Approach to asymptomatic paraesophageal hernia: watchful waiting or elective laparoscopic hernia repair?

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Abstract
Background There is no consensus on whether asymptomatic paraesophageal hernia (PEH) should be operated. Some argue that surgery is necessary prophylaxis against potentially catastrophic consequences of acute complications in untreated PEH. Others reason that the acute complications are rare and emergent operations have relatively low mortality. In the laparoscopic era, elective operations have become safer and less morbid. However, recent studies report high incidence of recurrent hernia, some of which affect quality of life and require further interventions. In light of these new findings, we investigated whether asymptomatic PEH should receive elective laparoscopic hernia repair (ELHR) or watchful waiting (WW).

Methods A Markov Monte Carlo microsimulation decision analysis model followed a hypothetical cohort of asymptomatic PEH patients who have predominantly female gender and normally distributed mean age of 62.5 years for the lifetime. Accrued health benefits expressed in quality-adjusted life months (QALM) were compared between two strategies: WW and ELHR. Two-dimensional simulations were performed to account for uncertainties in the model. Deterministic sensitivity analyses were performed to test key assumptions.

Results After considering both individual- and parameter-level uncertainties in the two-dimensional simulations, WW was the superior strategy in 82% of the simulations, accumulating mean 5 QALM more than ELHR (168 vs. 163). Our model was robust to deterministic sensitivity analyses and was internally validated, which supported the validity of our results.

Conclusions Patients with asymptomatic PEH are more likely to achieve greater health outcomes if they undergo WW as initial treatment than ELHR.

Keywords Hiatal hernia · Paraesophageal hernia · Laparoscopic surgery · Decision analysis · Markov model

Paraesophageal hernia makes up 5% of hiatal hernia [1]. Prevalence of asymptomatic paraesophageal hernia is not well known [1–4]. Traditionally, the finding of a paraesophageal hernia was considered an indication for surgical repair, irrespective of whether it was symptomatic or not. The rationale for immediate elective repair was to prevent mortality from catastrophic complications, particularly as a result of strangulation and organ necrosis [5–7]. However, more recent studies demonstrated that the incidence of progression to acute complications was lower than previously thought [8–12]. Further, a population-based analysis revealed that post-operative mortality rate after emergent paraesophageal hernia surgery was close to 5%, much
lower than previously reported [13]. In light of these findings, a decision analysis published in 2002 investigated whether watchful waiting (WW) or elective laparoscopic hernia repair (ELHR) should serve as the initial approach to asymptomatic paraesophageal hernia [13]. Using available data at the time, the authors developed a Markov Monte Carlo decision model to compare the accrued health benefits over lifetime between the two strategies. They found that WW was the superior strategy in 83% of cases and their results were influential in challenging the previously held perception that all paraesophageal hernias should be operated on.

Since this publication, there emerged new evidence on ELHR. First, population-based studies demonstrated that ELHR was associated with lower mortality and morbidity rates than previously reported [2, 14, 15]. Second, prospective data became available to better examine time-dependent variables such as recurrence rates [16, 17]. Several studies demonstrated that ELHR was associated with higher incidence of hernia recurrence than open repair [16–22]. Further, some recurrent hernias were symptomatic and required additional interventions [19, 20, 23–25]. Given the new findings of potential benefits and disadvantages of ELHR, it was imperative to re-investigate whether WW or ELHR was the optimal initial approach to patients with asymptomatic paraesophageal hernia. Due to absence of randomized controlled trials or long-term observational studies on this topic, we opted to perform a decision analysis using the a contemporary, more sophisticated methodological approach.

Materials and methods

Study design

We constructed a Markov model that used Monte Carlo microsimulation. It simulated a hypothetical patient’s clinical course through a set of distinct, mutually exclusive health states. We defined a microsimulation trial as a given hypothetical patient’s lifetime experience from entry into the model until death. Simulated life spans were divided into discrete intervals, called cycles, of one month duration. During the course of a cycle, a patient could either remain in the current health state or experience chance events resulting in transition to another. Ultimately, patients entered the “absorbing” death state after which their simulation finished. During each microsimulation trial, in a stochastic fashion, a given patient traversed the model structure representing one strategy, WW and then, in turn, ran through the structure representing the other strategy, ELHR. Microsimulation allowed for patient-level variability for factors such as age and gender that may influence the chance of transition among states. It also permitted model “memory” through tracking variables, which allowed certain events experienced by a hypothetical patient to affect the subsequent probability of transitions to other health states. Over the course of each patient’s simulation, accrued health benefits, expressed in quality-adjusted life months (QALM) were calculated for both strategies and then subtracted to produce the difference in quality-adjusted life span (i.e., incremental QALMs) experienced by the patient for WW versus ELHR. We arrived at the final estimates of the difference in quality-adjusted life expectancy between the two strategies by averaging incremental QALMs over a large number of simulated patients. We performed two-dimensional simulations to assess the effect of both individual- and parameter-level uncertainties. In addition, we performed deterministic sensitivity analyses in which key assumptions were tested. We used a trapezoidal, within-cycle adjustment to overcome the bias inherent in discrete time Markov models [26]. The future value of QALMs was discounted at 3% per annum [27]. All analyses were performed using TreeAge Pro 2016 (TreeAge Software, Williamstown, MA).

Model structure

Selection of hypothetical patients

Hypothetical patients were men and women with diagnosis of asymptomatic or minimally symptomatic paraesophageal hernia, henceforth known as asymptomatic paraesophageal hernia. The definition of this diagnosis was adopted from a previously published study [13]. Paraesophageal hernias were defined as type II and III hiatal hernias. Minimal symptoms included symptoms that did not affect the quality of life of a patient such as belching and intermittent heartburn. Patients who had previous upper gastrointestinal operations were excluded. The hypothetical patients had a normally distributed starting age with mean of 62.5 years [standard deviation (SD) of 13.9], and 71.6% of the patients were female [2].

Health states

A common Markov structure was used for both strategies. Hypothetical patients starting with WW strategy were able to transition to ELHR strategy health states if they progressed to symptomatic hernia and required an elective operation (Figs. 1 and 2). Those who started with ELHR strategy were able to transition to health states subsequent to ELHR, but not to the health states subsequent to WW.
Elective laparoscopic hernia repair

Multiple variations of laparoscopic paraesophageal hernia repair technique have been described [28–31]. In our model, we assumed that the operation involved complete dissection of the hernia sac with or without esophageal lengthening procedure, reduction of the hernia contents, closing of the hiatal defect with or without the use of prosthesis, and presence or absence of an anti-reflux procedure. All model parameters were obtained from studies that included any variation of laparoscopic paraesophageal hernia repair techniques defined in our assumption. In ELHR state, patients could have one of the following immediate outcomes—post-operative death, surgical complications, and uneventful recovery—before advancing to the next health state: Post-Repair state. We defined surgical complications as post-operative complications with severity equal to or greater than Clavien–Dindo grade 2, which include take-back operations [32]. We assumed that patients returned to full health in Post-Repair health state. Within this state, patients might die due to age- and sex-related factors, develop recurrence, or continue to live in the Post-Repair state. We made an assumption that hernia recurrence could occur only during 10 years after the operation. The longest follow-up period in prospective studies that reported hernia recurrence to date was 5 years [16]. We allowed for a longer time period for recurrence to occur in our model in order to be conservative in our estimation. Patients were assumed to develop either asymptomatic or symptomatic recurrent hernia. The proportion of those who developed symptomatic hernia recurrence was calculated from a pooled analysis of eight studies that reported both objective and symptomatic assessments of recurrences [19–21, 23–25, 33, 34]. We made a clinical assumption that patients with asymptomatic recurrent hernias continued to live in full health and did not require any further intervention. Patients with symptomatic recurrent hernias might progress further and end up choosing to have a second ELHR. Patients transitioned to second ELHR if they were younger than the age cutoff for surgery, which was chosen with expert consultations as a uniform distribution with lower bound 80 years and upper bound 85 years. Patients older than the cutoff age continued to live in the symptomatic hernia health state until death. This was a plausible clinical assumption as patients with symptomatic paraesophageal hernia are recommended to have ELHR unless unfit for surgery. While it is fitness, not age, that is the most important factor when deciding not to operate on a patient, we used age as the deciding characteristic, as patients’ fitness was not incorporated in our model [35]. The second ELHR state has the same immediate outcomes as the first ELHR state. Survivors of the second ELHR were assumed to return to full health and live in this state until they enter death due to age- and sex-related factors.

Watchful waiting strategy

Hypothetical patients starting in WW state could transition to one of three health states—ELHR, emergency surgery, and death—or remain in WW state on the next cycle. First, the patients could enter death state due to age- and sex-related factors. Survivors could progress to have paraesophageal hernias with severe symptoms, such as dysphagia, early satiety, post-prandial pain, and vomiting [13]. These patients would transition to ELHR if they were younger than the model’s age cutoff for surgery. Patients older than the age cutoff would live in symptomatic hernia health state until they entered death. Further, if the hypothetical patients on WW developed acute symptoms like complete esophageal or gastric obstruction, or strangulation of the paraesophageal hernia, they entered emergency surgery state regardless of age. Emergency surgery was performed through open transabdominal approach and consisted of dissection of hernia sac, reduction of hernia.
content, and repair of hiatal defect. Patients in emergency surgery state can have events, such as post-operative death and surgical complications. Some of the patients who underwent emergency surgery might require an organ resection, such as esophagectomy and/or gastrectomy. We made an assumption that these patients would not be able to develop hernia recurrence and live in the state of post-organ resection until they entered death. Patients who did not require an organ resection could develop hernia recurrence in subsequent cycles, which could be either asymptomatic or symptomatic. We made an assumption that recurrence could only occur within the first 10 years after the operation. Further, we assumed the recurrence rate after emergent paraesophageal hernia repair to be the same as that after ELHR. This is because there was no reliable study that reported long-term hernia recurrence rates after emergent paraesophageal hernia operations. Lastly, patients who developed symptomatic recurrent hernias may progress to require a second operation.

Model inputs

We searched MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials, and Cochrane Database of Systematic Reviews using key words “paraesophageal hernia” and “hiatal hernia” to identify studies that reported probabilities that were required in our model. We also performed manual review of the reference lists of key articles. Our search was limited to studies pertaining to adults only and written in English language.

Probabilities

All probabilities were converted to monthly probabilities from their respective study time scale by assuming a constant hazard rate. Event probabilities for post-operative death, take-back to the operating room, and surgical complications were obtained from population-based studies (Table 1). When available, estimates from randomized controlled trials were prioritized over those from observational studies to derive transition probabilities. When randomized trials were unavailable, we performed pooled analyses of estimates from observational studies to obtain model probabilities. Details of pooled analyses for time-independent and time-dependent probabilities are stated in Supplemental 1. The age- and sex-related mortality rates per month were calculated from the United States life table published from the Center for Disease Control [36].

Utilities

We assigned each health state with an incremental utility value representing patients’ preference for the state on a scale where 1.0 represents perfect health and 0 represents death (Table 1). There were no reliable estimates of utility values specific to paraesophageal hernia. However, we were able to estimate utility values from various studies reporting on similar disease states [37–40]. We assumed that patients with asymptomatic paraesophageal hernia and asymptomatic recurrent hernia were in perfect health. This was a reasonable assumption as we defined asymptomatic or minimally symptomatic paraesophageal hernia to have symptoms that did not affect quality of life. We assigned emergency surgery state the same baseline utility value as symptomatic hernia and added transition disutility value for undergoing emergency surgery. Calculations to derive disutility measures are detailed in Supplemental 2.

Two-dimensional simulation

We performed two-dimensional simulations to assess the effect of individual- and parameter-level uncertainties on the incremental QALMs for WW versus ELHR strategies. In this simulation, parameters were represented by distributions of possible values rather than single-point estimates. We assumed beta distributions for probabilities and utilities and log-normal distributions for hazard ratios [41] (Table 1). We randomly sampled parameters along their respective distributions 10,000 times. For each sample of randomly chosen parameters, 1000 microsimulation trials were performed. Our methods to determine adequate parameter sample size are reported in Supplemental 3. To adjust for individual-level uncertainty, we varied starting age of hypothetical patients along a normal distribution for each microsimulation trial. Further, we varied gender selection to approximate 72% chance of being female along a uniform distribution. Then, we estimated the proportion of two-dimensional simulations in which one strategy was superior over the other.

Sensitive analyses

We performed deterministic sensitivity analyses in which key assumptions in our model were varied. We tested robustness of our model by changing the number of years during which recurrence could occur, the age cutoff for surgery, and the per-cycle recurrence probability after emergency surgery. Further, we performed separate pooled analyses of pertinent studies to derive recurrence rates after ELHR performed by three different hiatal defect closure techniques: suture-only closure, closure with absorbable mesh, and closure with non-absorbable mesh (Jung et al., not yet published). We then ran two-dimensional simulations for different scenarios to assess whether there was
variability in our results. Details of our sensitivity analyses are reported in Supplemental 4.

Results

Two-dimensional simulations

WW strategy resulted in a greater quality-adjusted life expectancy over ELHR approach in 82% of two-dimensional simulations (Fig. 3). Hypothetical patients accumulated a mean of 5 QALMs more over their lifetime when they underwent WW as initial approach to asymptomatic paraesophageal hernia over ELHR (Table 2). Thus, less than one in five patients with asymptomatic paraesophageal hernia accrued better health outcomes over their lifetime when they were offered ELHR.

Sensitive analyses

We tested robustness of our model by varying key assumptions of the model (Table 2). First, the number of years during which hernia recurrence could occur following either ELHR or emergency operation were changed. At both 5 and 15 years, WW was superior strategy over ELHR. A slightly smaller proportion of simulations (74%) benefited from WW when the number of recurrence-allowed years was 5 years. Second, we increased the age cutoff distribution for surgery from 80–85 years old to 90–95 years old. WW was the superior strategy in 86% of simulations. Further, we changed
the recurrence rate after emergent paraesophageal hernia operation from 15.9% annually to 1.9% per annum, the rate chosen by the previous decision analysis [13]. Our model was robust to this sensitive analysis as 83% of simulations demonstrated superiority in WW strategy. Finally, we examined the results of our model when we varied hiatal defect closure techniques. Two-dimensional simulations with the suture-only closure, the closure with absorbable mesh, and the closure with non-absorbable mesh scenarios demonstrated that WW was the superior strategy in 89, 80, and 88% of the time, respectively. Therefore, our model was robust to variations in key clinical assumptions.

Table 2 Results of two-dimensional simulations and deterministic sensitive analyses

<table>
<thead>
<tr>
<th>Scenario</th>
<th>WW (QALM)</th>
<th>ELHR (QALM)</th>
<th>Simulations when WW had better outcome than ELHR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Base case with 10,000 parameter samples</td>
<td>168</td>
<td>163</td>
<td>82</td>
</tr>
<tr>
<td>Base case with 1000 parameter samples</td>
<td>168</td>
<td>163</td>
<td>84</td>
</tr>
<tr>
<td>Recurrence allowed for 5 years</td>
<td>169</td>
<td>167</td>
<td>74</td>
</tr>
<tr>
<td>Recurrence allowed for 15 years</td>
<td>168</td>
<td>163</td>
<td>83</td>
</tr>
<tr>
<td>Age cutoff 90–95 years old</td>
<td>168</td>
<td>163</td>
<td>86</td>
</tr>
<tr>
<td>Recurrence rate after emergent operation set at 1.9% annually</td>
<td>168</td>
<td>164</td>
<td>83</td>
</tr>
<tr>
<td>Hiatal defect closure with suture only</td>
<td>166</td>
<td>157</td>
<td>89</td>
</tr>
<tr>
<td>Hiatal defect closure with absorbable mesh</td>
<td>168</td>
<td>163</td>
<td>80</td>
</tr>
<tr>
<td>Hiatal defect closure with non-absorbable mesh</td>
<td>166</td>
<td>159</td>
<td>88</td>
</tr>
</tbody>
</table>

WW watchful waiting, ELHR elective laparoscopic hernia repair, QALM quality-adjusted life months

Discussion

The present analysis demonstrated that WW approach to asymptomatic paraesophageal hernia, on average, resulted in greater quality-adjusted life expectancy than ELHR strategy. Further, 82% of hypothetical patients in our model accumulated more health benefits with WW approach than ELHR over their lifetime. Our results corroborate the views expressed by Stylopoulos et al. in their decision analysis, despite the advent of new evidence in the literature related to laparoscopic paraesophageal hernia repair [13]. Specifically, compared to the previous decision analysis, our model’s post-operative mortality and severe morbidity after ELHR were lower (mortality: 0.5 vs. 1.38%; severe morbidity: 7.9 vs. 14.36%) [13]. Second, we used randomized trial data to obtain a recurrence rate after ELHR, which was not available in the previous decision analysis study [16]. Our model’s annual recurrence rate was 15.9%, which was a lot higher than the assumed annual recurrence rate of 1.9% used in the previous study [13]. Finally, our pooled analysis of eight studies that reported both objective and symptomatic assessment of hernia recurrence showed that 55% (SD 27%) of the recurrent hernias were symptomatic [19–21, 23–25, 33, 34]. This had an impact on our analysis as symptomatic recurrent hernias had different quality of life weights than asymptomatic recurrent hernias. Therefore, our results are relevant to the current surgical communities as they reflect the newly emerged evidence available to date.

There are limitations to our study. Like all models, our study was based on some key assumptions, which did not represent all subtleties of clinical practices. In order to mitigate this expected shortcoming, we performed sensitive analyses to determine if variations in these key assumptions had significant impact on our overall results. Indeed, we demonstrated that our model was robust to variations in our clinical assumptions. Second, despite our best efforts to accurately estimate parameters used in the model, there were undoubtedly some degrees of uncertainty. To address...
for parameter-level uncertainty, we randomly sampled parameters along their respective distributions 10,000 times. Further, we internally validated our model structure by comparing our model’s incidence of hernia recurrence after ELHR to that published in another study [22] (Supplementary 5). We did not take into consideration the varying technical difficulty of operating on paraesophageal hernia of different sizes and grades, which may result in variable mortality and morbidity. There was a lack of data on natural progression of untreated asymptomatic hernia. Thus, we made an assumption that all operations to repair symptomatic hernia were of the same technical difficulty. Future studies should attempt to elucidate the true incidence and pattern of natural progression from asymptomatic to symptomatic paraesophageal hernia. Our results should be revised as future studies refine these estimates. Finally, we performed a decision analysis study because there was absence of high-quality data on this clinically important topic. Clinicians must continue to make decisions for patients with asymptomatic paraesophageal hernia whether or not there is high-quality empiric evidence. The results from our decision analysis at least objectively explore the potential consequences of clinical decisions made for patients with asymptomatic paraesophageal hernia.

Despite these limitations, this study adopted a carefully constructed model using the best available data and modeling techniques. We used a complex model structure to better reflect patients’ clinical course. We used prospective data to derive key transition probabilities. We also used large population-based studies to obtain key event probabilities. Further, our model addressed for individual- and parameter-level uncertainties by performing two-dimensional simulations. Our model structure was internally validated. Lastly, our model was subjected to rigorous sensitive analyses and demonstrated its robustness, which supports validity of our results. Our model demonstrates that in the majority of its simulations, WW was the superior initial strategy over ELHR. An average of 5 QALMs gain over lifetime is a significant health benefit. Our results suggest that WW may be an acceptable initial strategy for patients with asymptomatic paraesophageal hernia. These findings are important when discussing treatment options with surgical patients and making a decision for the treatment of this complex and still not sufficiently studied clinical entity.

Compliance with ethical standards

Disclosures Dr. Grantcharov received grants from Ethicon Canada, Medtronic Canada, Olympus Canada, Takeda Canada, and Baxter Canada and owns intellectual properties from Surgical Safety Technologies Inc. Drs. Jung, Naimark, and Behman have no conflicts of interest or financial ties to disclose.

References


