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A semi-Markov model comparing the lifetime cost-effectiveness of mesh prophylaxis to prevent parastomal hernia in patients undergoing end colostomy creation for rectal cancer

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ABSTRACT

Aim: Parastomal hernia (PSH) is a common problem following colostomy. Using prophylactic mesh during end colostomy creation may reduce PSH incidence, but concerns exist regarding the optimal type of mesh, potential long-term complications, and cost-effectiveness of its use. We evaluated the cost-effectiveness of mesh prophylaxis to prevent PSH in patients undergoing end colostomy creation for rectal cancer.

Methods: We developed a decision-analytical model, stratified by rectal cancer stages I–IV, to estimate the lifetime costs, quality-adjusted life-years (QALYs) and net monetary benefits (NMBs) of synthetic, biologic and no mesh from a UK NHS perspective. We pooled the mesh-related relative risks of PSH from 13 randomised controlled trials (RCTs) and superimposed these on the baseline (no mesh) risk from a population-based cohort. Uncertainty was assessed in sensitivity analyses.

Results: Synthetic mesh was less costly and more effective than biologic and no mesh to prevent PSH for all rectal cancer stages. At the willingness-to- pay threshold of £20,000/QALY, the incremental NMBs (95% CI) ranged between £1,706 (£1,692 to £1,720) (stage I) and £684 (£678 to £690) (stage IV) for synthetic versus no mesh, and £2,038 (£1,997 to £2,079) (stage I) and £1,671 (£1,653 to £1,689) (stage IV) for synthetic versus biologic mesh. Synthetic mesh was more cost-effective than no mesh unless the relative risk of PSH was ≥0.95 for stages I–III and ≥0.93 for stage IV.

Conclusions: Synthetic mesh was the most cost-effective strategy to prevent the formation of PSH in patients after end colostomy for any rectal cancer stage; however, conclusions are dependent on which subset of RCTs are considered to provide the most robust evidence.

KEYWORDS

biologic mesh, cost-effectiveness, Markov model, parastomal hernia, stoma, synthetic mesh

What does this paper add to the literature?

Based on meta-analyses of all available RCTs, we developed a decision-analytical model to estimate the "lifetime" cost-effectiveness of synthetic, biologic and no mesh to prevent the formation of PSH in patients who underwent end colostomy for rectal cancer. Synthetic mesh was the most cost-effective strategy for all rectal cancer stages.

INTRODUCTION

Despite the recent advances in medical care and surgical techniques (e.g., robotic surgery and transanal total mesorectal excision), a large proportion of patients with rectal cancer continue to have a permanent colostomy created [1]. The most common problem following initial colostomy creation is parastomal hernia (PSH); estimates of its incidence range from 20% to 50% depending on the length and type of follow-up [2-6]. PSH may be asymptomatic or symptomatic [7-9]. Symptoms of PSH can negatively affect patients' health-related quality-of-life [9-12] due to pain, stoma leakage due to poorly-fitting stoma appliances and skin irritation [13,14], and limit their social interaction and ability to work [8,12]. PSH can also cause serious problems such as bowel obstruction or strangulation which may require emergency treatment in hospital [6,15]. Registry data from Denmark has demonstrated that, regardless of the underlying intestinal disease that led to stoma creation, the development of "bulging" (a composite of true PSH and subdermal prolapse of the afferent stoma limb) immediately adjacent to a stoma is common [16] and up to a third of patients with parastomal bulging undergo surgery to treat it. Recurrence of parastomal bulging is a significant problem and a third of patients who have had surgical repair will go on to have further surgery [16].

Given the high incidence rates of PSH and difficulties in its treatment, there has been considerable interest in preventing PSH by implanting prophylactic mesh during initial stoma creation [15,17-19]. Potentially, the use of mesh might prevent, delay or reduce the severity of PSH. There are several options available to surgeons including mesh type (synthetic or biologic), surgical approach (open or laparoscopic) and mesh placement (onlay, sublay/retrorectus or intraperitoneal) [8,18]. Permanent synthetic meshes have been in clinical use since the 1950s and are cheap and widely available, with an extensive evidence base for their effectiveness in the treatment and prevention of hernias generally. Delayed absorbable synthetic (also known as bioabsorbable) meshes and biologic meshes have been in clinical use for less than 20 years, are much more costly [7,17,20] and have a more limited evidence base regarding their utility in the treatment or prophylaxis of hernia generally [21]. However, the adoption of mesh prophylaxis in practice has been limited because of concerns about long-term mesh-related complications [22].

Previous systematic reviews of randomised controlled trials (RCTs) reported significant reductions in PSH in patients who underwent a mesh placement during their initial stoma creation [23-25]. However, these reviews included single-centre RCTs with small sample sizes [26-28] and methodological weaknesses [13,15], including the lack of blinding of outcome assessors. The largest multicentre RCT (STOMAMESH) [5] found no significant difference in the incidence of PSH between the synthetic mesh and no mesh groups over a 12-month follow-up period; relative risk of 0.92 (95% CI: 0.63–1.34). However, a recent Cochrane review and meta-analysis of 10 RCTs concluded that the use of prophylactic mesh results in lower incidence of PSH; relative risk of 0.53 (95% CI: 0.43–0.66) [15].

Whilst attempts to reinforce the stomal defect are logical, concerns exist regarding the optimal type of mesh and cost-effectiveness of its use [13,20,29,30]. One Canadian study of the cost-effectiveness of mesh

3

prophylaxis to prevent PSH concluded that the use of synthetic mesh compared to no mesh in patients with rectal cancer stages I–III would decrease costs and improve outcomes, but the benefit for patients with rectal cancer stage IV would be minimal [31]. However, their conclusions are based on a 5-year timeframe and the results of a meta-analysis of only three RCTs with smaller sample sizes. Furthermore, their conclusions may not be applicable for the UK National Health Service (NHS) [13].

In the UK, the National Institute for Health Research has prioritised research to understand factors influencing the risk of PSH and funded the Cohort study to Investigate the prevention of Parastomal HERnia (CIPHER study) [32]. This study has recruited >2,400 patients since 1 January 2018 from 80 NHS acute trusts across the UK. Patients are followed up at 6-monthly intervals for a minimum period of 2 years to establish the incidence of PSH and health-related quality-of-life. As part of the CIPHER study, we conducted a model-based cost-effectiveness analysis comparing permanent synthetic mesh, biologic mesh and no mesh to prevent PSH in rectal cancer patients who underwent end colostomy. Our model is based on current evidence, and differs from the Canadian cost-effectiveness model in the following ways: (a) we included more recent and larger RCTs with longer follow-up to estimate the relative risks of PSH incidence with mesh (synthetic or biologic) compared with no mesh; (b) we incorporated EQ-5D-5L [33] quality-of-life data from the CIPHER study; (c) we adjusted the risk of PSH and its repair to account for competing risks (an event such as death that reduces the risk of PSH occurrence); and (d) we conducted the first "lifetime" cost-effectiveness analysis of mesh prophylaxis from a UK NHS perspective.

METHODS

Model type and structure

We used a decision-tree combined with a semi-Markov process consisting of "No PSH", "PSH", "Repair", "Repeat repairs" and "Dead" health states, to compare the lifetime cost-effectiveness of synthetic mesh, biologic mesh and no mesh to prevent PSH in patients undergoing end colostomy creation for rectal cancer stages I–IV. A schematic of the decision-analytical model is shown in Figure 1; the model structure was informed by clinical input.

Initially, all patients underwent the index operation, where patients either survived (with or without peristomal complications) or experienced a perioperative death. Those who survived then entered the Markov model via the "No PSH" health state. Based on data from several RCTs [2,28,34-36], the mean age of the patient cohort was estimated to be 65 years at the index operation and the gender ratio was approximately 65% male to 35% female. Patients in whom PSH developed moved into the "PSH" health state. PSH may be asymptomatic or symptomatic; 48 out of 202 (23.8%) patients did not report any particular problems related to their PSH within a retrospective study of ostomy patients [14]. Some patients required surgical repair of their PSH and consequently moved into the "Repair" health state. After the primary PSH repair, some patients had repeat PSH repair(s) due to recurrence and moved into the "Repeat repairs" health

4

state—patients were assumed to have a maximum of four PSH repairs [16]. Patients in any health state could die; the risk of death was assumed to be dependent on age and rectal cancer stage.

We used a cycle length (period of time when patients may move from one health state to another, "transition") of 6 months to track changes in costs and outcomes, as the median time from a stoma surgery to the occurrence of PSH was 6 months in patients with colostomy [16]. Given that a PSH can occur up to 30 years after stoma creation [5], we ran our model over the lifetime of patients. All costs and health outcomes were discounted at an annual rate of 3.5% [37]. We assumed that transitions between health states occurred halfway through each cycle. Patient health-related outcomes were valued in terms of quality-adjusted life-years (QALYs; a composite measure of the impact on health status) gained using the EQ-5D-5L utility (measure of health-related quality-of-life) data from the CIPHER study; and a UK NHS perspective was adopted for costs. Each health state was assigned with a utility value on a scale anchored at 0 (death) and 1 (best health). We calculated the QALYs by multiplying the health state-specific utility value by the time spent in that health state [38].

<Figure 1>

Model parameters
We used four sets of parameters (Table 1): (a) decision-tree probabilities; (b) Markov transition probabilities; (c) cost parameters; and (d) utility parameters. The sources of these parameters are described below.

Decision-tree parameters
Based on the NBOCA 2020 annual report [1], we considered a perioperative death rate of 0.03 for the index surgery, and assumed that this rate was the same for procedures with and without a mesh placement in patients at any rectal cancer stage [31]. Based on a meta-analysis of eight RCTs, we included short-term peristomal complications such as infection, necrosis and/or stenosis for the mesh (6.9%) and no mesh (7.0%) groups [13].

Markov parameters
Baseline PSH incidence
The incidence of PSH is highest within the first year after end colostomy creation, but is common up to 5 years [39]. However, the risk of PSH may persist for more than 20 years [5,7,14,40]. The 1-year and 5-year cumulative incidence rates of PSH were 10.9% and 37.3%, respectively, within a retrospective study of 165 patients who underwent an end colostomy [39]. To estimate the cycle-specific baseline (no mesh) transition probabilities, we converted the 1-year and 5-year PSH incidence data (Table 1), adjusting for the competing risk of death [41]. After 5 years, we assumed that the risk of PSH incidence halved every year, and therefore approached zero over the patients' lifetime [5].

<Table 1>

Relative risk of PSH

A recently published Cochrane review and meta-analysis of 10 RCTs (771 patients) reported a reduction in the incidence of PSH in patients who had a prophylactic mesh placed during the index operation compared with no mesh [15]. However, new evidence has emerged from three more RCTs [34,44,53] since the Cochrane review. Furthermore, the Cochrane review did not analyse the incidence of PSH by synthetic and biologic mesh types. We meta-analysed 13 RCTs (1,070 patients) in a random-effects model to estimate the relative risk of PSH in terms of synthetic and biologic mesh types compared with no mesh (Table 1; Figures S1 and S2 in Appendix S1). Due to limited follow-up in RCTs, it is unclear whether any initial reduction in PSH for patients with a mesh is sustained in the longer-term (i.e., mesh may prevent or merely delay PSH). In our base-case analysis, we conservatively assumed that reduction in the incidence of PSH ceased after 5 years.

Primary and recurrent PSH repair

The proportion of patients requiring surgical repair of PSH varies depending on whether a patient has a mesh placed or not during the initial stoma creation. Using the competing risks formula [41], the cycle-specific baseline risk of primary PSH repair was estimated based on the incidence rates of 9% at 1-year and 19% at 5-year reported in a retrospective register-based study on 1,016 patients with a permanent stoma [16]. The relative risk of primary PSH repair for mesh compared with no mesh was derived from a random-effects meta-analysis of 10 RCTs including 336 patients (Table 1; Figure S3 in Appendix S1). We assumed that a patient who underwent a PSH repair was hospitalised for a mean of 5 days [54]. We also assumed that the risk of primary PSH repair ceased after 5 years for patients in any strategy [16].

Suture repair of PSH has a high recurrence rate of up to 69.4% [55]; mesh repair reduces the recurrence rate compared with suture repair [55,56]. We assumed that any patient who underwent a PSH repair would have a synthetic mesh placed, as recommended in the ACPGBI statement [20]. Biologic mesh has been used in PSH repair as an alternative, but it is very expensive and results do not vary from synthetic mesh repair [55,57]. Furthermore, there is no superiority of biologic over synthetic mesh for PSH repair concerning recurrence and mesh-related infection [58]. The risk of recurrent PSH repair was higher than the risk of primary PSH repair (Table 1); 1-year and 5-year cumulative incidence rates of ≥2 repairs were 12% and 33%, respectively [16]. Of all patients who required a recurrent PSH repair, we estimated that 63.3% would have two repairs, 33.3% have three repairs and 3.3% have four repairs [16].

Non-operative mortality

The initial 1-year and 5-year cycle-specific probabilities of death from any health state were estimated using the competing risks formula [41] based on age- and sex-specific ONS cancer survival statistics in England for adults diagnosed with rectal cancer between 2013 and 2017 and followed-up to 2018 (Table 1) [47]. The probability of death was stratified according to rectal cancer stages I–IV. Beyond the initial 5-year period, we

assumed that survival gradually converged with general population rates, estimated using age- and sex-specific ONS UK lifetables for the years 2016–2018 [48].

Long-term complications

Long-term complications such as bowel obstruction, bowel perforation, infection, hematoma and nonhealing wound may occur following bowel surgery and stoma creation [49]. Based on a registry-based cohort study, we used a 5-year cumulative risk of long-term complications (requiring treatment by surgical intervention) of 4.9% (142/2,876) for patients in the mesh groups and of 0.8% (3/366) for patients in the no mesh group [49]. Long-term complications were assumed to be comparable for both types of mesh [55,57]. We assumed that the risk of long-term complications ceased after 5 years following the most recent surgery.

Cost parameters

Insertion of mesh accounts for only a small fraction (around 6 minutes) of the whole colostomy procedure [15]. In addition, evidence suggests that there is very little difference in post-procedural hospital stay between the groups treated with or without a prophylactic mesh [15]. Therefore, the predominant incremental cost of using mesh is the cost of the implant itself; no differences in operative time costs were included. The mean unit costs of 10×15cm synthetic and biologic meshes are reported to be £33 and £1,650, respectively [17]. The costs of a PSH repair and treatment for long-term complications were obtained from the NHS reference costs for 2018–2019 (Table 1). These costs represent the overall weighted average cost of the procedure, including hospital stay, operation and care, not inclusive of the mesh.

Utility parameters

We incorporated a mean utility value of 0.80 (95% CI: 0.78–0.82; EQ-5D: CIPHER; Table S1 in Appendix S1) for cancer patients with no PSH at 12-month follow-up after colostomy. We applied disutility (decrement in utility) values of 0.086 (95% CI: 0.039–0.134; EQ-5D: CIPHER; Table S1 in Appendix S1) for patients with symptomatic PSH and 0.083 (95% CI: 0.080–0.086; EQ-5D) [50] for patients during their stay in hospital undergoing a surgical repair of PSH. We also applied an estimated EQ-5D utility decrement of 0.09 for patients with long-term complications [51]. We assumed no difference in quality-of-life between the mesh and no mesh groups [2,46].

Probabilistic sensitivity analysis (PSA)

PSA was performed using 10,000 Monte Carlo simulations to empirically estimate the uncertainty in the model outputs by assigning a plausible range and specific distribution to each of the model inputs (Table 1). The 95% CIs were obtained from the 10,000 simulations using the formula described elsewhere [59]. The model was built in Microsoft Excel, and programmed in Visual Basic for Applications.

We produced the cost-effectiveness acceptability curves (CEACs) to demonstrate how the NHS willingness-to-pay threshold (maximum amount the NHS is willing to pay for an additional QALY) affects the probability

that a strategy is considered cost-effective. We estimated the cost-effectiveness of synthetic versus no mesh, biologic versus no mesh and synthetic versus biologic mesh based on the incremental net monetary benefit (iNMB) [52]. An iNMB value represents the difference in NMB between alternative strategies; a positive iNMB value indicates that a strategy is cost-effective compared with the alternative at a given willingness-to-pay threshold. We used the lower UK NICE willingness-to-pay threshold of £20,000 per QALY gained to calculate the iNMBs [60].

Deterministic sensitivity analysis (DSA)

To assess the robustness of model outputs, we performed several DSAs. The costs of mesh types vary; we used a cost of £33 for synthetic mesh and £1,650 for biologic mesh in our base-case analysis [17]. We increased the cost of synthetic mesh by 50% to £50 (DSA1) and then decreased the cost of biologic mesh by 50% to £825 (DSA2) for assessing the sensitivity of model outputs. We assumed that the baseline (no mesh) risk of PSH would halve every year after 5 years, but it is plausible that the risk might end after 5 years (DSA3). We also assumed that the risk of long-term complications would cease after 5 years following the most recent surgery, but the risk might continue over the lifetime of patients (DSA4). Furthermore, we performed a threshold analysis to explore how much higher the relative risk of PSH incidence must go before synthetic mesh is no longer cost-effective over no mesh (DSA5).

RESULTS

Cost-effectiveness results are shown in Table 2, with results presented in terms of mean costs and QALYs per patient. Synthetic mesh was dominant as it produced less costs and more QALYs than biologic mesh and no mesh over the lifetime of patients across all four rectal cancer stages. Biologic mesh was substantially more costly than synthetic mesh (and no mesh) but was comparable with synthetic mesh in QALYs. In contrast, no mesh was slightly more costly than synthetic mesh (and substantially less costly than biologic mesh) but produced fewer QALYs than either of the other strategies. However, the differences in mean QALYs between the three strategies were small for patients with stage IV cancer (synthetic mesh 3.283, biologic mesh 3.281 and no mesh 3.251). This was because life-expectancy is much shorter for patients with stage IV cancer than with other cancer stages.

<Table 2>

At the lower UK NICE willingness-to-pay threshold of £20,000 per QALY gained, synthetic versus no mesh produced larger iNMBs (95% CI): stage I £1,706 (£1,692 to £1,720); stage II £1,565 (£1,552 to £1,578); stage III £1,505 (£1,493 to £1,517) and stage IV £684 (£678 to £690) than biologic versus no mesh: stage I -£332 (-£373 to -£292); stage II -£411 (-£449 to -£374); stage III -£447 (-£483 to -£412) and stage IV -£987 (-£1,005 to -£969). The iNMBs for synthetic versus biologic mesh were: stage I £2,038 (£1,997 to £2,079); stage II £1,976 (£1,939 to £2,014); stage III £1,952 (£1,916 to £1,988) and stage IV £1,671 (£1,653 to £1,689). This

indicates that synthetic mesh was more cost-effective across all four rectal cancer stages, but the estimated gain in iNMB was comparatively small for patients with stage IV cancer due to shorter life-expectancy.

<Figure 2>

Figure 2 shows the probability of cost-effectiveness at varying thresholds that a decision-maker is willing to pay to gain an additional QALY. At the £20,000 per QALY gained threshold, synthetic mesh had approximately 87% probability of being the most cost-effective strategy for patients with stage I, stage II or stage III cancer, while biologic mesh had 12% probability and no mesh only had <1% probability. For patients with stage IV cancer, synthetic mesh had approximately 96%, biologic mesh 3% and no mesh <1% probability of being the most cost-effective strategy.

Despite increasing the unit cost of synthetic mesh by 50% (DSA1), it remained the most cost-effective strategy (Table S2 in Appendix S1). This conclusion held even when the cost of biologic mesh was decreased by 50% (DSA2; Table S3 in Appendix S1). Allowing the baseline risk of PSH to end after 5 years did not change the conclusion either (DSA3; Table S4 in Appendix S1). Likewise, continuing the risk of long-term complications over the patients' lifetime did not change the conclusion (DSA4; Table 3).

<Table 3>

Figure 3 (DSA5) shows that the relative risk of PSH incidence had to be <0.95 for synthetic mesh to remain cost-effective over no mesh for rectal cancer stages I–III and <0.93 for stage IV.

<Figure 3>

DISCUSSION

It is essential to establish the balance of costs and benefits of mesh prophylaxis during intestinal stoma creation due to concerns regarding the optimal type of mesh and cost-effectiveness of its use [13,20,29,30]. Based on relative risk estimates from meta-analyses of all available RCTs, the use of synthetic mesh was found to be the most cost-effective strategy to prevent PSH in patients who underwent end colostomy for any rectal cancer stage even though the effect of mesh on PSH incidence was assumed to dissipate after 5 years and even when the risk of long-term complications was projected over the patients' lifetime (DSA4). Biologic mesh was more costly and slightly less effective than synthetic mesh.

RCTs have produced widely ranging results for the incidence of PSH in mesh and no mesh groups. It is unclear if this is due to differences between RCTs in surgical technique (e.g., open vs. laparoscopic), mesh placement (e.g., retrorectus vs. intraperitoneal), method to assess and define PSH (e.g., clinical vs. radiological), RCT methods (e.g., blinding vs. nonblinding of outcome assessors), or publication bias. Hence, it is unsurprising

that meta-analyses, including our own, show high levels of heterogeneity [13,15,61-63]. In the threshold sensitivity analysis (DSA5), we found that the relative risk (synthetic vs. no mesh) of PSH incidence had to be close to one for no mesh to be cost-effective (≥0.95 for stages I–III and ≥0.93 for stage IV). We note that three [5,34,44] of the four largest multicentre RCTs did not provide strong evidence to exclude the possibility that synthetic mesh has no effect in reducing the incidence of PSH. In contrast, the fourth RCT [2] reported a much lower rate of PSH incidence in the group who received prophylactic mesh. Therefore, conclusions about the cost-effectiveness of synthetic mesh are dependent on which subset of RCTs are considered to provide the most robust evidence of effectiveness.

We developed a decision-analytical model to track costs and patient outcomes using time-dependent probabilities and adjusting the risk of PSH, its repair and mortality to account for the dynamics of competing risks. Our analysis was based on estimates from a random-effects model of 13 RCTs to pool the relative risks of synthetic and biologic meshes compared with no mesh. We explored the cost-effectiveness of biologic mesh which was not done before. This is the first study to report the "lifetime" cost-effectiveness of mesh prophylaxis to prevent PSH from a UK NHS perspective.

We used South Korean data [39] to impute the baseline risk of PSH in patients with no mesh since this was the only source that provided age-specific long-term follow-up data of more than 5 years. Pooled mesh-related relative risks of PSH from all available RCTs were superimposed on the baseline risk of PSH. The relative risk estimate for biologic compared with no mesh included a small number of patients with an ileostomy; no RCTs were identified that included patients with a colostomy only. A stoma care nurse (SCN) looks after patients following a stoma creation; the cost associated with community stoma care was not included. However, synthetic mesh will likely be more cost-effective if, for example, it results in fewer interactions with community SCNs due to a lower incidence or severity of PSH. We focussed on costs to the health service, rather than wider costs falling on social care, patients, or informal carers. Our estimate of the quality-of-life decrement of symptomatic PSH is based on the CIPHER prospective cohort study. However, in our analysis, PSH status was defined by patients reporting that they had been told by a doctor or nurse that they had a PSH. In further CIPHER analyses, PSH status will be defined using radiological findings and patient-reported symptoms, which may result in a different estimate of the quality-of-life decrement of symptomatic PSH.

Despite the high prevalence of PSH, there is surprisingly little research on the economic impact of mesh prophylaxis. Figel et al. [64] conducted a value analysis of 16 patients and reported that use of bioprosthetic mesh during initial stoma creation might be cost-effective if the cost of this mesh is lower or a large number of PSH repairs are avoided. Findlay et al. [17] performed a cost analysis and found that synthetic mesh was associated with substantial cost savings. Lee et al. [31] conducted a model-based cost-effectiveness analysis of synthetic mesh in Canada and concluded that this strategy would be cost-effective for all rectal cancer stages, but marginally for stage IV cancer. However, the acknowledged limitations of Lee et al.'s [31] analysis

are that they included estimates from only three RCTs with smaller sample sizes, they used a time horizon of only 5 years and they did not explore the cost-effectiveness of biologic mesh. Although we used different parameter estimates, our study provides a robust lifetime cost-effectiveness conclusion.

The use of synthetic mesh may reduce the risk of PSH and could lead to improvements in the health of patients, a reduction in costs and fewer PSH repairs. This offers the potential for significant savings for healthcare providers as well as benefit for individual patients. Although synthetic mesh is relatively cheap, a hurdle to implementing synthetic mesh in practice is that there is no clear consensus on the surgical approach or most effective location of mesh placement [3,7,8,20]. Further studies are needed to understand better the influence of various surgical factors, both mesh and non-mesh related, on the risk of PSH. To this end, although the ongoing CIPHER study predominantly includes patients who do not have mesh prophylaxis [32], its results will be useful in providing better evidence on the extent to which other surgical factors influence the risk of PSH. This evidence could be used to update the model described here and determine priorities for future research [65].

CONCLUSIONS

Based on relative risk estimates from meta-analyses of all available RCTs, synthetic mesh was the most cost-effective strategy to prevent PSH in patients undergoing end colostomy creation for any rectal cancer stage. However, RCTs have produced widely ranging results, and conclusions about the cost-effectiveness of synthetic mesh are dependent on which subset of RCTs are considered to provide the most robust evidence. Biologic mesh was more costly and slightly less effective than synthetic mesh. More research is needed before synthetic mesh can be considered routinely for any patient population undergoing a stoma creation.

CONFLICT OF INTEREST
The authors have no conflict of interest to declare.

AUTHOR CONTRIBUTIONS
SM developed the model and performed the model analysis in conjunction with WH. SM and WH identified the model parameters, including use of meta-analyses conducted by SM. SM drafted the manuscript in conjunction with WH, while NS and BR reviewed and revised the manuscript critically.

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ETHICS STATEMENT

The CIPHER study has been reviewed and given favourable opinion by West Midlands – Black Country Research Ethics Committee on the 8th of November 2017 (REC reference: 17/WM/0401).

DATA AVAILABILITY STATEMENT

The data that supports the findings of this study are available within the article.

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Table 1. Decision-tree, Markov, cost, and utility parameters used in the decision-analytical model

Parameter	Mean estimate	Distribution in PSA	Source
Decision-tree parameter			
Perioperative death after index surgery	0.03	Beta (476, 15635)	NBOCA [1]
Peristomal complications for no mesh	0.07	Beta (16, 211)	Cornille et al. [13]
Peristomal complications for mesh	0.07	Beta (15, 203)	Cornille et al. [13]
Markov parameter			
Probability of PSH incidence for no mesh (Yr1)[a]	0.11	Beta (18, 147)	Sohn et al. [39]
Probability of PSH incidence for no mesh (Yr2-5)[a]	0.30	Beta (44, 103)	Sohn et al. [39]
Relative risk (synthetic vs. no mesh) of PSH incidence	0.54	LN (-0.62, 0.19 SE)	Meta-analysis [2,5,27,28,34-36,42-45]
Relative risk (biologic vs. no mesh) of PSH incidence	0.55	LN (-0.59, 0.68 SE)	Meta-analysis [26,46]
Prob. of primary PSH repair, if no mesh placed (Yr1)[a]	0.09	Beta (91, 925)	Krogsgaard et al. [16]
Prob. of primary PSH repair, if no mesh placed (Yr2-5)[a]	0.11	Beta (102, 823)	Krogsgaard et al. [16]
Relative risk of primary PSH repair, if a mesh placed	0.93	LN (-0.07, 0.23 SE)	Meta-analysis [2,5,27,28,34-42-46]
Probability of ≥2 PSH repairs (Yr1)[a]	0.12	Beta (22, 158)	Krogsgaard et al. [16]
Probability of ≥2 PSH repairs (Yr2-5)[a]	0.24	Beta (38, 121)	Krogsgaard et al. [16]
Probability of death, rectal cancer stages I–IV (Yr1)[a]	0.017 (I) 0.059 (II) 0.062 (III) 0.449 (IV)	Beta (73, 4193) Beta (175, 2799) Beta (334, 5049) Beta (1428, 1753)	ONS [47]
Probability of death, rectal cancer stages I–IV (Yr2-5)[a]	0.038 (I) 0.162 (II) 0.238 (III) 0.561 (IV)	Beta (158, 4036) Beta (452, 2346) Beta (1200, 3849) Beta (983, 770)	ONS [47]
Probability of death, rectal cancer stages I–IV (Yr≥6)[b]	Age/sex variant	Fixed	ONS [48]
Other parameter			
Proportion of patients without symptoms of PSH	0.238	Beta (48, 154)	Ripoche et al. [14]
Proportion of patients with 2 repairs	0.633	Dirichlet (19, 10, 1)	Krogsgaard et al. [16]
Proportion of patients with 3 repairs	0.333	Dirichlet (19, 10, 1)	Krogsgaard et al. [16]
Proportion of patients with 4 repairs	0.033	Dirichlet (19, 10, 1)	Krogsgaard et al. [16]
Probability of long-term complications for no mesh[b]	0.001	Beta (0.3, 365.7)	Kokotovic et al. [49]
Probability of long-term complications for mesh[b]	0.005	Beta (14, 2862)	Kokotovic et al. [49]
Cost parameter			
Synthetic mesh	£33	Uniform (15, 75)[c]	Findlay et al. [17]
Biologic mesh	£1,650	Uniform (800, 2400)[c]	Findlay et al. [17]
Peristomal complications (infection/necrosis/stenosis)	£1,636	Uniform (636, 2636)[c]	NHS reference costs (FD10A-C)[d]
Surgical repair of PSH	£3,908	Uniform (2908, 4908)[c]	NHS reference costs (FD10A-H)[e]
Surgical treatment for long-term complications	£3,316	Uniform (2316, 4316)[c]	NHS reference costs (WH07A-G)[f]
Utility parameter			
Utility of no PSH	0.80	Beta (888, 222)[g]	CIPHER QoL (Table S1; Appendix S1)[h]
Disutility of symptomatic PSH	0.086	Beta (12, 124)[g]	CIPHER QoL (Table S1; Appendix S1)[h]
Disutility of hospital stay	0.083	Beta (2370, 26183)[g]	Coronini-Cronberg et al. [50]
Disutility of long-term complications	0.09[i]	Uniform (0.05, 0.12)	Gheorghe et al. [51]

Abbreviations: LN, log normal; NBOCA, National Bowel Cancer Audit; NHS, National Health Service; ONS, Office for National Statistics; PSA, probabilistic sensitivity analysis; PSH, parastomal hernia; QoL, quality-of-life; SE, standard error; Yr, year.

[a]Probabilities for Yr1 and Yr2-5 were used in the formulae for adjusting competing risks described elsewhere [41], to yield 6-monthly cycle-specific probabilities.

[b]6-monthly cycle-specific probability.

[c]Ranges were estimated based on expert opinion.

[d]Difference in costs (non-elective short stay; 2018-19) between the HRG codes FF20C and the weighted average of FF20A & FF20B.

[e]Weighted average cost (elective; 2018-19) of the HRG codes FD10A to FD10H.

[f]Weighted average cost (nonelective long stay; 2018-19) of the HRG codes WH07A to WH07G.

[g]Gamma and Beta parameters were determined using the methods of moments described elsewhere [52].

[h]This included a very small number of patients who had a loop rather than end colostomy.

[i]Estimated mean utility decrement that ranged between 0.05 (at 7 days) and 0.12 (at 30 days) after surgery [51].

Table 2. Cost-effectiveness results for rectal cancer stages I–IV

Strategy	Mean lifetime cost per patient[a]	Mean lifetime QALYs per patient[a]	NMB[b, c] (95% CI)	iNMB[b, c] (95% CI) for mesh vs. no mesh	iNMB[b, c] (95% CI) for synthetic vs. biologic
Rectal cancer stage I					
Synthetic mesh	£586	10.071	£200,749 (£200,684 to £200,815)	£1,706 (£1,692 to £1,720)	£2,038 (£1,997 to £2,079)
Biologic mesh	£2,210	10.067	£198,711 (£198,635 to £198,787)	-£332 (-£373 to -£292)	N/A
No mesh	£631	9.985	£199,044 (£198,975 to £199,112)	N/A	N/A
Rectal cancer stage II					
Synthetic mesh	£589	8.658	£172,543 (£172,480 to £172,605)	£1,565 (£1,552 to £1,578)	£1,976 (£1,939 to £2,014)
Biologic mesh	£2,212	8.654	£170,567 (£170,494 to £170,639)	-£411 (-£449 to -£374)	N/A
No mesh	£647	8.580	£170,978 (£170,913 to £171,043)	N/A	N/A
Rectal cancer stage III					
Synthetic mesh	£601	8.015	£159,711 (£159,654 to £159,768)	£1,505 (£1,493 to £1,517)	£1,952 (£1,916 to £1,988)
Biologic mesh	£2,225	8.012	£157,759 (£157,692 to £157,826)	-£447 (-£483 to -£412)	N/A
No mesh	£669	7.941	£158,206 (£158,146 to £158,266)	N/A	N/A
Rectal cancer stage IV					
Synthetic mesh	£548	3.283	£65,046 (£65,009 to £65,084)	£684 (£678 to £690)	£1,671 (£1,653 to £1,689)
Biologic mesh	£2,172	3.281	£63,375 (£63,334 to £63,417)	-£987 (-£1,005 to -£969)	N/A
No mesh	£627	3.251	£64,363 (£64,325 to £64,401)	N/A	N/A

Abbreviations: CI, confidence interval; iNMB, incremental net monetary benefit; NMB, net monetary benefit; QALYs, quality-adjusted life-years.

[a]Deterministic analysis.

[b]Probabilistic sensitivity analysis.

[c]At the willingness-to-pay threshold of £20,000 per QALY gained.

Table 3. Cost-effectiveness results for rectal cancer stages I–IV (DSA4)

Strategy	Mean lifetime cost per patient[a]	Mean lifetime QALYs per patient[a]	NMB[b, c] (95% CI)	iNMB[b, c] (95% CI) for mesh vs. no mesh	iNMB[b, c] (95% CI) for synthetic vs. biologic
Rectal cancer stage I					
Synthetic mesh	£858	10.068	£200,417 (£200,351 to £200,483)	£1,442 (£1,428 to £1,457)	£2,032 (£1,992 to £2,073)
Biologic mesh	£2,481	10.064	£198,385 (£198,308 to £198,462)	-£590 (-£630 to -£549)	N/A
No mesh	£677	9.985	£198,975 (£198,906 to £199,044)	N/A	N/A
Rectal cancer stage II					
Synthetic mesh	£813	8.655	£172,204 (£172,142 to £172,265)	£1,337 (£1,324 to £1,350)	£1,982 (£1,944 to £2,020)
Biologic mesh	£2,437	8.651	£170,222 (£170,150 to £170,293)	-£645 (-£683 to -£607)	N/A
No mesh	£686	8.580	£170,867 (£170,803 to £170,931)	N/A	N/A
Rectal cancer stage III					
Synthetic mesh	£802	8.012	£159,374 (£159,317 to £159,430)	£1,286 (£1,274 to £1,299)	£1,952 (£1,916 to £1,988)
Biologic mesh	£2,426	8.009	£157,422 (£157,355 to £157,489)	-£665 (-£701 to -£630)	N/A
No mesh	£703	7.941	£158,087 (£158,028 to £158,147)	N/A	N/A
Rectal cancer stage IV					
Synthetic mesh	£609	3.282	£65,011 (£64,973 to £65,048)	£617 (£612 to £623)	£1,689 (£1,670 to £1,707)
Biologic mesh	£2,232	3.280	£63,322 (£63,281 to £63,364)	-£1,071 (-£1,089 to -£1,053)	N/A
No mesh	£637	3.251	£64,393 (£64,355 to £64,431)	N/A	N/A

Abbreviations: CI, confidence interval; iNMB, incremental net monetary benefit; NMB, net monetary benefit; QALYs, quality-adjusted life-years.

[a]Deterministic analysis.

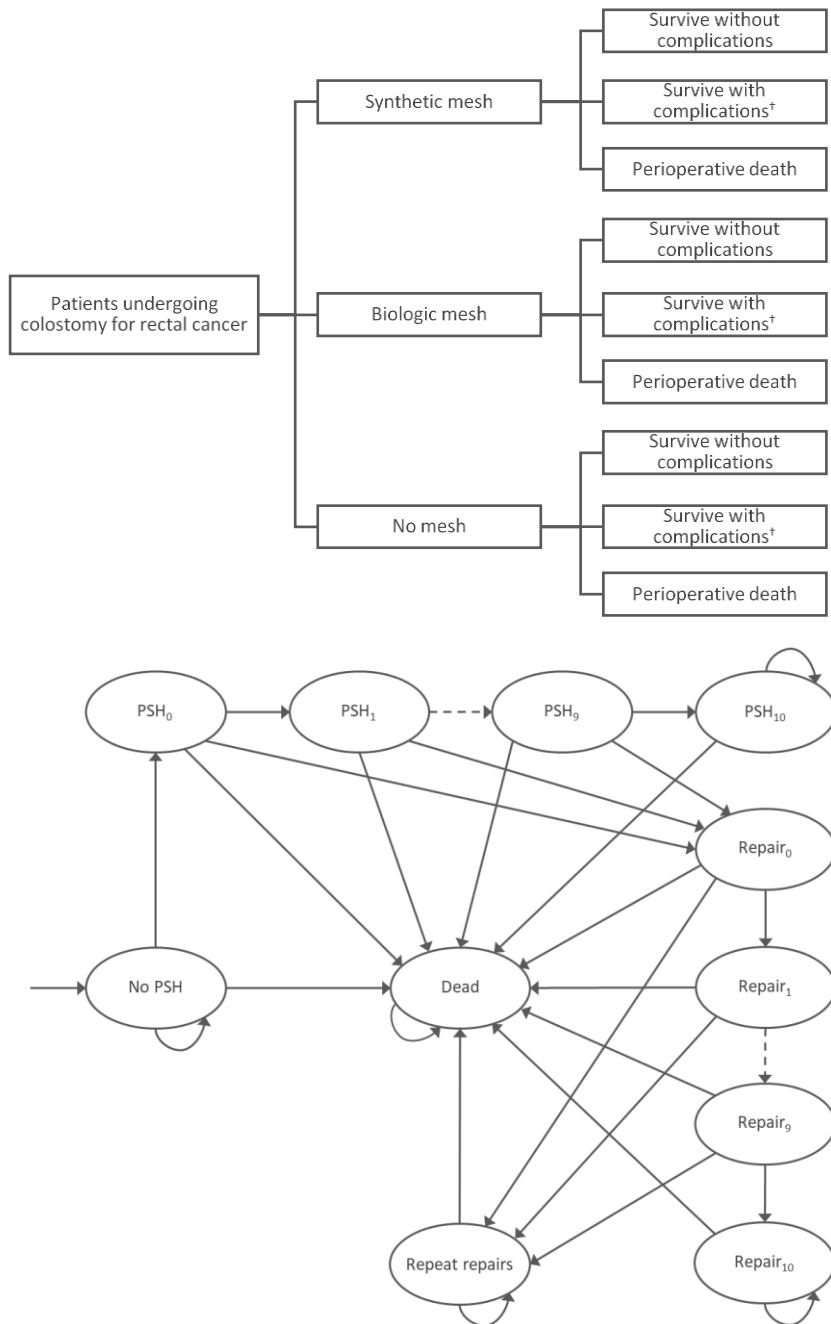[b]Probabilistic sensitivity analysis.

[c]At the willingness-to-pay threshold of £20,000 per QALY gained.

Figure 1. Schematic diagram of the decision-analytical model that combined a decision-tree (rectangular shapes) with a Markov model (oval shapes) to represent the decision between synthetic, biologic and no mesh. Decision-tree mapped out the initial costs and perioperative outcomes of surgery, while the Markov model tracked the lifetime costs and health outcomes for patients who survived the initial surgery. A Markov cohort model was selected because the patients were assumed to be independent of each other and their possible prognoses were adequately represented by this type of model over a lifetime without the need for an excessive number of health states. The "PSH" (PSH_0 to PSH_{10}) and "Repair" ($Repair_0$ to $Repair_{10}$) health states each included ten tunnel states (temporary health states that can only be visited in a specific sequence) to account for time-dependent transition probabilities. †Peristomal complications included infection, necrosis and/or stenosis occurring within the first 30 days after the index surgery.
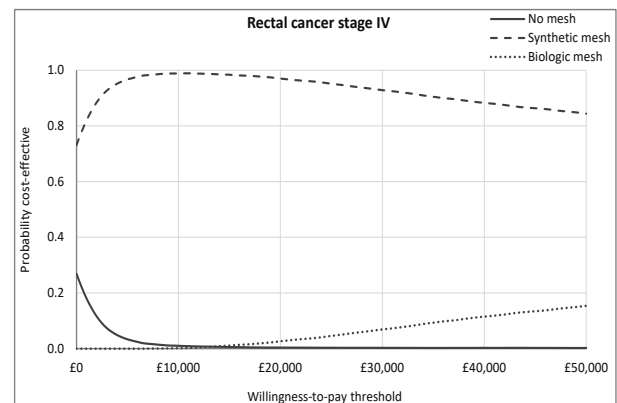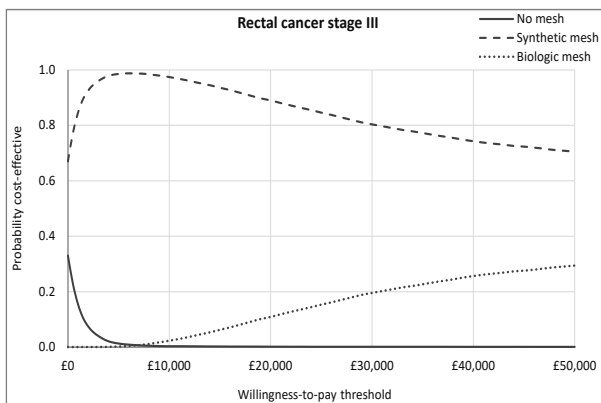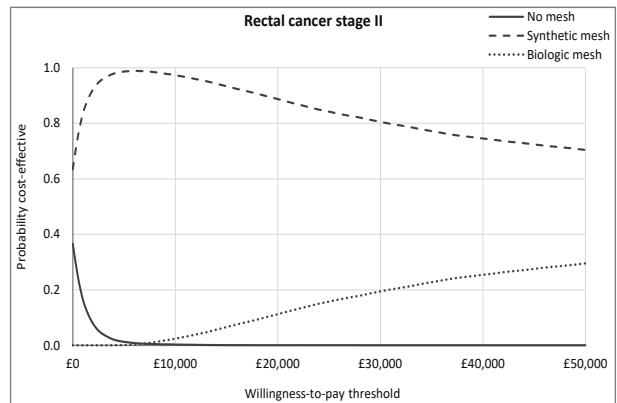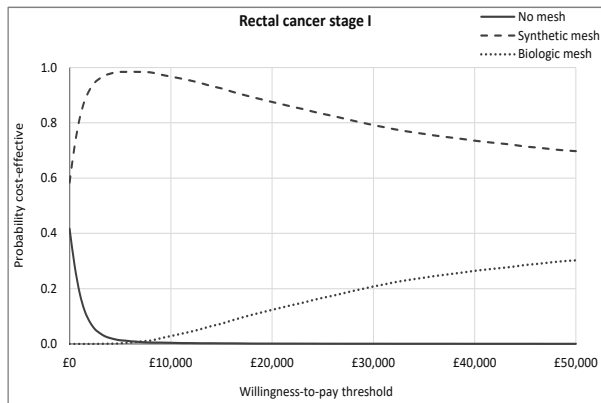
Figure 2. Cost-effectiveness acceptability curves for rectal cancer stages I–IV

Figure 3. Threshold analysis of relative risk of PSH incidence between synthetic and no mesh. Mean (0.54), 95% lower confidence interval (LCI; 0.37) and 95% upper confidence interval (UCI; 0.77) are meta-analysed estimates (Figure S1 in Appendix S1).

Figure 1. Schematic diagram of the decision-analytical model that combined a decision-tree (rectangular shapes) with a Markov model (oval shapes) to represent the decision between synthetic, biologic and no mesh. Decision-tree mapped out the initial costs and perioperative outcomes of surgery, while the Markov model tracked the lifetime costs and health outcomes for patients who survived the initial surgery. A Markov cohort model was selected because the patients were assumed to be independent of each other and their possible prognoses were adequately represented by this type of model over a lifetime without the need for an excessive number of health states. The "PSH" (PSH_0 to PSH_{10}) and "Repair" ($Repair_0$ to $Repair_{10}$) health states each included ten tunnel states (temporary health states that can only be visited in a specific sequence) to account for time-dependent transition probabilities. †Peristomal complications included infection, necrosis and/or stenosis occurring within the first 30 days after the index surgery.

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