by one way sensitivity analysis were the same (when present) in all 4 clinical scenarios. Therefore, only the results of scenario #1 (all 4 options available) are presented.

When all 4 options are available, one-way sensitivity analysis suggests that the least costly strategy changes (at threshold values) as the risk of common bile duct stones increases from 0% to 100%.(**Graph 1**) From 0-10%, expectant management is least costly, from 11-55% EUS is least costly, and for all levels of risk > 55%, initial ERCP is least costly. IOC is never the preferred strategy in this scenario, since its cost ratio is higher than that of EUS.

Two-way sensitivity analysis revealed that changes the following variables produced a significant change in the thresholds identified by one-way sensitivity analysis (i.e. between expectant management and EUS and between EUS (or IOC) and ERCP: the risk of *any* symptoms, the proportion of recurrent symptoms presenting as *complications*, the ICU and ward length of stay and cost for complications due to retained stones, the sensitivity of EUS and IOC, the risk of indeterminate EUS and IOC, and the EUS and IOC cost ratios.

The greatest changes in overall costs, and hence in the different thresholds, were obtained by varying the risk of developing *any* symptoms due to retained stones and/or the proportion of recurrent symptoms that present as severe complications. When overall cost-minimization is the primary goal, the indication for preoperative testing appears to disappear for all levels of stone risk when the risk of *any* recurrent symptoms falls below 15%.(**Graph 2**) If the cost of complications is increased by 500%, this thresholds falls to approximately 5%. The threshold between EUS and ERCP is insensitive to changes in these variables (i.e. it remains stable at approximately 55%).

When an alternative to ERCP or expectant management seems warranted, the choice between EUS or IOC appears to depend most strongly on their procedural cost. **Graph 3** illustrates that the width of the "window" of indication for EUS (or IOC) (between expectant management and ERCP) decreases rapidly as the EUS or IOC cost ratio increases. Since both tests have the similar operating characteristics, the window between expectant management and ERCP tends to be filled by the least costly of the two tests. However, if the cost ratio for either procedure is not below approximately 0.8 (i.e. if their procedural cost is more than 80% that of an ERCP), their potential value seems to disappear completely. However, practically speaking, to be truly useful, their cost ratio must probably be lower than 0.8; since, unless it is below approximately 0.6, the window of indication is very narrow (i.e. width less than 15 percentage points).

Reducing the sensitivity and procedural success rates for EUS and/or IOC produced notable reductions in the thresholds between EUS and/or IOC and ERCP – thus reducing their potential value as cost-saving interventions. Reducing these variables *individually* produced a constant and proportional drop in the threshold for ERCP.(**Table 5**) However, since reduced sensitivity and lower procedural success rates are likely to go hand in hand (since they are both manifestations of operator inexperience), we studied the effects of *simultaneously* reducing both parameters. Not surprisingly, there was an almost additive effect -- with simultaneous 5% reductions in both parameters producing an 8% lowering of the ERCP threshold.

The value of IOC appears particularly vulnerable to these effects. When EUS is unavailable and the choice is between ERCP, IOC, and expectant management the model suggests that IOC reduces overall costs when used selectively in patients with a risk of stones between 17% and 34%.(**Graph 1**) If the sensitivity of IOC is reduced by 5% (from 90%to 85%) and its procedural success rate is reduced simultaneously by 5% (from 91% to 87%), the ERCP threshold drops from 34% to 26%. This degree of threshold reduction tends to reduce the width of its "window" to a point where IOC may no longer be clinically useful (i.e. only those with a risk of stones between 17 and 26% would benefit, so the width of the window would be only 9%). EUS seems somewhat less vulnerable to these changes since simultaneous reductions in sensitivity in procedural success rates of 5% (sensitivity 87%; success rate 93%) reduce the ERCP threshold to 43% (leaving a window of 32% [between 11% and 43%]) and simultaneous reductions of 10% (sensitivity 83%; success rate 88%) lower the ERCP threshold to 35% (leaving a window of 24% [between 11% and 35%]).

The remaining variables produced significant (>5%) threshold changes only at the extremes of the ranges set for sensitivity analysis. The length of hospitalization for severe complications due to missed stones affected the threshold between expectant management and EUS and/or IOC; but significant changes began only after the length of stay was reduced to ≤ 2 days in an ICU and/or ≤ 7 days in a regular ward.

DISCUSSION

Now that symptomatic gallstones are routinely managed by LC, the proper selection of patients for peri-operative common bile duct imaging is crucial. Due to advances in non- or minimally invasive biliary imaging techniques, the potential to manage patients more cost-effectively would appear to be increasing. Whether these tests actually reduce costs is unclear. Many authors have correlated the risk of common bile duct stones with constellations of clinical parameters such as symptoms, liver enzyme abnormalities, bilirubin levels, and common bile duct diameter (assessed by trans-abdominal ultrasound). Clinicians can therefore estimate the risk that an individual patient awaiting LC has common bile duct stones. The primary aims of this study were to determine risk thresholds that could be used to triage patients for appropriate management and to determine which variables most affect overall costs. However, the results may permit us to answer two other questions, "Is there really is a place for safer, but non-therapeutic alternatives to ERCP in the management of LC patients?"; and, if so, "How reliable and inexpensive do such tests have to be for them to compete with ERCP?"

ERCP is not inexpensive and is technically demanding. However, years of clinical use have established its clinical value. Consequently, physicians are eager to learn ERCP and institutions are willing to invest in the required equipment. Newer alternatives such as EUS and IOC are appealing, but have emerged in an era where new technologies must first prove their value (e.g. in terms of cost-effectiveness, ability to improve quality of life, etc.) *before* physicians and payers will accept them as part of

the "standard of care". Unfortunately, this creates a "catch 22" situation where a lack of clinical outcomes prevents the widespread clinical use necessary to obtain such outcomes data.

It is unlikely the optimal management strategy for laparoscopic cholecystectomy patients will be determined through a prospective trial, since expectant management for patients with a moderate to high risk of common bile duct stones poses serious ethical questions. In this regard, we feel decision modeling can help assess whether newer techniques like EUS and IOC have any hope of *ever* being clinically useful -- and can do so *before* they are widely used in clinical practice. The results may help clinicians and payers decide whether it is worthwhile to invest precious resources (especially time and money) into these procedures.

Based on a consensus of expert opinion, we constructed a plausible model of clinical problem that confronts gastroenterologists and surgeons on a regular basis. Literature-based probability estimates were used when available. When objective data were unavailable, estimates were formulated and then tested over the widest possible, yet clinically relevant, range of values. In order to permit generalization of the results to other centers, *costs* (instead of *charges*) were used and procedural costs were expressed in the form of *ratios* of the cost of ERCP.

This analysis documents several clinically useful principles that have been intuitively accepted, but never verified. First, as a patient's risk of common bile duct stones increases from 0 to 100%, there appear to be thresholds at which different strategies become desirable or undesirable with respect to their impact on overall costs.

As suspected, expectant management appears least costly for low risk patients and initial ERCP appears least costly for high risk patients. However, this analysis *quantifies* "high risk" as greater than approximately 50% "low risk" as approximately less than 10%; and suggests that safer, but purely diagnostic tests such as EUS and IOC may indeed reduce costs in "intermediate risk" (10-50%) patients.

Since the spectrum of intermediate risk is relatively wide (ranging from 10% to 50%) the model suggests that, when cost minimization is a primary goal, patients who are not either clearly high or low risk may benefit from less invasive testing. Note that if EUS and IOC are unavailable, the threshold between expectant management and ERCP is approximately 22%.(**Graph 1**) It may be difficult to consistently and accurately define this threshold with clinical predictors that are currently available -- increasing the risk for over- or underuse of ERCP. In this respect, the model suggests that alternatives to ERCP may help reduce some of the "guesswork" in managing laparoscopic cholecystectomy patients – since they appear to be useful in the subgroup of patients in whom clinical predictors may be least accurate at predicting bile duct stones.

If the primary goal is cost minimization, the decision whether to test at all appears to depend foremost on the risk of symptoms and complications due to retained common bile duct stones.(**Graph 2**) If the risk of *any* symptoms is below approximately 15%, the cost-reduction potential of any form of pre-operative testing appears limited (i.e. expectant management appears to be the least costly strategy). In other words, the costs of testing appear to outweigh the costs of treating complications. Initially, it was assumed that all retained stones would eventually become symptomatic. This is

because the fear of recurrent symptoms will likely continue to be the strongest incentive for pre- and post-LC common bile duct imaging; unless future studies prove that it is safe to leave *all* common bile duct stones untreated. Although it is possible that smaller stones may be more likely to pass without symptoms[30,31], practically speaking, this cannot affect the decision to image the common bile duct, since it is impossible to accurately predict stone size before images are requested. Similarly, the proportion of *any* recurrent symptoms that present as complications was set initially at 50%. This estimate should be considered conservative, since good data on the true risk of complications are currently unavailable and because it is doubtful whether clinicians will ever be able to predict if some stones are "safer" than others. Physicians can however determine which patients are likely to better tolerate symptom recurrences. It may therefore be useful to incorporate the patient's ability to *tolerate* complications into the assessment of the risk of leaving stones untreated.

Again, it is important to remember that the primary outcome for this analysis was overall cost-minimization. Patient preferences and quality of life measures were not factored into the model for two reasons. First, stone-related complications usually produce only *short-term* morbidity and second, there are no validated disease-specific instruments to measure their impact. Furthermore, costs may be somewhat easier to quantify and tend to be directly proportional to the severity of stone-related short-term morbidity. In this sense, costs may indirectly reflect the potential impact of stone-related complications on quality of life. This begs the question as to the cost of death in terms of dollars. This is an inevitable concern in economic analyses of health care.

Unfortunately, at some point, health care systems are forced to balance the cost to society against the cost to the individual. Fortunately, deaths due stone-related complications are extremely rare. Therefore, even if death was assigned a high dollar value and incorporated into the model, it would affect the final outcome minimally, if at all. This is corroborated by sensitivity analysis showing that extreme increases in the cost of severe complications has a limited effect on the results.(**Graph 2**)

Overall costs are also very dependant on the procedural costs of IOC, EUS, and ERCP. (**Graph 3**) Whether the "window" between expectant management and ERCP is filled by EUS or IOC seems to depend essentially on which has the lowest procedural cost. And neither appear clinically useful if they cost more than 60-70% of ERCP. Surprisingly, IOC is more costly than EUS (at least at our institution). However, IOC costs result primarily from operating room fees; so that even minor reductions in procedure time would make IOC less costly than EUS. Theoretically, immediate laparoscopic clearance of stones found at IOC (by duct exploration or by flushing stones through the papilla) could lower the overall cost of the IOC strategy (by obviating post-operative ERCP) -- however post-operative ERCP will remain less costly if operating room times are inordinately increased.

Although the cost data we used reflects the conditions of a single center, it was obtained by a formal cost analysis. The actual values will likely differ in other centers (especially those in other countries and health systems). However, the exact extent to which this is true will remain unclear until each center performs their own cost analysis. For the purposes of this study, we believe the figures cited are a reasonable

representation of the situation in the United States and can serve as an objectively-obtained starting point for analysis.

The model also highlights the importance of adequate operator expertise in EUS and IOC. If sensitivity and procedural success rates drop below 90%, the value of these tests as cost-reducing interventions seems to fall precipitously. The operating characteristics for IOC and EUS that were factored into the model were set to reflect the documented potential of these procedures in the hands of operators with sufficient training. At the present time, relatively few physicians have this level of expertise. Hopefully, the results of this analysis will encourage interested parties to obtain sufficient training to provide information that benefits both patients and payers.

CONCLUSIONS

The optimal management strategy for patients awaiting LC appears highly dependent on the estimated risk of common bile duct stones. After initial clinical evaluation is completed (including history, physical examination, liver profile, and possibly trans-abdominal ultrasound), patients awaiting LC may be classified according to their estimated risk of common bile duct stones: "low risk" (< 10%) and "high risk" (> 50%). If cost minimization is the primary goal, low risk patients seem best managed expectantly, with no common bile duct imaging before or during surgery. High risk patients appear best-served by pre-operative ERCP. Patients that do not fit into either group (i.e. intermediate risk) may benefit from EUS (or IOC -- if the cost of IOC is less than that of EUS). The most important variables to consider when deciding who and

how to test appear to be the risk of symptoms due to retained common bile duct stones, the relative procedural costs of the competing technologies, and the local availability of operators with sufficient expertise.

Safer but purely diagnostic tests like EUS and IOC may reduce overall costs, but appear to do so only when: 1) the risk of symptoms due to retained stones is sufficiently high (greater than 15%); 2) their procedural cost is less than 60-70% that of ERCP; and 3) their sensitivity and procedural success rates are greater than approximately 90%. Theoretically, these findings also apply to procedures with similar characteristics, such as laparoscopic ultrasonography, magnetic resonance cholangiography, and intravenous computed tomography cholangiography. It would appear useful to better determine the natural history of untreated choledocholithiasis since, if the risk of symptoms and/or complications is sufficiently low, pre-operative testing may not be cost-effective.

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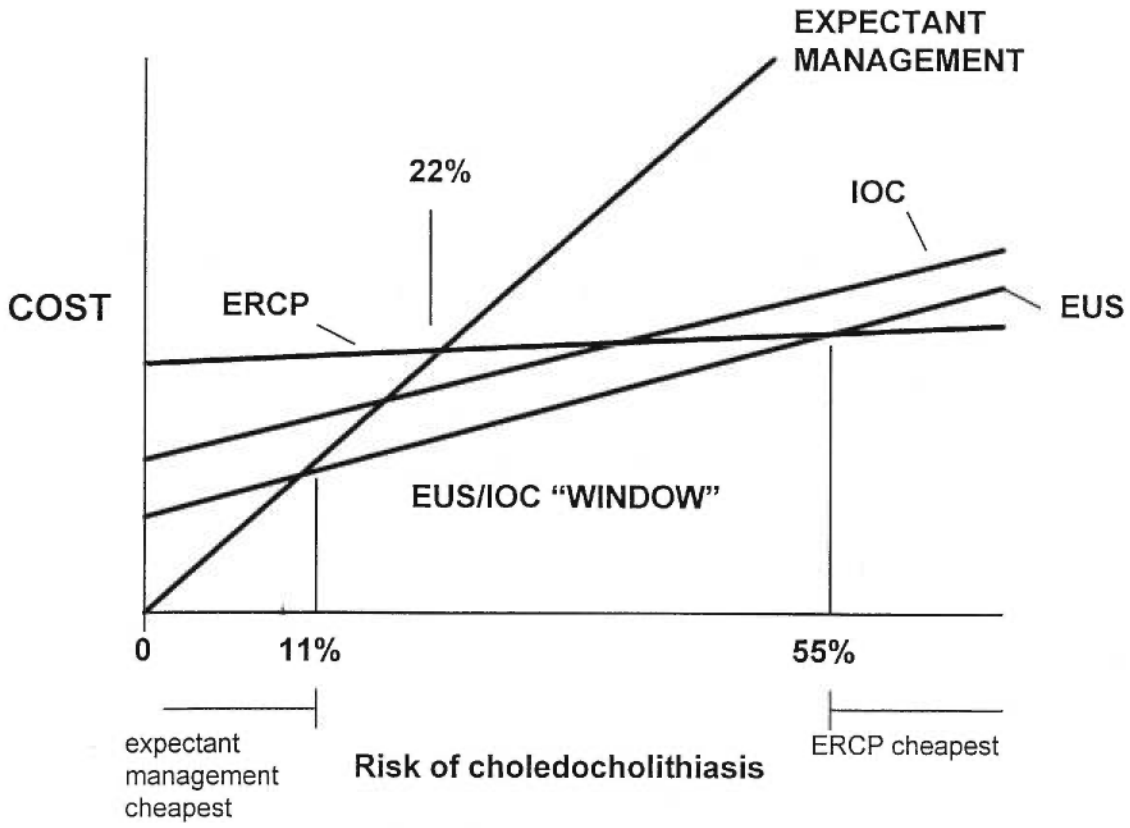
Graph 1:

1 Way Sensitivity analysis:

Overall cost of each strategy vs Risk of choledocholithiasis



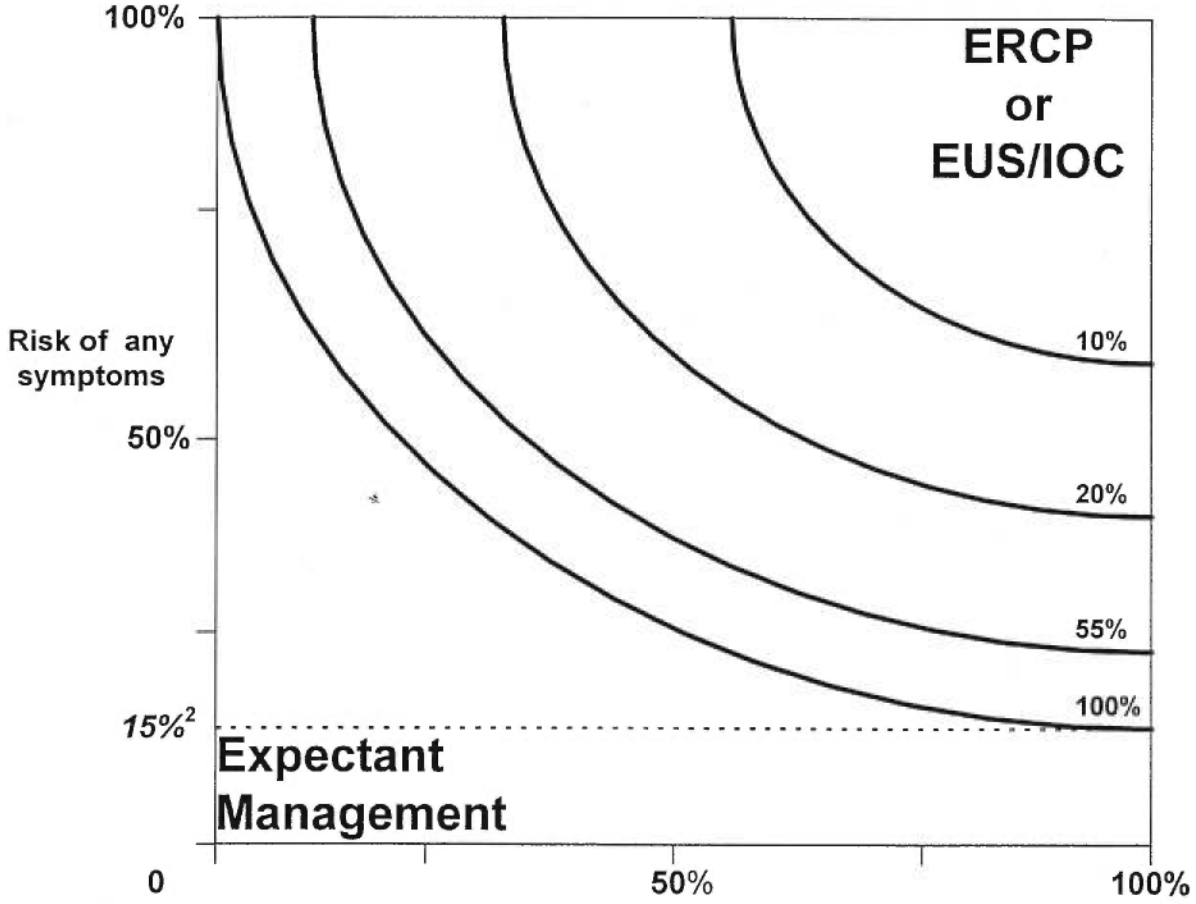
Graph 2:

3 Way Sensitivity analysis:

Proportion of recurrent symptoms presenting as a *complication* (*x* axis)vs

Risk of *any* recurrent symptoms due untreated choledocholithiasis (*y* axis) vs

Risk of choledocholithiasis (curved lines)[1]



[1]Each curved line represents the threshold between expectant management (to the left of the line) and testing (to the right of the line). The position of the line moves to the left as the risk of common bile duct stones increases (Lines for 4 levels of risk are shown: 10%, 20%, 55%, and 100%). When testing is the preferred option, ERCP is the test of choice if the risk of stones is *less* than 55% and EUS (or IOC) is the test of choice is *greater* than 55%.

[2]Increasing the cost of complications by 500% lowers this threshold to approximately 5%

Graph 3:

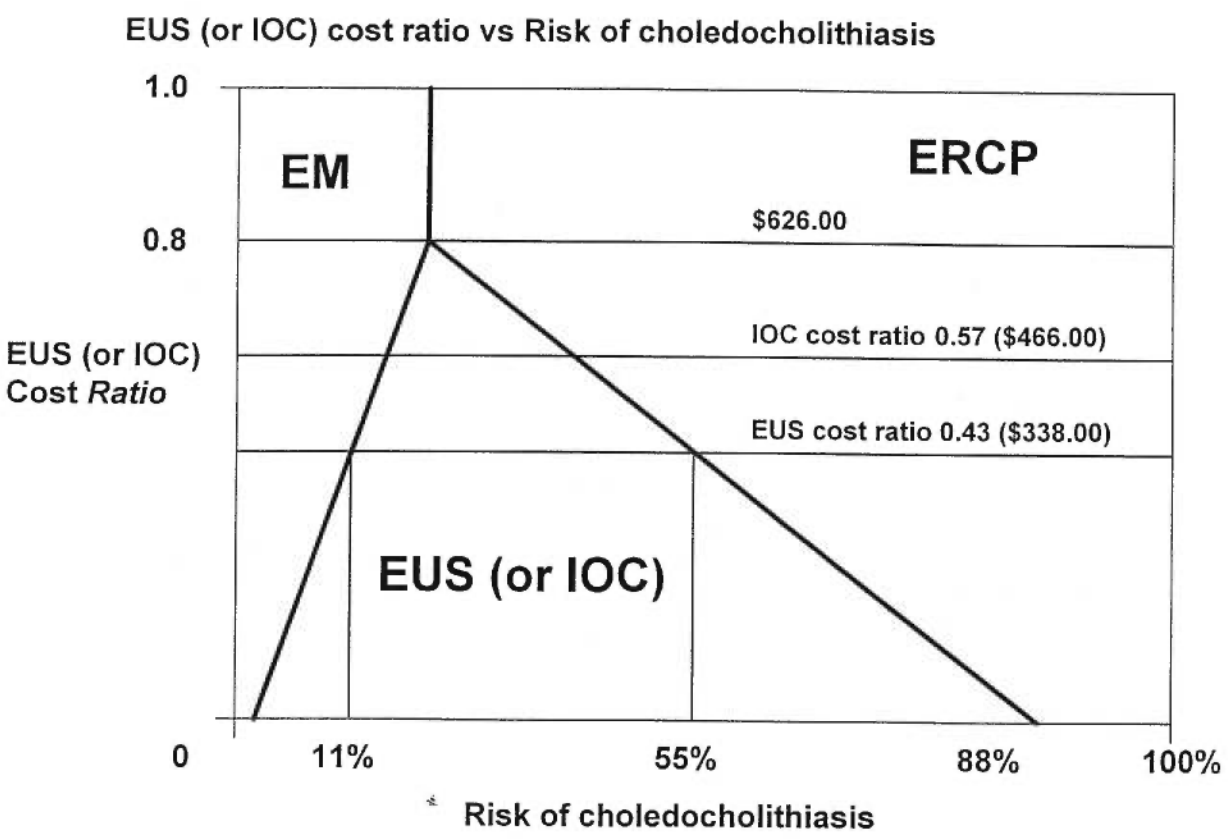

EUS (or IOC) cost ratio vs Risk of choledocholithiasis
1.0
0.8
0
EUS (or IOC)
Cost *Ratio*
EM
ERCP
$626.00
IOC cost ratio 0.57 ($466.00)
EUS cost ratio 0.43 ($338.00)
EUS (or IOC)
11%
55%
88%
100%
Risk of choledocholithiasis

Table 1:

Prospective studies of EUS success rates for common bile duct imaging and accuracy for diagnosing choledocholithiasis

%	*n*	success	sensitivity	specificity
Norton et al[32]	50	92	88	96
Atomi et al[33]	142	96	96	100
Aubertin et al[34]	50	100	100	97
Amouyal et al[35]	62	100	97	100
Prat et al[36]	119	100	93	97
Denis et al[37]	60	–	92	100
Canto et al[38]	64	–	84	95
Edmundowicz et al[39]	20	100	75	100
Weighted averages		**97**	**92**	**98**

Table 2:

Prospective studies of IOC success rates for common bile duct imaging and accuracy for diagnosing choledocholithiasis

%	*n*	success	sensitivity	specificity
Catheline et al[40]	150	83	78	97
Ohtani et al[41]	65	83	80	97
Nies et al[42]	138	80	--	--
Aubertin et al[34]	50	94	--	--
Pietrabissa et al[43]	71	90	--	--
Barteau et al[44]	125	100	93	76
Rothlin et al[45]	100	100	75	99
Birth et al[46]	518	93	100	98
Flowers et al[20]	150	91	100	98
Blatner et al[47]	33	97	--	--
Weighted averages		**91**	**90**	**95**

Table 3:

Cost breakdown for diagnostic ERCP, stone extraction, EUS, and IOC

		Diagnostic ERCP	Stone extraction	EUS	IOC
IV - O_2 - Monitoring[1]		105	--	105	--
Drugs	Meperidine	9	--	9	--
	Midazolam	27	--	27	--
	Glucagon	44	--	--	--
Endo. Room + Staff		339	--	77	--
Physician fees[2]		120	--	120	60
Non-reusables	Catheter	70	--	--	--
	Guidewire	--	59	--	--
	Balloon	--	91	--	--
	Sphincterotome	--	156	--	--
OR time (30 min.)		--	--	--	241
OR staff/Anesthesia		--	--	--	74
Fluoroscopy		72	--	--	72
Total cost		**$786**	**$306**	**$338**	**$448**
Cost ratio		**1**	**0.39**	**0.43**	**0.57**

IV = insertion of intravenous line + intravenous kit
Endo. = endoscopy
OR = operating room
min. = minutes

[1]includes 1 hour of recovery time
[2]$120 per hour

Table 4:

The potential impact of EUS/IOC operator proficiency:
Effects of reducing EUS/IOC sensitivity and/or the procedural success rate on the threshold between EUS/IOC and ERCP

	THRESHOLDS[1]	
	EUS	**IOC**
Change in Sensitivity[2]		
+5%	69	39
(Original threshold) **0**	**55**	**34**
- 5%	46	29*
- 10%	40	25*
- 15%	35	22*
- 20%	31	20*
Change in Success rate[3]		
+5%	58	38
(Original threshold) **0**	**55**	**34**
-5%	51	30*
-10%	47	26*
-15%	42	22*
-20%	37	18*
Simultaneous change in sensitivity and procedural success rate		
+5%	59	44
(Original threshold) **0**	**55**	**34**
- 5%	43	26*
- 10%	35	22*
- 15%	22*	20*
- 20%	20*	19*

[1]Values represent % risk of common bile duct stones *above* which ERCP becomes the least costly option. *Below* this threshold EUS or IOC (as the case may be) is the least costly option

[2]Original *sensitivity* inputs: EUS 92%, IOC 90%

[3]Original *success rate* inputs: EUS 97%, IOC 91%

* at this threshold level, the width of the "window" between expectant management and ERCP (see **Graph 1**) is < 15% and the test is therefore appears to be of limited *practical* value

DISCUSSION

La fréquence de la maladie lithiasique et la "popularité" de la cholécystectomie par voie laparoscopique font en sorte que le problème du diagnostic péri-opératoire de la cholédocholithiase se présente fréquemment et peut avoir un impact important sur le bien-être des malades ainsi que sur le coût des soins. On estime actuellement que plus que 500,000 cholécystectomies sont pratiquées par année en Amérique du Nord.[1] Le manque de données objectives quant à l'importance relative des nombreuses variables pouvant affecter la décision finale d'intervenir s'ajoute à l'incertitude inhérente à l'évaluation clinique du risque de cholédocholithiase chez un patient individuel. En conséquence, chez les patients en attente de CVL, il y a un potentiel énorme de sur- ou de sous-utiliser des ressources et/ou de soumettre des patients à des risques inutiles.

Notre analyse confirme que l'intervention appropriée varie en fonction du risque initial de cholédocholithiase; mais ajoute un élément de précision en suggérant quel niveau de risque justifie quel niveau d'intervention. L'approche par modeling décisionnel convient bien à la comparaison des bénéfices et des inconvénients des différentes stratégies diagnostiques. En évitant les contraintes éthiques, on peut clarifier quelles variables ont le plus grand impact sur le résultat final (même lorsque parfois les estimations de probabilités ne sont pas

disponibles dans la littérature) et on peut déceler des sujets intéressants pour de la recherche prospective ultérieure.

Il n'est pas facile de déterminer prospectivement le coût véritable d'une conduite expectative car il serait éthiquement controversé de ne pas investiguer les patients à haut risque de cholédocholithiase ou de ne pas extraire des calculs une fois diagnostiqués. C'est vraisemblablement pour cette raison qu'il existe si peu de données sur l'histoire naturelle des calculs cholédociens. De façon similaire, il serait dificile de concevoir une étude soumettant tous les patients à *faible* risque de calculs à un test coûteux et potentiellement dangereux tel que la CPRE.

D'un coté pratique, nos résultats peuvent aider les cliniciens à mieux évaluer les patients en attente de CVL. Le modèle suggère qu'uniquement les patients à très faible risque semblent mériter une conduite expectative et que seulement les patients à très haut risque semblent mériter une CPRE d'emblée. Entre ces deux extrêmes, un test moins invasif, tel que la CIO ou l'échoendoscopie peut-être utile. Ceci est particulièrement intéressant, car c'est chez ce groupe de patients (risque "intermédiaire") que les prédicteurs cliniques de cholédocholithiase sont le moins fiables. Donc, un test comme la CIO ou l'échoendoscopie semble le plus utile quand l'incertitude associée à l'évaluation clinique est maximale.

L'analyse de sensibilité supporte ces conclusions en démontrant que la valeur potentielle des tests moins invasifs semble se maintenir même dans des conditions suboptimales comme par exemple, lorsque le risque et la sévérité des complications reliées aux calculs manqués sont relativement élevés. Par contre, l'analyse de sensibilité démontre également que la valeur potentielle des alternatives à la CPRE peut être très dépendante de leur coût relatif à cet examen et de l'expertise de l'opérateur. L'analyse suggère également que l'utilité de *tous* les tests semble disparaître si le risque de symptômes reliées aux calculs est suffisamment bas.

L'effet puissant du coût relatif des différent tests et du niveau d'expertise de l'opérateur sur le coût *total* des diverses stratégies peut avoir des implications cliniques importantes. L'innovation continuelle dans le domaine de l'imagerie médicale amène une augmentation constante du nombre de techniques non-invasives disponibles pour visualiser le cholédoque. En plus de la CIO et l'échoendoscopie, on dispose d'autres techniques telles que la cholangiographie par résonnance magnétique, l'échographie laparoscopique, et la cholangiographie intraveineuse. Tous ces tests ont en commun une précision diagnostique relativement élevée, un faible risque de complications, mais une absence de potentiel thérapeutique. Lors de la phase initiale de l'évaluation d'une nouvelle

technologie, on évalue surtout l'efficacité et le profil de sécurité. L'analyse de l'impact économique est faite tardivement, sinon jamais.

Notre analyse est la première à comparer les coûts de la CPRE à des alternatives moins invasives et avec la conduite expectative en termes de coût. Nos résultats suggèrent qu'aucune des alternatives à la CPRE ne semble réduire les coûts hospitaliers si leur coût (en tant que procédure individuelle) est plus élevé que celui de la CPRE. Il est possible que le coût relatif des diverses procédures ainsi que la disponibilité de l'équipement et de l'expertise soient différents selon les régions géographiques. En conséquence, si un clinicien désire minimiser les coûts en employant une alternative à la CPRE, il doit s'assurer que, dans son milieu de pratique particulier, le coût de ce test sera suffisamment bas en rapport avec le coût local de la CPRE et que l'expertise nécessaire soit disponible localement.

Bien qu'une évaluation du coût relatif des procédures est cruciale pour choisir entre les tests disponibles, notre analyse suggère qu'une connaissance de l'histoire naturelle d'une cholédocholithiase non-traitée est encore plus importante; car si le risque de symptômes est suffisamment faible, la conduite expectative semble être la moins coûteuse. Donc, le modèle renforce l'utilité potentielle d'entreprendre des études prospectives pour mieux documenter ces risques.

En conclusion, l'évaluation préopératoire des patients en attente de CVL est un problème clinique fréquent, avec des répercussions potentiellement importantes autant au niveau du bien-être des malades qu'au niveau économique. Aucune comparaison prospective du coût de la CPRE, des alternatives moins invasives, et de la conduite expectative n'a été publiée; probablement à cause de contraintes éthiques. L'approche par analyse décisionelle est donc utile dans ce contexte. Cette étude a pu identifier une approche diagnostique qui pourra minimiser le coût des soins des patients en attente de CVL et a décelé les variables clefs méritant un intérêt spécial lors de la planification d'études prospectives dans ce domaine.

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Annexe:

Lettre de l'Éditeur de *Gastrointestinal Endoscopy*

GASTROINTESTINAL ENDOSCOPY

Official Journal

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October 15, 1998

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RE: OA 9706275.rev2: Bile duct stones and laparoscopic cholecystectomy: a decision analysis to assess the roles of intra-operative cholangiography (IOC), endoscopic ultrasound (EUS), and endoscopic retrograde cholangiopancreatography (ERCP)

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