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ORIGINAL RESEARCH ARTICLE

The Potential Health Economic Value of Adding Magnetomotive Ultrasound to Current Diagnostic Methods for Detecting Lymph Node Metastases in Rectal Cancer

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Abstract

Background Local resection of early rectal cancer (RC) is a desirable treatment option compared with surgery, offering reduced morbidity, mortality, health care costs and avoidance of stoma. However, local resection is restricted to cases without suspicion of lymph node metastases (LNM). Current methods to diagnose LNM and risk estimations based on histopathology cannot reliably identify patients eligible for local resection. The NanoEcho diagnostic system is based on a novel method for lymph node staging in RC. The aim of this study was to perform a health economic analysis at an early stage of clinical development to estimate the potential value of adding NanoEcho diagnostics to current diagnostic methods in RC.

Methods A Markov model for RC diagnosis was developed where the costs and health outcomes, including quality-adjusted life years (QALYs), for adding the NanoEcho diagnostics to current diagnostic methods were compared with current diagnostic methods alone. The diagnostic performance of the NanoEcho diagnostic system is still unknown and the base-case analysis was performed at an assumed 85% sensitivity and 85% specificity. Two testing strategies corresponding to two alternative ways of implementing the diagnostic test in clinic were evaluated: (1) examine all patients diagnosed with RC and (2) examine only patients diagnosed with clinical stages T1 and T2.

Results Adding the NanoEcho diagnostic system resulted in a gain of 0.032 life years and 0.124 QALYs per patient in the target population compared with current diagnostic methods alone. At a cost-neutral level, the estimated justifiable price of NanoEcho diagnostics was SEK 6995 in the first testing strategy and SEK 50,658 in the second testing strategy. The justifiable price of the NanoEcho diagnostics at a willingness to pay of 500,000 SEK/QALY was SEK 10,654 in the first testing strategy and SEK 65,132 in the second testing strategy.

Conclusion The results indicate that adding NanoEcho diagnostics to standard of care can potentially reduce healthcare costs and increase quality of life in RC patients, assuming a sensitivity and specificity of 85%.

1 Introduction

Colorectal cancer (CRC) is the third most frequent cancer and second cause of cancer-related death worldwide. Rectal cancer (RC) accounts for approximately one-third of all CRC cases [1] and is mainly treated by surgical resection, with or without the addition of preoperative chemo/radiotherapy. However, surgical resection of RC is commonly performed as total mesorectal excision, where both the rectum and surrounding mesorectum are removed, and is associated with substantial morbidity and high rates of temporary or permanent stoma [2]. Early RC can be defined as a lesion localized to the rectal wall in which the likelihood of mesorectal disease, nodal positivity, or deposits is low, and, correspondingly, the risk of recurrence after local resection is at an acceptable level [3]. The staging of rectal cancer describes how advanced the cancer is, how far it has spread and the depth of tumor invasion. The staging follows the TNM system (tumor, node, metastasis) [4]. T stage describes how deep the tumor has invaded the layers of the rectal wall, where T1 means that the tumor has grown only into the submucosa and T4 means that the tumor has invaded nearby organs. N stage describes the spread of tumor cells to nearby lymph nodes; it ranges from no lymph node involvement (N0) to N1 (1–3 nodes involved) and N2 (4 or more nodes involved). Staging is first

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Key Points for Decision Makers

Local resection of early rectal cancer (RC) is a desirable treatment option compared with surgery, but preoperative diagnosis of lymph node metastasis is notoriously difficult, leading to overtreatment with surgery.

The NanoEcho diagnostic system is a new and promising method for lymph node staging in rectal cancer, where iron oxide-based nanoparticles are injected adjacent to the tumor and a magnetomotive ultrasound is performed.

The addition of the NanoEcho diagnostic system to standard of care has the potential to reduce healthcare costs and increase quality of life for patients with clinical T1 rectal cancer and clinical suspicion of lymph node metastasis.

performed pretreatment (surgery) and is referred to as clinical staging (c), and is then determined after surgery by examining the removed tumor, known as pathological staging (p).

In light of this, local resection has become a desirable treatment option for early-stage clinical T1 RC, offering significantly reduced morbidity, mortality and healthcare cost compared with surgical resection, while maintaining an intact bowel [5]. Local resection is a minor surgical procedure that involves removing the tumor and small amount of surrounding healthy tissue from the rectum without removing the entire rectum. However, lymph nodes are not harvested during local resection and incidence of lymph node metastasis (LNM) in clinical T1 RC has been reported to range from 12 to 16% [6–11]. Thus, the risk of leaving concomitant LNM untreated hampers local resection as the predominant treatment option for early RC.

Preoperative diagnosis of lymph nodes is notoriously difficult in the work up of RC. MRI is the recommended primary investigation technique according to current guidelines and constitutes a pivotal part of the preoperative work-up due to its ability to distinguish factors that define the need for neoadjuvant treatment. However, MRI has limited accuracy in diagnosing LNM . A recent study investigating the accuracy of MRI in early RC showed that most (74%) patients with LNM were inaccurately staged as clinical node negative (cN0) while the majority (56%) of cases staged as clinically node positive (cN1–2) by MRI had no LNM [12]. Thus, preoperative lymph node staging by MRI is inaccurate and cannot be used to reliably select cases eligible for local resection. Currently, the risk of LNM is assessed based on certain risk factors in the resected specimen following local resection. Guidelines recommend subsequent surgery in high-risk lesions, which are defined as harboring one or more predefined risk factors. Despite the actual incidence of LNM in clinical T1 cases being only around 10%, nearly 70% of clinical T1 RCs are classified as high risk, leading to substantial overtreatment with surgery according to current guidelines [13]. In this context, it is important to note that implementation of CRC screening programs has induced a shift in T stage with the incidence of early RC steadily increasing [14, 15]. Thus, new and more accurate ways to preoperatively stage lymph nodes in early RC are urgently needed to reduce the risk of overtreatment with surgery, thereby reducing morbidity, mortality and healthcare costs.

The NanoEcho diagnostic system is based on magnetomotive ultrasound (MMUS) and is a new and promising approach to stage lymph nodes in patients with RC. Iron oxide-based nanoparticles are injected adjacent to the tumor and translocate to draining lymph nodes. An ultrasound is later performed with a rotating magnet attachment to set the nanoparticles in motion [16]. The nanoparticles have been shown to distribute differently in lymph nodes with and without tumor cells, potentially enabling the detection of metastatic lymph nodes [17]. Estimating the value of The NanoEcho diagnostic system for detecting LNM in RC is important to incentivize development and implementation of the method. Health economic early-decision modeling is an established way to estimate the potential health and cost consequences of new interventions [18, 19].

The aim of this study was to perform a health economic analysis at an early stage of the clinical development to estimate the potential value of adding the NanoEcho diagnostic system to current diagnostic methods for detecting LNM in early RC.

2 Methods

2.1 Overview

This study was performed in accordance with Swedish and international guidelines for economic evaluation [20, 21]. A healthcare perspective was used, in which only healthcare-related costs were considered. No health economic analysis or statistical analysis plan was registered prior to the start of the study. In this cost–utility analysis, the addition of

the NanoEcho diagnostic system to current diagnostic methods was compared with current diagnostic methods alone in terms of costs and health outcomes. The current gold standard for diagnostic methods for nodal staging of RC is MRI.

2.2 Model Structure

A health economic model for diagnosis of RC was developed using Microsoft Excel. The model is not made publicly available. The model consists of a decision tree (Fig. 1A) and a Markov model (Fig. 1B). In the decision tree, the modeled cohort receive either local resection or surgical resection based on diagnostics. After the local or surgical resection, the modeled cohort enters the Markov model. This consists of a set of health states which the cohort moves between, which are determined by true lymph node status and received treatment. The probability of moving from one health state to another is determined by user-defined transition probabilities. The model uses monthly cycles and a lifetime perspective. Each health state is assigned a health-related quality-of-life weight and an associated level of resource use and costs. Further details of the treatment paths and health states included in the model are reported in following sections.

2.3 Population

The model analyzes two populations: the tested population, which includes all patients who will receive the NanoEcho diagnostic system in addition to current diagnostic methods, and the target population, which includes patients with clinical T1 RC and clinical suspicion of LNM who would receive surgical resection in current clinical practice and thus potentially benefit from NanoEcho diagnostic system.

Two different testing strategies were evaluated, corresponding to two alternative ways of implementing the diagnostic test in clinic. In the first strategy, the tested population was all patients newly diagnosed with RC, and in the second strategy, the tested population comprised only patients with newly diagnosed clinical T1–T2 RC.

The modeled cohort consisted of patients with and without LNM (Fig. 1A). In this model we assume that for patients with LNM, surgical resection would be the optimal treatment, and for patients without LNM, local resection would be the optimal treatment.

2.4 NanoEcho Diagnostic System

The value of the NanoEcho diagnostic system is the potential of correctly selecting patients in need of surgical resection (true positives) and those for whom local resection is sufficient (true negatives). Depending on the sensitivity of the NanoEcho diagnostic system, some patients would be incorrectly diagnosed with no LNM (false negatives) and receive local resection, with an increased risk of dying from RC. Depending on the specificity of the NanoEcho diagnostic system, some patients would be incorrectly diagnosed with LNM (false positives) and receive unnecessary surgical resection.

The diagnostic performance of the NanoEcho diagnostic system is still unknown and the analysis was performed at an assumed 85% sensitivity and 85% specificity that would be a reasonable and desirable performance. In addition, the sensitivity and specificity were varied between 65% and 85% to explore the added value even at a lower diagnostic performance. The value for implementing a novel diagnostic tool performing at $< 65\%$ seems not relevant.

2.5 Data Sources

Input data were based primarily on information from the Swedish Colorectal Cancer Register (SCRCR) [22]. For data not found in the register, a pragmatic literature search was performed using PubMed. When no Swedish studies were found, studies from the Nordics, Europe, and other high-income countries were used. Population characteristics for patients with RC were based on information from the SCRCR. To account for temporal variations in diagnosis rates, an annual average was calculated using data from a 5-year period (2018–2022). However, information on the number of patients in the target population was only available for 2019–2021 [23]. Assumptions and input values have been validated by two clinical experts in the field, and references are found in Table 1.

2.6 Rectal Cancer

A population-based screening program for RC is successively being implemented in Sweden and is expected to shift the stage at diagnosis to earlier stages and thus more patients that would benefit from a better diagnostic approach to avoid surgical resection. In previous studies, T1–T2 RC increased by 6–27% after the implementation of population-based screening [23], and consequently, a 15% rise in the target population was assumed. To reflect the implementation of the screening program, the same increase was used for the number of tested patients with T1–T2 RC (in the second testing strategy). The proportion of the target population with LNM was based on a Swedish study that

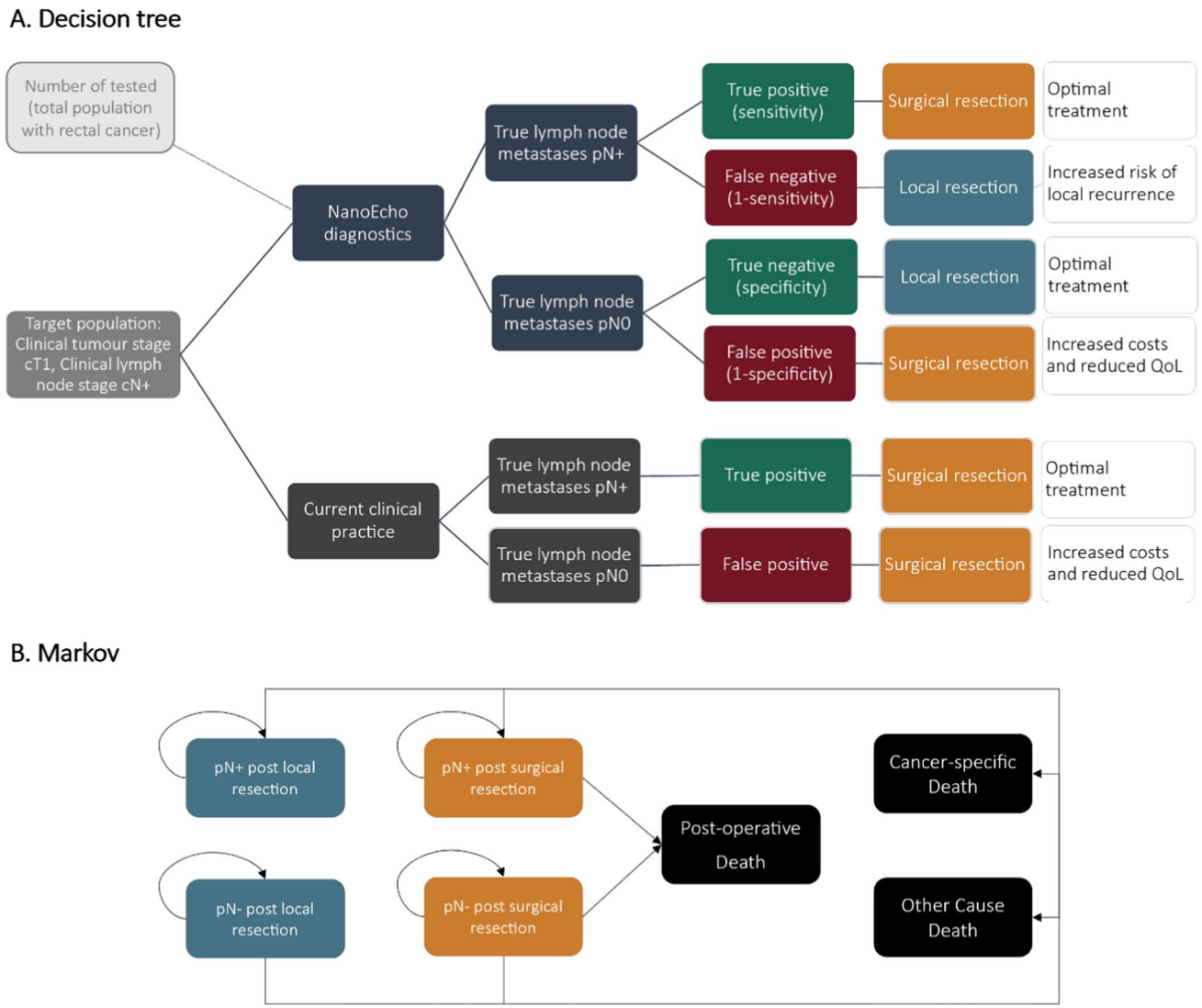


Fig. 1 Two-stage model representations: (**A**) Decision tree. Describes the diagnostics and treatment pathway. Patients diagnosed with false- or true-negative LNM, based on NanoEcho diagnostics, are treated with local resection. Patients diagnosed with false- or true-positive LNM, based on NanoEcho diagnostics or current clinical practise, are treated with surgical resection. (**B**) Long-term Markov model. Illustrates the possible transitions between health states. Patients diagnosed with false- or true-negative LNM can remain in the health state or transition to either cancer-specific death or other cause death. Patients diagnosed with false- or true-positive LNM can remain in the health state or transition to either post-operative death, cancer-specific death or other cause death. Pathological staged as LNM (pN+); Pathological staged as no LNM (pN0)

found that 12% of patients with early-stage clinical T1 RC who had received surgical resection had LNM on postsurgical examination of the resected tissue [6].

2.7 Surgical Complications and Postoperative Mortality

Rates of postoperative mortality, major complications, and permanent stoma after surgical resection of the rectum were sourced from the SCRCR [22]. Major complications were defined as those requiring more significant interventions, such as surgery or intensive care. The reported 30-day postoperative mortality rate was used in the base-case analysis, whereas 90-day postoperative mortality was tested in the sensitivity analysis. The proportion of patients with permanent stoma included patients with permanent stoma after surgical resection (57%) and patients with protective stoma that was later converted to permanent stoma (8%).

Complications following local resection in the rectum are rare and mainly managed conservatively, without the need for surgical intervention [24, 25]. Potential complications following local resection were therefore not included in the analysis, since they were assumed to have minimal impact on quality of life and health care costs.

Table 1 Input values used in the health economic model

Variable	Value	References
Population		
Age (years)	72	[22]
Patients in target population (N)	122	[23]
Tested patients, first testing strategy (N)	2066	[22]
Tested patients, second testing strategy (N)	522	[22]
Lymph node metastases (%)	12	[6]
NanoEcho diagnostic system (%)		
Sensitivity	85	Assumption
Specificity	85	Assumption
Surgical resection (%)		
30-day postoperative mortality	0.7	[22]
Major complications	10	[22]
Permanent stoma	63	[22, 46]
Cancer-specific mortality (% per month)		
LNM, surgical resection	0.48	[27]
LNM, Local resection	0.82	[27]
No LNM, surgical resection	0.18	[27]
No LNM, Local resection	0.18	[27]
Years with cancer-specific mortality	5	Assumption
Quality of life		
Quality of life in general population	0.78	[47]
Disutility after surgical resection	0.123	[28]
Months with disutility after surgical resection	2	Assumption
Disutility for permanent stoma	0.03	[29]
Years with disutility for permanent stoma	7	Assumption based on [30]
Total QALY loss for metastatic disease	0.142	[31]
Healthcare costs (SEK)		
NanoEcho diagnostic system healthcare visits, event cost	7776	[32]
Local resection, event cost	51,045	[33]
Surgical resection, event cost	269,590	[33]
Major complications, event cost	35,990	[32]
Permanent stoma, event cost	7179	[32, 34]
Permanent stoma, annual cost	15,474	[36]
Metastatic disease, one-time cost	989,309	[31]

LNM lymph node metastasis, *QALY* quality-adjusted life year, *SEK* Swedish krona

2.8 Cancer-Specific Mortality

In addition to postoperative mortality, the model included cancer-specific mortality and other-cause mortality. Moreover, it was assumed that death from cancer was preceded by a period of metastatic disease. Age-related other-cause mortality was based on life tables from Statistics Sweden [26]. No Swedish study on cancer-specific survival that was stratified by T stage and LNM was found. Instead, an American study of 5-year survival after surgical resection, stratified by LNM, was used [27]. The 5-year survival was used to estimate a yearly cancer-specific mortality risk using a constant risk equation. The cancer-specific mortality risk was applied during the first 5 years. The risk was then set to zero to account for an expected decrease in cancer-specific mortality over time.

The modeled cancer-specific mortality for patients without LNM receiving surgical resection was based on the survival of patients with T1 RC without LNM in the American study [27]. The same cancer-specific mortality was used for local resection, as surgical resection was not expected to increase survival in patients without LNM. The cancer-specific mortality for patients with LNM receiving surgical resection was estimated from the survival of patients with T1–T2 RC and LNM stage 1–2 in the American study. The survival of patients with LNM receiving local resection is

unknown, as lymph node status is based on postsurgical examination of the resected tissue. Instead, based on input from clinical experts in the field, the survival of patients with T3 RC and LNM stage 1 was used as a proxy.

2.9 Quality of Life

Health effects were estimated as life years and quality-adjusted life years (QALYs). The disutility for surgical resection was based on a multinational study reporting quality of life measured by EQ-5D in patients with RC before and 4 weeks after open surgical resection [28], and it was assumed that the disutility would last for 2 months after surgical resection. Information of the disutility due to permanent stoma was obtained from a recent Spanish study reporting EQ-5D 1 year after surgical resection [29]. The duration of the disutility due to permanent stoma was based on a Swedish study that reported disutilities due to permanent stoma up to 7 years after surgical resection [30]. The total QALY loss associated with metastatic disease was sourced from a health economic evaluation of population-based screening for colorectal cancer by the Swedish National Board of Health and Welfare [31].

2.10 Healthcare Costs

All costs were calculated in Swedish kronor (SEK) at the 2023 price level. Costs for the NanoEcho diagnostic system healthcare visits, major complications, and permanent stoma were sourced from the price list of the Southern healthcare region in Sweden [32]. Costs for the NanoEcho diagnostic system healthcare visits were assumed to correspond to two physician visits in the gastroenterology department.

Healthcare costs for local resection and surgical resection were based on information from the cost-per-patient database (KPP) held by the Swedish Association of Local Authorities and Regions [33]. The average cost for local resection and surgical resection were calculated using procedure codes and mean cost per healthcare episode (procedure codes are presented in Supplementary Table 1, see electronic supplementary material [ESM]).

Major complications typically require inpatient care, and healthcare costs were assumed to be equivalent to the cost of 4 days of inpatient care in the gastroenterology department, based on the average number of days spent in inpatient care in 2021.

Costs for healthcare visits related to permanent stoma were applied during the first year with permanent stoma, and the number of visits was based on a Swedish report of national guidelines for healthcare related to stoma [34]. The cost per healthcare visit was assumed to be equivalent to the cost of one nurse visit in outpatient care in the gastroenterology department [32]. The annual cost of stoma equipment was applied each year with permanent stoma and sourced from a report by the Dental and Pharmaceutical Benefits Agency in Sweden, adjusted to 2023 price levels [31, 35].

Costs for metastatic disease were sourced from the evaluation of population-based screening for colorectal cancer by the National Board of Health and Welfare and adjusted to 2023 prices [36]. A yearly discount rate of 3% was used to discount all simulated costs and health benefits according to Swedish recommendations [21].

2.11 Outcomes

Model outputs were calculated for the addition of the NanoEcho diagnostic system to current rectal diagnostic methods, current diagnostic methods alone, and the increment between them. Model outputs included the number of tested patients per patient in the target population, given treatments, complications and deaths from surgical resection, RC or other causes. Costs and QALYs were calculated based on modeled events.

The price of the NanoEcho diagnostic system is not yet known. Therefore, the potential value, or economically justifiable price [37], of the NanoEcho diagnostic system was estimated. The justifiable price was first calculated at a cost-neutral level, resulting in no increase in healthcare costs. It was then calculated at a willingness to pay (WTP) of 500,000 SEK/QALY, representing the threshold between moderate and high cost per QALY according to the Swedish National Board of Health and Welfare [38]. The robustness of the results was tested using one-way sensitivity analyses.

3 Results

The results are presented at an assumed 85% sensitivity and 85% specificity of the NanoEcho diagnostic system in Table 2. In the first testing strategy (examining all patients with RC), it was calculated that 16.9 patients needed to be examined to identify one patient in the target population. In the second testing strategy (examining patients with clinical T1–T2 RC), 4.3 patients needed to be examined.

By definition, all patients in the target population had surgical resection in current clinical practice, whereas it was estimated that adding the NanoEcho diagnostic system would lead to 23.2% of patients receiving surgical resection and 76.8% receiving local resection. As a consequence, the rate of major complications decreased from 9.9 to 2.3%. In addition, the proportion of patients in the target population requiring permanent stoma decreased from 65.0 to 15.1%.

The addition of the NanoEcho diagnostic system to current diagnostic methods was estimated to decrease the postoperative mortality in the target population from 0.7 to 0.2%, while at the same time increase the cancer-specific mortality from 11.0 to 11.3%. Consequently, adding the NanoEcho diagnostic system yielded a gain of 0.032 life years and 0.124 QALYs per patient in the target population compared with current diagnostic methods alone.

In the first testing strategy, the calculated cost for NanoEcho diagnostic system healthcare visits was SEK 131,777 per patient in the target population. In the second testing strategy, the corresponding cost was SEK 33,311 per patient in the target population. The shift from surgical resections to local resections resulted in a decrease in the cost of surgical resection by SEK 207,072 per patient in the target population, accompanied by an increase in the cost of local resection by SEK 39,208. In addition, there was an estimated decrease in costs due to complications, with average cost savings per patient in the target population of SEK 2737 for major complications and SEK 81,806 for permanent stoma. However, the cost for metastatic diseases increased by SEK 2671 compared with current diagnostic methods. In total, adding the NanoEcho diagnostic system was estimated to decrease healthcare costs by SEK 118,542 per patient in the target population in the first testing strategy and by SEK 217,009 in the second treating strategy excluding the yet unknown cost of the diagnostic system.

At a cost-neutral level, resulting in no increase in healthcare costs, the justifiable price of the NanoEcho diagnostic system was estimated to be SEK 6995 in the first testing strategy and SEK 50,658 in the second testing strategy. The justifiable price, at a WTP of 500,000 SEK/QALY, was estimated to be SEK 10,654 in the first testing strategy and SEK 65,132 in the second testing strategy.

Table 2 Cost-effectiveness results at 85% sensitivity and 85% specificity for the NanoEcho diagnostic system

	Current clinical practice	NanoEcho diagnostic system			
		Absolute values		Incremental differences	
		Test all	Test T1–T2	Test all	Test T1–T2
Events					
Tested	0.000	16.947	4.284	16.947	4.284
Local resection	0.000	0.768	0.768	0.768	0.768
Surgical resection	1.000	0.232	0.232	−0.768	−0.768
Major complications	0.099	0.023	0.023	−0.076	−0.076
Permanent stoma	0.650	0.151	0.151	−0.499	−0.499
Metastatic disease	0.110	0.113	0.113	0.003	0.003
Mortality					
Post operative	0.007	0.002	0.002	−0.005	−0.005
Cancer specific	0.110	0.113	0.113	0.003	0.003
Other cause	0.883	0.886	0.886	0.002	0.002
Survival					
Life years	10.465	10.498	10.498	0.032	0.032
QALYs	8.020	8.144	8.144	0.124	0.124
Costs (SEK)					
NanoEcho diagnostic system healthcare visits	0	131,777	33,311	131,777	33,311
Local resection	0	39,208	39,208	39,208	39,208
Surgical resection	269,590	62,518	62,518	−207,072	−207,072
Major complications	3563	826	826	−2737	−2737
Permanent stoma	112,441	30,581	30,581	−81,860	−81,860
Metastatic disease	102,674	105,345	105,345	2671	2671
Total costs	488,268	370,255	271,789	−118,013	−216,479
Justifiable price of the NanoEcho diagnostic system (SEK)					
Cost neutral				6964	50,534
WTP of 500,000 SEK/QALY				10,623	65,008

QALY quality-adjusted life year, *SEK* Swedish krona, *T1* tumor stage 1 rectal cancer, *T2* tumor stage 2 rectal cancer, *WTP* willingness to pay

The justifiable price of the NanoEcho diagnostic system, using different assumptions of sensitivity and specificity, is shown in Table 3. At a cost-neutral level, the justifiable price ranged from SEK 3565 to SEK 7256 in the first testing strategy and from SEK 37,090 to SEK 51,689 in the second testing strategy. The corresponding numbers, at a WTP of 500,000 SEK/QALY, ranged from SEK 5903 to SEK 10,654 in the first testing strategy and from SEK 46,339 to SEK 65,132 in the second testing strategy. In both testing strategies, a higher specificity yielded a higher justifiable price, whereas a higher sensitivity resulted in a lower justifiable price at a cost-neutral level (due to the cost of more surgical resections) but a higher justifiable price at a WTP of 500,000 SEK/QALY.

Results from the one-way sensitivity analysis are presented in a tornado plot (Fig. 2) and in Supplementary Table 2 (see ESM). The justifiable price at a cost-neutral level, in both testing strategies, was mainly affected by the cost of surgical resection, with other important parameters being the cost of the NanoEcho diagnostic system healthcare visits, discount rate, stage-shift toward T1 RC due to cancer screening, and occurrence of LNM. The cost of surgical resection remained the most influential parameter at a WTP of 500,000 SEK/QALY. Another important factor was the duration of disutility for permanent stoma. In addition, the effects of discount rate, stage-shift toward T1 RC, and the prevalence of LNM were larger at a WTP of 500,000 SEK/QALY.

Table 3 The justifiable price of the NanoEcho diagnostic system (SEK) at sensitivity and specificity values ranging from 65 to 85%

	Cost neutral		WTP of 500,000 SEK/QALY	
	Test all	Test T1–T2	Test all	Test T1–T2
Sensitivity 85%				
Specificity 85%	6964	50,534	10,623	65,008
Specificity 75%	5253	43,765	8427	56,322
Specificity 65%	3541	36,995	6231	47,636
Sensitivity 75%				
Specificity 85%	7094	51,048	10,446	64,310
Specificity 75%	5382	44,278	8251	55,624
Specificity 65%	3671	37,509	6055	46,938
Sensitivity 65%				
Specificity 85%	7224	51,561	10,270	63,613
Specificity 75%	5512	44,792	8074	54,927
Specificity 65%	3801	38,023	5878	46,240[1L]

QALY quality-adjusted life year, *SEK* Swedish krona, *T1* tumor stage 1 rectal cancer, *T2* tumor stage 2 rectal cancer, *WTP* willingness to pay

4 Discussion

This study is the first published cost-effectiveness analysis of the NanoEcho diagnostic system for detecting LNM in RC. The findings of this study indicate a potential health economic value of adding the NanoEcho diagnostic system to current diagnostic methods for detecting LNM in RC. Two testing strategies were examined, and the estimated justifiable price of the NanoEcho diagnostic system, at a cost-neutral level, was estimated to be SEK 6995 in the first testing strategy (examining all patients with RC) and SEK 50,658 in the second testing strategy (examining patients with clinical T1–T2 RC). In addition to the number of tested patients, the justifiable price was driven mainly by reductions in the costs of surgical resection and permanent stoma.

At a WTP of 500,000 SEK/QALY, the justifiable price of the NanoEcho diagnostic system increased to SEK 10,654 in the first testing strategy and SEK 65,132 in the second testing strategy. The estimated health gains were related to reductions in postoperative mortality and the avoidance of permanent stoma, both resulting from fewer surgical resections. It should be noted that the EQ-5D is a generic instrument that may not capture the true disutility of permanent stoma, indicating that the value of the NanoEcho diagnostic system might potentially be even higher.

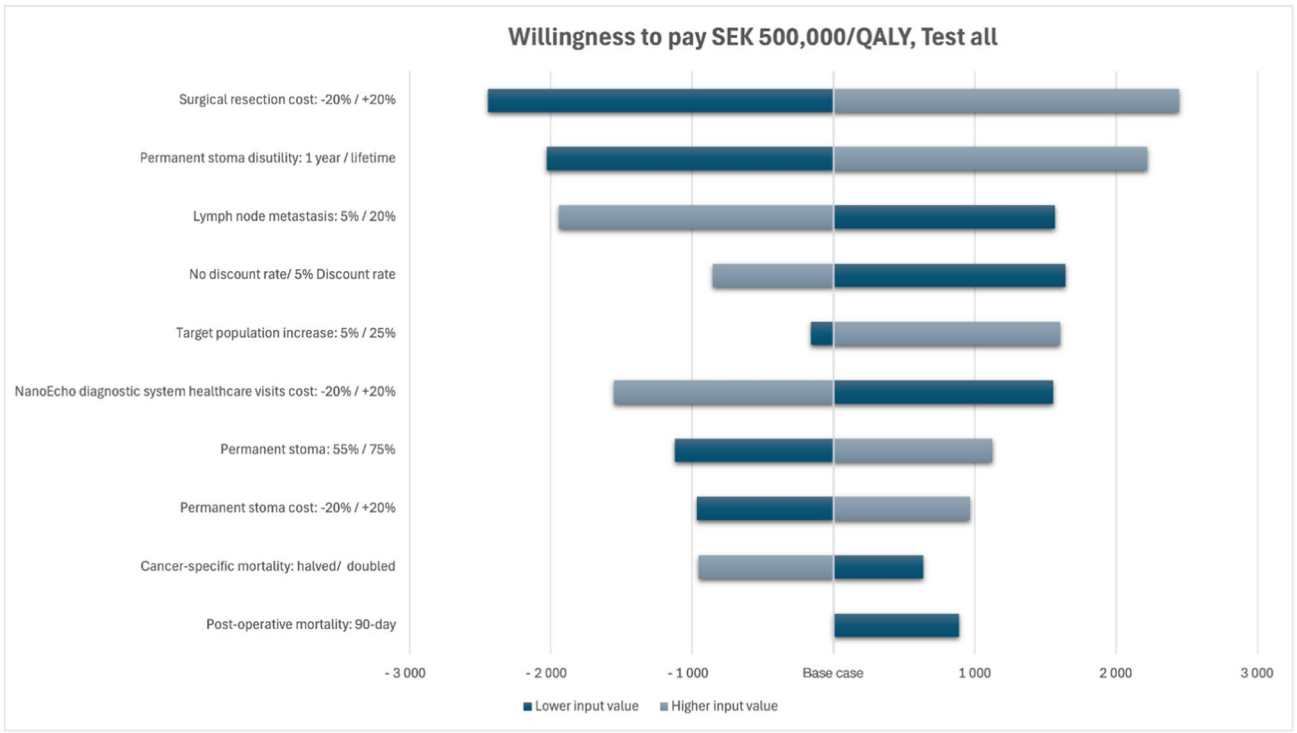
In the model, the addition of the NanoEcho diagnostic system to current diagnostic methods led to some patients with LNM not being treated with surgical resection (false negatives), which increased their risk of dying from RC. However, the estimated reduction in postoperative mortality was larger than the increase in cancer-specific mortality, yielding a total of 0.032 life years gained per patient in the target population. In the sensitivity analysis, using the 90-day postoperative mortality from the SCRCR instead of 30-day postoperative mortality, the life years gained increased to 0.074 per patient in the target population.

The results of this study are mostly relevant for countries with similar diagnostic methods, treatment patterns, and healthcare systems to Sweden. The health economic model, however, can be readily adapted to analyze the value of the NanoEcho diagnostic system in other settings. This trait is particularly important because better diagnostics for LNM are needed worldwide.

There are several studies on potential biomarkers (protein expression, mRNA levels, microRNA) [39–45] and risk of lymph node metastasis. These are completely different methods than the method described here and have so far not shown proven data for a clinical setting. To our knowledge, there is no data on the cost effectiveness of those methods.

Fig. 2 Incremental changes to the justifiable price in the one-way sensitivity analyses. Center of tornado is represented by the base-case value, showing the incremental changes compared with the base-case values (SEK). (**a**) A cost-neutral analysis where the base-case value to test all is 6995 SEK, (**b**) a cost-neutral analysis where the base-case value to test only T1–T2 is 50,658 SEK, (**c**) an analysis were the WTP is 500,000 SEK/QALY where the base-case value to test all is 10,654 SEK and (**d**) an analysis where the WTP is 500,000 SEK/QALY where the base-case value to test only T1–T2 is 65,132 SEK[1]. In all figures, the 10 parameters affecting the value most are shown; for more parameters see supplementary Table 2 in the electronic supplementary material. *QALY* quality-adjusted life year, *SEK* Swedish krona, *T1* tumor stage 1 rectal cancer, *T2* tumor stage 2 rectal cancer, *WTP* willingness to pay

c)



d)

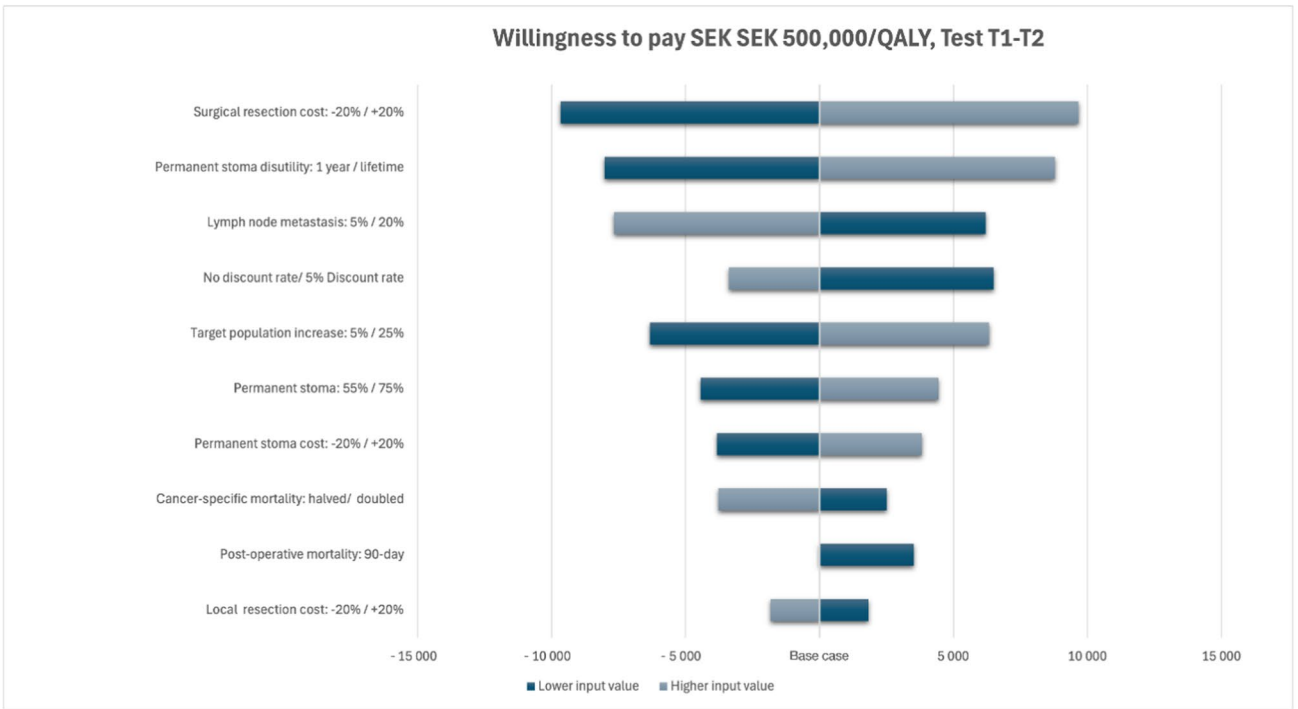


Fig. 2 (continued)

A strength of this analysis is its use of high-quality Swedish registry data for several key parameters, including the costs of local resection and surgical resection; postoperative mortality; and the rates of major complications and permanent stoma. Another strength is the use of information on the occurrence of LNM in Swedish patients who have undergone surgical resection for clinical T1 RC with clinical suspicion of LNM.

A limitation of the present study is the lack of data on the sensitivity and specificity of the NanoEcho diagnostic system for detecting LNM in RC. As such, the analysis was repeated using different assumptions of sensitivity and specificity. The lowest estimated justifiable price, at a cost-neutral level, was SEK 3565 in the first strategy and SEK 37,090 in the second strategy. The corresponding values with a WTP of 500,000 SEK/QALY were SEK 5903 and SEK 46,339, respectively. Another limitation is the use of disutilities and cancer-specific mortality from international studies, which may differ from Swedish patients. However, our sensitivity analysis indicated that the results were robust, even when cancer-specific mortality was halved or doubled. A third limitation is that the exact magnitude of the stage-shift toward T1 RC resulting from the Swedish colorectal cancer screening program is not yet known. A fourth limitation is that the analysis only included the value for patients with clinical T1 RC and clinical suspicion of LNM who would otherwise receive surgical resection, whereas there is potential value in the NanoEcho diagnostic system for patients outside of this population.

Health economic modeling of new technologies early in their development is an established method of estimating their value. Having the model available in an early stage of clinical development allows for updated calculations of the value of the NanoEcho diagnostic system throughout clinical development and implementation. The model can be used to identify factors that drive the justifiable price of the NanoEcho diagnostic system, enabling specification of criteria that should be met to ensure its cost effectiveness, thus guiding further research and price considerations.

5 Conclusion

The results indicate that the addition of the NanoEcho diagnostic system to standard of care has the potential to reduce healthcare costs and increase quality of life for patients with clinical T1 RC and clinical suspicion of LNM. The estimated cost-neutral justifiable price of the NanoEcho diagnostic system, at an assumed sensitivity and specificity of 85%, was SEK 6995 if all patients newly diagnosed with RC are examined and SEK 50,658 if only patients with clinical T1–T2 RC are examined. The corresponding justifiable price, at a WTP of 500,000 SEK/QALY, was estimated to be SEK 10,654 and SEK 65,132, respectively.

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Declarations

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Conflict of interest UA and LP are employees of NanoEcho. UA and LP own shares in NanoEcho. CFR and HT are consultants to NanoEcho. EA and AF are employees of the Swedish Institute for Health Economics, which provides consulting services for governmental bodies, academic institutions, and commercial life science enterprises. The authors report no other conflict of interests in this work.

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Availability of data and material The model is not made publicly available.

Code availability Not applicable.

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