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Oncological Safety and Potential Cost Savings of Routine vs Selective Histopathological Examination After Appendectomy

Results of the Multicenter, Prospective, Cross-Sectional FANCY Study

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Objective: To investigate the oncological safety and potential cost savings of selective histopathological examination after appendectomy.

Background: The necessity of routine histopathological examination after appendectomy has been questioned, but prospective studies investigating the safety of a selective policy are lacking.

Methods: In this multicenter, prospective, cross-sectional study, inspection and palpation of the (meso)appendix was performed by the surgeon in patients with suspected appendicitis. The surgeon's opinion on additional value of histopathological examination was reported before sending all specimens to the pathologist. Main outcomes were the number of hypothetically missed appendiceal neoplasms

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VPB, MGWD, and WAB made substantial contributions for the conception or design of this study. All authors and collaborators acquired the data, which were analysed by VPB. VPB, PJT, MGWD, and WAB interpreted the results. VPB drafted the initial manuscript with assistance from PJT, MGWD, and WAB. JJ, BJAGC, EAJSL, ACK, HAS, JLPV, GJDA, AAWG, KHH, LK, PRR, CCR, GDS, and VT interpreted the results and revised and contributed to the intellectual content of the manuscript. All authors approved the final version of the manuscript to be submitted. All authors agreed to be accountable for all aspects of the work and ensuring that questions related to the accuracy or integrity of any part of the Article are appropriately investigated and resolved. VPB and WAB had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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with clinical consequences benefiting the patient (upper limit two-sided 95% confidence interval below 3:1000 considered oncologically safe) and potential cost savings after selective histopathological examination.

Results: Seven thousand three hundred thirty-nine patients were included. After a selective policy, 4966/7339 (67.7%) specimens would have been refrained from histopathological examination. Appendiceal neoplasms with clinical consequences would have been missed in 22/4966 patients. In 5/22, residual disease was completely resected during additional surgery. Hence, an appendiceal neoplasm with clinical consequences benefiting the patient would have been missed in 1.01:1000 patients (upper limit 95% confidence interval 1.61:1000). In contrast, twice as many patients (10/22) would not have been exposed to potential harm due to re-resections without clear benefit, whereas consequences were neither beneficial nor harmful in the remaining seven. Estimated cost savings established by replacing routine for selective histopathological examination were €725,400 per 10,000 patients.

Conclusions: Selective histopathological examination after appendectomy for suspected appendicitis is oncologically safe and will likely result in a reduction of pathologists' workload, less costs, and fewer re-resections without clear benefit.

Keywords: appendectomy, appendicitis, histopathology, pathology, routine, selective

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Appendectomy for acute appendicitis is one of the most frequently performed surgical procedures worldwide.[1] Despite the rarity of aberrant histopathological findings with clinical significance, current practice in the Netherlands entails histopathological examination of all appendiceal specimens to rule out the presence of unexpected pathology. Owing to increasing emphasis on cost containment in healthcare and rising workload of pathology departments, the necessity of this routine policy has been questioned for several decades. The relevance of this research topic is further demonstrated by the growing interest in the nonsurgical management of appendicitis.[2–7] As incidental appendiceal pathology will likely be undetected for some time in case of a nonoperative strategy, definitive conclusions on whether routine histopathological examination after appendectomy is necessary may help in deciding the safety of this nonsurgical policy.

To save costs and reduce the workload of pathologists, a more selective policy might be justified. This strategy entails macroscopic assessment of the specimen by the surgeon, only followed by histopathological examination by the pathologist in case of abnormal macroscopic findings. The main argument used by opponents of a selective policy is that it may lead to an increased risk of missing appendiceal neoplasms, with potential unfavorable outcomes for the patient.[8-11] Proponents argue that tumors that are not detected during macroscopic assessment are usually of early stage and therefore likely will not change clinical management.[12–14] Unfortunately, prospective studies investigating the ability of surgeons to identify clinically relevant neoplasms by macroscopic assessment of the resected specimen are lacking. This study aimed to prospectively investigate both the oncological safety and costs of selective histo-pathological examination of appendiceal specimens, which was intended to provide definitive conclusions regarding the appropriate histopathological strategy after appendectomy. It was hypothesized that a selective policy is oncologically safe and will save costs.

METHODS

This study followed the strengthening the reporting of observational studies in epidemiology statement.[15] The study protocol and statistical analysis plan were published before.[16] This study was conducted in accord with the ethical standards of the Helsinki Declaration of 1975.

Study Design

This was a Dutch multicenter, prospective, cross-sectional study, registered with ClinicalTrials.gov on April 27, 2018 before recruitment of any participants (trial identification number NCT03510923). The study was performed in 59 (40 teaching, 13 nonteaching, and six academic hospitals) of 74 Dutch hospitals (80%) between May 1, 2018 and August 31, 2019. The study protocol was reviewed by the Institutional Review Board of the Amsterdam UMC, which decided that the Dutch Medical Research Involving Human Subjects Act was not applicable. In all participating centers, approval for execution of the study was obtained from the local Institutional Review Board before the start of inclusion of patients. Each center included patients for a period of nine months.

Participants

Patients of all ages with (recurrent) appendicitis scheduled for appendectomy were eligible for inclusion. Recurrent appendicitis was defined as a second episode of appendicitis in patients in whom conservative treatment with antibiotics failed. Exclusion criteria were (1) strong clinical/radiological suspicion or preoperative histopathological proof of an appendiceal neoplasm; (2) appendix removed as part of more extensive surgery (eg, right colectomy), and (3) inclusion in the ACCURE trial.[17] An opt-out procedure was offered to patients the opportunity to refuse the use of their nonidentifiable data.

Study Procedures

All removed appendices were systematically assessed by the operating surgeon (attending surgeon and/or resident) for macroscopic abnormalities. The macroscopic examination included inspection and palpation of the appendix and mesoappendix. The specimen was not opened, as this might impede proper histopathological examination. All steps of the macroscopic examination were discussed during the site initiation visits and shown in an instruction video, which was available for all local investigators during the entire study period. After this systematic assessment, the surgeon reported on a predefined scoring form whether macroscopic abnormalities suspicious for an appendiceal neoplasm were present, and if he or she believed additional assessment by the pathologist was indicated. Subsequently, all appendiceal specimens were sent for further assessment by the pathologist. Histopathological examination was conducted according to the local protocol of the pathology department where the specimen was assessed.

Outcomes

The 2 main outcomes were oncological safety and potential cost savings of selective histopathological examination after appendectomy. Oncological safety was assessed by calculating the number of patients in whom the histopathological diagnosis of an appendi-ceal neoplasm with clinical consequences benefiting the patient would have been missed in case of selective histopathological examination. Clinical consequences included all diagnostic and therapeutic

TABLE 1. Baseline Characteristics

		Total (n = 7339)
Age in years, median (IQR)		33 (19–51)
Sex, No. (%)	Female	3656 (49.8)
	Male	3683 (50.2)
Preoperative imaging, No. (%)	Ultrasound	5116 (69.7)
	Ultrasound + CT	1250 (17.0)
	Ultrasound + MRI	246 (3.4)
	Ultrasound + CT + MRI	3 (0.0)
	CT	689 (9.4)
	MRI	18 (0.2)
	No preoperative imaging	17 (0.2)
Hospital, No. (%)	Academic hospital	117 (1.6)
	Teaching hospital	6222 (84.8)
	Nonteaching hospital	1000 (13.6)
Macroscopic assessment performed by, No. (%)	Surgeon	3411 (46.5)
	Resident	3365 (45.9)
	Both	555 (7.6)
	Missing	8 (0.1)

CT indicates computed tomography; IQR, interquartile range; MRI, magnetic resonance imaging.

procedures initiated within 6 months after the histopathological diagnosis of the appendiceal neoplasm (including care provided in tertiary referral centers). The following consequences were considered beneficial: (1) presence of residual tumor and/or positive lymph nodes in the re-resection specimen, (2) treatment with (adjuvant) systemic or locoregional chemotherapy, radiotherapy, or any other oncological treatment with curative intent, (3) palliative treatment for metastases detected during staging procedures, and (4) diagnosis of serrated polyposis syndrome or removal of (pre)malignant lesion(s) during colonoscopy. When an additional resection was performed and no residual disease was found, this was considered harmful due to the surgical risks the patient was exposed to. Clinical consequences were considered to be neither beneficial nor harmful if a patient only underwent diagnostic procedures and/or was subjected to periodic surveillance without receiving further treatment. Cost-minimization and budget impact analyses were performed to determine the potential cost savings of a selective policy. The reliability and quality of the main outcomes were assured by (1) reviewing all pathology reports, (2) verifying source data by remote monitoring, and (3) estimating the incidence of appendiceal neoplasms in the group of eligible patients that were unintentionally not included.

Secondary outcomes were described in detail in the previously published study protocol[16], and included (1) the clinical outcomes of patients with an appendiceal neoplasm, both in terms of benefit and harm, (2) the ability of the surgeon to detect an appendiceal neoplasm during macroscopic examination, and (3) the incidence of other histo-pathological diagnoses after appendectomy. In a posthoc analysis, the different reasons for histopathological examination described by the surgeons were evaluated and allocated into categories. Results of these secondary outcomes and predefined subgroup analyses are reported in Supplemental Digital Content Appendix 1, http://links.lww.com/SLA/D468.

Statistical Analysis

Details concerning the group size calculation are reported in the statistical analysis plan.[16] In short, it was assumed that (1) less than 1 out of 1000 examined specimens will contain an appendiceal neoplasm with clinical consequences benefiting the patient that is not recognized by the surgeon, and (2) selective histopathological examination is considered safe if the upper limit of the two-sided 95% confidence interval (CI) of the proportion of missed appendiceal neoplasms with clinical consequences benefiting the patient is below 3 per 1000 examined specimens, within the group of specimens that would have been refrained from histopathological examination. A sample size of 4462 specimens was needed to achieve 84% power to detect a difference of 0.002 using a one-sided binominal test at a target significance level of 0.025, assuming a baseline and actual proportion of 0.001, and a noninferiority limit of 0.00299. Assuming that the rate of histopathological examination could be reduced to 20%, 5578 patients (4462/0.8) had to be included.

Categorical variables are presented as frequencies and percentages. Continuous variables are summarized as medians with interquartile ranges. For the analysis of oncological safety, only data from patients whose appendix would have been refrained from histopathological examination with a selective policy were included. The sample was bootstrapped 5000 times to estimate the upper limit of the two-sided 95% CI of the proportion of missed appendiceal neoplasms with clinical consequences benefiting the patient. Type of assessor was the only missing data in 8 patients. Therefore, complete-case analyses were performed without imputation.

The economic evaluation was performed from a health care provider perspective, using a decision tree model comparing routine with selective histopathological examination. The potential cost impact of the selective strategy was assessed as a trade-off between initial histopathological examination and subsequent interventions not being performed on the one hand and (extra) costs of delayed treatment of missed appendiceal neoplasms on the other hand. Details regarding methodology and results of the economic cost-analysis will be reported elsewhere. All statistical analyses were performed by the first author, health economist, and principal investigator using IBM SPSS statistics, version 26.0 (IBM Corp).

RESULTS

Patients

Between May 1, 2018 and August 31, 2019, a total of 7398 patients were enrolled. Fifty-nine patients were excluded for the following reasons: incidental appendectomy during another abdominal procedure (n = 48), radiological suspicion of appendiceal neoplasm (n = 10), appendectomy as part of more extensive surgery (n = 1). This resulted in the inclusion of 7339 patients. Baseline characteristics of all included patients are presented in Table 1.

A total of 130 patients (1.77%) were diagnosed with an appendiceal neoplasm. Details can be found in Supplemental Digital Content Tables 1 and 2, http://links.lww.com/SLA/D468. Median age was 55 years (interquartile range 41 –68) and 68 patients (52.3%) were women. Histopathological examination revealed noninvasive epithelial neoplasms in 56/7339 (0.76%), neuroendocrine neoplasms in 39/7339 (0.53%), and invasive epithelial neoplasms in 35/7339 patients (0.48%).

Data from the Dutch nationwide network and registry of histopathology and cytopathology (Pathologisch-Anatomisch Landelijk Geautomatiseerd Archief) showed that 9929 appendectomies were performed in the participating hospitals during

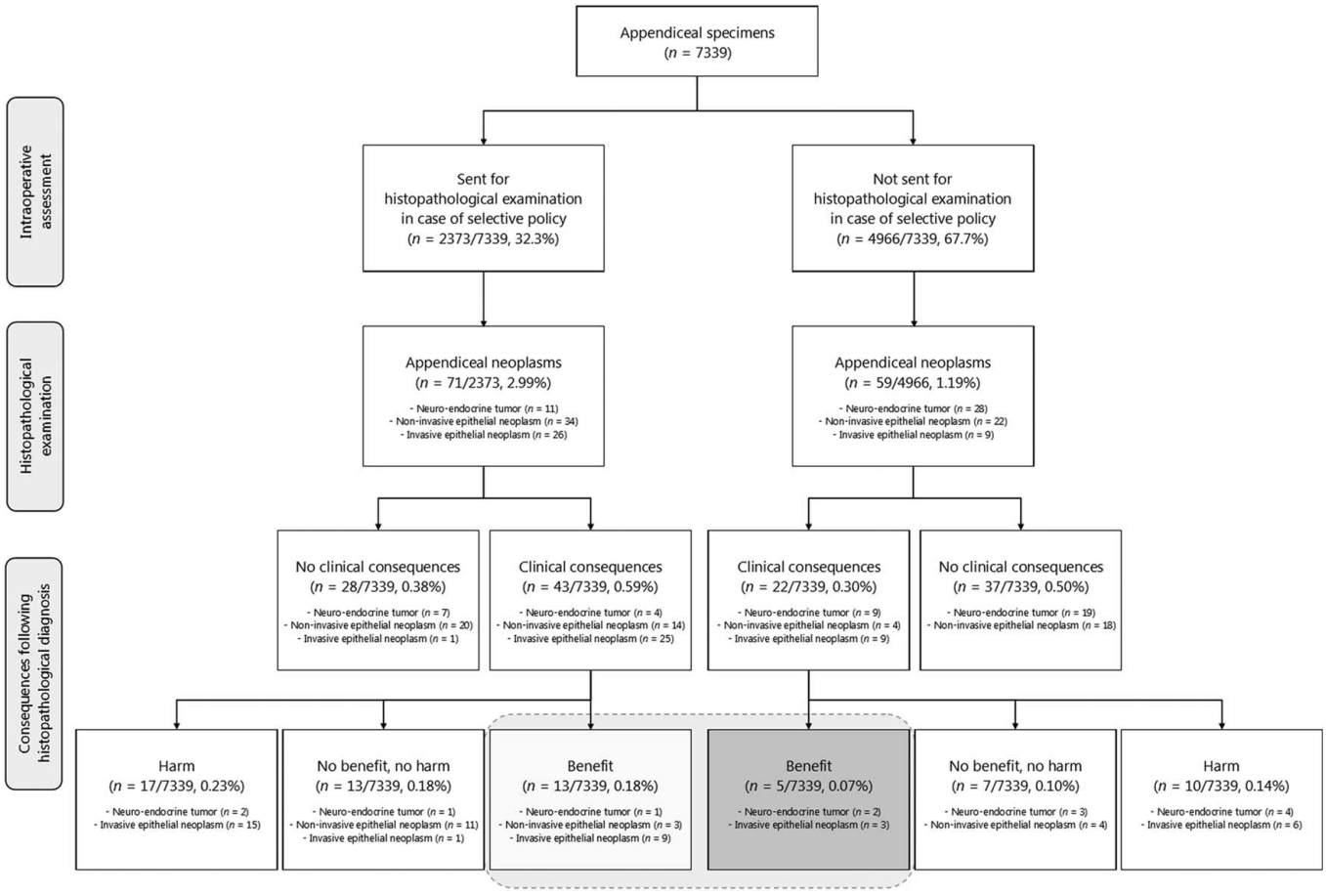

FIGURE 1. Patients with appendiceal neoplasms. Number of patients with an appendiceal neoplasm with clinical consequences benefiting the patient that would have been diagnosed (light grey box) and missed (dark grey box) in case of a selective policy. The gray dotted line indicates the total number of patients benefiting from clinical consequences of an appendiceal neoplasm, that would have been diagnosed in case of a routine policy.

the study periods, and 198 patients (1.99%) were diagnosed with an appendiceal neoplasm.[18] This implied that our cohort included approximately 74% of eligible patients with a comparable incidence of appendiceal neoplasms.

Specimens that would not Have Been Sent for Histopathological Examination

After systematic macroscopic examination, surgeons judged that histopathological examination was not indicated in 4966 patients (67.7%). Of these, 59 (1.19%) were diagnosed with an appendiceal neoplasm (Fig. 1, Table 2, Supplemental Digital Content Table 3, http://links.lww.com/SLA/D468). These concerned neuroendocrine neoplasms in 28, noninvasive epithelial neoplasms in 22, and invasive epithelial neoplasms in nine patients.

Clinical Consequences

The diagnosis had clinical consequences for nine of 28 patients with a neuroendocrine neoplasm (Fig. 1, Supplemental Digital Content Table 3, http://links.lww.com/SLA/D468). An additional resection was performed in six patients, and residual disease was found in two re-resection specimens. One patient underwent imaging, which did not show any signs of metastases. It was decided that further treatment or follow-up were not indicated. The remaining 2 patients with neuroendocrine neoplasms did not undergo any diagnostic or therapeutic procedures within 6 months after the diagnosis, but were subjected to periodic surveillance. A colonoscopy was performed in 4 of 22 patients with a noninvasive epithelial neoplasm, with no (pre)-malignant lesions detected in any of them. All 9 patients with an invasive epithelial neoplasm were scheduled for additional surgery, and residual disease was radically removed in 3 of them. Adjuvant systemic treatment was only indicated in one of these 59 patients, but not administered because of postoperative complications. Details of the clinical consequences after the diagnosis of an appendiceal neoplasm in these patients can be found in Supplemental Digital Content Table 2, http://links.lww.com/SLA/D468.

Thus, with a selective policy, an appendiceal neoplasm with clinical consequences benefiting the patient would have been missed in 5 patients (0.07%, Supplemental Digital Content Table 3, http://links.lww.com/SLA/D468). Within the group of specimens that would have been refrained from histopathological examination (n = 4966), the proportion of missed appendiceal neoplasms with clinical consequences benefiting the patient was 1.01 per 1000 specimens (upper limit two-sided 95% CI 1.61 per 1000 specimens), demonstrating oncological safety of selective histopathological examination. At the same time, ten

TABLE 2. Histopathological Diagnoses After Appendectomy for Appendicitis

Histopathological Diagnosis		Total (n = 7339)	Scored as Indication for HPE* (n = 2373)	Scored as No Indication for HPE* (n = 4966)
	Normal appendix, No. (%)	83 (1.13)	17 (0.72)	66 (1.33)
	Acute inflammation, No. (%)	6803 (92.70)	2170 (91.45)	4633 (93.29)
	Chronic inflammation and/or reactive changes, No. (%)	206 (2.81)	64 (2.70)	142 (2.86)
	Peri-appendicitis, No. (%)	29 (0.40)	10 (0.42)	19 (0.38)
Appendiceal neoplasms	Neuroendocrine neoplasm, No. (%)	39 (0.53)	11 (0.46)	28 (0.56)
	Noninvasive epithelial neoplasm, No. (%)	56 (0.76)	34 (1.43)	22 (0.44)
	Invasive epithelial neoplasm, No. (%)	35 (0.48)	26 (1.10)	9 (0.18)
Non-neoplastic aberrant findings	Parasitic infection, No. (%)	39 (0.53)	13 (0.55)	26 (0.52)
	Endometriosis, No. (%)	28 (0.38)	15 (0.63)	13 (0.26)
	Granulomatous disease, No. (%)	12 (0.16)	6 (0.25)	6 (0.12)
	Other, No. (%)	9 (0.12)	7 (0.29)†	2 (0.04)‡

HPE indicates histopathological examination.
*According to the operating surgeon or surgical resident.
†No appendiceal tissue detected (n = 5), assessment not possible due to coagulation artefacts (n = 1), peri-appendicular foreign body material with inflammatory response (n = 1).
‡No appendiceal tissue detected (n = 2).

patients would not have been exposed to the surgical risks of re-resections without a clear benefit by selective histopathological examination.

Specimens that would Have Been Sent for Histopathological Examination

Of 2373 patients (32.3%) whose appendix would have been sent for histopathological examination as indicated by the surgeon, 71 (2.99%) were diagnosed with an appendiceal neoplasm (Fig. 1, Table 2, Supplemental Digital Content Table 3, http://links.lww.com/SLA/D468).

Clinical Consequences

Four of 11 patients with a neuroendocrine neoplasm experienced clinical consequences. One patient was subjected for periodic surveillance. A right colectomy was performed in the other three patients, and one of the re-resection specimens contained a tumorpositive lymph node.

Clinical consequences were observed in 14 of 34 patients with a noninvasive epithelial neoplasm. Two patients were planned for additional surgery. One of these patients was diagnosed with pseu-domyxoma peritonei (PMP) during diagnostic laparoscopy and referred for cytoreductive surgery combined with hyperthermic intraperitoneal chemotherapy. The other patient underwent a wedge resection for removal of a suspicious polyp found during colonos-copy, followed by an additional right colectomy as the polyp was proven to be malignant. Seven patients underwent a colonoscopy, with removal of two premalignant lesions in one of them. A baseline CT was performed in three patients with a low-grade appendiceal neoplasm and showed no signs of pseudomyxoma peritonei in any of them. Two patients were referred for periodic surveillance.

The diagnosis of an invasive epithelial neoplasm resulted in a change of postoperative management in 25 of 26 patients, and the remaining patient preferred no further diagnostic or therapeutic procedures because of his age. One patient was diagnosed with an appendiceal metastasis from prior known gastric cancer. At the time the histopathological report became available, the patient was readmitted because of obstructive ileus for which emergency explorative laparotomy was performed. The remaining 24 patients all underwent an additional resection, and pathological examination revealed residual disease in eight of them. Three patients (2 patients with residual disease, 1 patient without residual disease) were referred for adjuvant chemotherapy (Supplemental Digital Content Table 2, http://links.lww.com/SLA/D468).

TABLE 3. Comparison of Routine and Selective Histopathological Examination After Sppendectomy

	Routine HPE	Selective HPE	No HPE
Number of appendectomies	7339	7339	7339
Appendiceal specimens analyzed by pathologist, No. (%)	7339 (100)	2373 (21.9)	0 (0.0)
Histopathological diagnosis of appendiceal neoplasm, No. (%)	130 (1.77)	59 (0.80)	0 (0.0)
Diagnosed appendiceal neoplasms with clinical consequences, No. (%)	65 (0.89)	43 (0.59)	0 (0.0)
Benefit, No. (%)	*18 (0.25)*	*13 (0.17)*	*0 (0.0)*
Harm, No. (%)	*27 (0.37)*	*17 (0.23)*	*0 (0.0)*
No benefit, no harm, No. (%)	*20 (0.27)*	*13 (0.17)*	*0 (0.0)*
Missed appendiceal neoplasms with clinical consequences, No. (%)	0 (0.0)	22 (0.30)	65 (0.89)
Benefit owing to avoidance of harm, No. (%)	*0 (0.0)*	*10 (0.14)*	*27 (0.37)*
Harm owing to withheld benefit, No. (%)	*0 (0.0)*	*5 (0.07)*	*18 (0.25)*
No benefit, no harm, No. (%)	*0 (0.0)*	*7 (0.10)*	*20 (0.27)*
Estimated costs*	€1,848,401	€1,316,029	€999,278

HPE, histopathological examination.
*Based on price-indexed costs obtained from the Dutch Costing Manual for Health Care Research, the tariffs ledger of the initiating hospital, including personnel, material, and overhead costs, and Pharmacotherapeutic Compass. Delayed treatment costs under the selective and no histopathological examination strategies included a preplanned 50% penalty to prevent overestimation of cost savings.

Thus, 43 of 71 patients with an appendiceal neoplasm that would have been diagnosed with a selective policy experienced clinical consequences (Fig. 1). Of these, 13 patients experienced benefit, whereas harm was observed in 17. Consequences were neither beneficial nor harmful in the remaining 13 patients.

Hence, if all appendiceal specimens were submitted for histopathological examination (ie, routine policy, Table 3), 18 of 7339 patients (0.25%) who underwent an appendectomy for suspected appendicitis experienced benefit from the clinical consequences after the diagnosis of an appendiceal neoplasm. Harm was observed in 27 patients (0.37%), and consequences were neither beneficial nor harmful in 20 patients (0.27%).

Costs

A strategy of selective histopathological examination would reduce the mean per patient costs of pathology and consequential costs of imaging, surgery, oncological care and (multidisciplinary) specialist consultations by €76.76 in comparison with routine histopathological examination. However, the potential extra mean per patient costs of postponing treatment of missed appendiceal neoplasms would amount to €4.22. The potential cost savings per 10,000 patients would be approximately €725,400.

DISCUSSION

This multicenter study including 7339 patients prospectively investigated both the clinical consequences and costs of selective histopathological examination of appendices removed for suspected appendicitis. A selective policy would reduce histopathological examinations by approximately two-thirds of appendiceal specimens. The results of this study provide robust evidence that a selective strategy is oncologically safe and demonstrate that the implementation of this approach might save at least €700,000 per 10,000 patients.

The main objection to selective histopathological examination is the risk of appendiceal neoplasms being missed by surgeons, thereby potentially depriving patients from further treatment they might benefit from. The results of the present study, however, showed that the diagnosis of an appendiceal neoplasm with clear beneficial consequences would have been missed in only 5 of 7339 patients (0.68:1000) by a selective policy. Meanwhile, 17 patients with an incidental appendiceal neoplasm did not experience any benefit from the initiated postoperative management. In fact, ten of these patients would not have been exposed to additional surgery without a clear benefit in case of selective histopathological examination. In five of them, postoperative complications including anastomotic leakage would not have occurred.

Given the present data, one might even postulate that complete refrainment from histopathological examination is justified as well. This scenario is relevant given the recent interest in the treatment of appendicitis with antibiotics.[2–7] After all, if appendicitis will be treated more often conservatively in the future, some unexpected pathology will be discovered with delay or not even diagnosed and treated at all. If all appendiceal specimens were omitted from histopathological assessment, 18 patients would have been withheld from clear beneficial treatment, whereas surgical risks of additional surgery with a considerable complication rate (31.9%) would have been avoided in 27 patients. The clinical consequences of routine, selective, and no histopathological examination and corresponding costs are reported in Table 3.

Some might disagree with the assumption that, after the diagnosis of an appendiceal neoplasm, a re-resection is harmful if no residual tumor tissue is found. It might be argued that these patients potentially benefited from the resection of micrometastases. The presence of these small cancer cells measuring between 0.2 mm and 2.0 mm in size seems to be associated with advanced tumor stage and nodal involvement. The Dutch guideline therefore states that adjuvant chemotherapy to eliminate these cancer cells is indicated in patients with pT4 cancer and/orpositive lymph nodes.[19] In the FANCY study, both the removal of residual disease (primary tumor tissue and/or positive lymph nodes) and receiving adjuvant chemotherapy were considered beneficial. This means that only patients with a pT4 appendiceal adenocarcinoma without residual disease in the re-resection specimen who have rejected adjuvant chemotherapy might have been incorrectly considered as patients experiencing harm. This was the case in 2 patients, of whom the appendectomy specimen would have been sent to the pathology department in case of a selective policy in both. Nevertheless, even if it was concluded that these 2 patients did not experience harm, our conclusion would have remained unchanged with still more patients experiencing harm than benefit.

Proponents of routine histopathological examination also argue that aberrant findings other than neoplasms can be missed. In case of a selective policy, parasitic infections, endometriosis, and granulomatous diseases would have been missed in 26 (0.35%), 13 (0.18%), and 6 patients (0.08%), respectively (Table 2). Although we did not collect data on clinical consequences of these histopathological findings, it is expected that the majority of these patients would not be harmed by the undiagnosed diseases. Parasitic infections only require treatment in case of symptoms, and antihelminthic therapy would probably have been initiated in case of (persisting) symptoms (eg, anal pruritus) after appendectomy. Consultation with a gynecologist for medical treatment of endometriosis is not required in asymptomatic patients without any other foci of endometriosis. As almost 80% of appendectomies are performed laparoscopically, surgeons should be encouraged to routinely check the reproductive organs in women who undergo an appendectomy.[20] Referral to a gynecologist should only be considered in patients with visible extra-appendiceal locations of endometriosis during exploration and/or persisting abdominal complaints after surgery. Granulomatous appendicitis rarely represents a manifestation of Crohn disease, sarcoidosis or tuberculosis.[21,22] The most common cause seems to be recurrent appendicitis with interval appendectomy inducing a granulomatous reaction resulting from a protracted secondary inflammatory response to appendicitis and nonsurgical management such as antibiotics.[22] Most patients with this condition are therefore treated with appendectomy alone.

To our knowledge, the ability of surgeons to macroscopically identify appendiceal neoplasms in a resection specimen has never been studied prospectively in a multicenter cohort of more than 7000 patients. Therefore, we believe this study provides the best available evidence regarding the oncological safety and potential cost savings of selective histopathological examination after appendectomy. Moreover, this is the first study showing the clinical and financial consequences of a policy of no histopathological examination at all, which is a relevant scenario if treatment of appendicitis becomes more conservative in the future. Furthermore, implementation of a selective strategy is assumed to be easy, as no comprehensive teaching program is required to perform a systematic macroscopic assessment. Other strengths are the reliability as well as external

validity of our findings, based on the participation of almost 80% of the Dutch clinical centers, the almost 100% completeness of the data, and plausible incidence of appendiceal neoplasms. The main limitation of this study is the short follow-up interval, potentially resulting in patients with curable recurrent disease discovered beyond six months to be incorrectly designated to the "neither beneficial nor harmful" or "harmful" group. Another main limitation is that we were not able to investigate our main outcomes for children and adults separately, as the sample sizes of these cohorts were not sufficient. Furthermore, surgeons were prohibited to split the appendiceal specimen in half, as it might impede proper assessment by the pathologist. Opening of the appendix might help surgeons in their decision to omit the appendix from histopathological examination, thereby saving even more costs. Further research should focus on the identification of risk factors for appendiceal neoplasms, to provide surgeons some guidance in their decision making (Supplementary Digital Content - Supplementary Table 4.docx, http://links.lww.com/SLA/D469. Supplementary Digital Content - Supplementary Table 5.docx, http://links.lww.com/SLA/D470. Supplementary Digital Content - Supplementary Table 6.docx, http://links.lww.com/SLA/D471. Supplementary Digital Content - Supplementary Table 7.docx, http://links.lww.com/SLA/D472. Supplementary Digital Content -Supplementary Table 8.docx, http://links.lww.com/SLA/D473).

In conclusion, appendectomy specimens should no longer be routinely submitted for histopathological examination. A selective policy after macroscopic examination by the surgeon is oncologically safe and will likely result in a significant reduction of costs, pathologists' workload and additional resections without clear benefit. In fact, as both routine and selective histopathological examination resulted in clinical consequences which were more often harmful than beneficial for patients, even omitting any pathological assessment might be justified. These results imply that, from an oncological perspective, the nonsurgical treatment of appendicitis seems safe.

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