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Cost-effectiveness of new technologies for staging endometrial cancer

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To ensure the dissemination of new imaging technology, radiologists must demonstrate that diagnostic information is worth more than the cost of the test. Methodology of cost-effectiveness is complex and new to the radiological community. In this review an evaluation of diagnostic imaging for patients with endometrial cancer is used to illustrate numerous methods to define value of imaging. Receiver operating characteristics (ROC) analysis determines value of test efficacy while Bayesian analysis determines value in the context of disease prevalence. The value of imaging tests for clinical practice, however, depends on the patient's specific circumstance. This value can be defined by cost-effectiveness analysis which can assist in developing imaging guidelines that are patient specific.

Technology development vs dissemination

During the twentieth century, the remarkable evolution of diagnostic radiology has depended on the development and dissemination of new technologies. New technology was rapidly adapted into clinical practice, and the pace of evolution was largely governed by the product development cycle. However, health care reform introduced by managed care and cost containment has constrained the dissemination of new technology. Indeed, in many circumstances technology dissemination is now the "choke point" for the advancement of medical imaging.

To ensure the dissemination of new technology, radiologists must demonstrate to the medical community including clinical colleagues and health administrators that the diagnostic information provided by the technology is worth the costs of obtaining the information. For most radiologists, technology assessment and health care are an unfamiliar and difficult endeavor. This paper evaluates the use of modern imaging in the management of endometrial cancer to illustrate how radiologists can analyze the value of new technology in clinical practice.

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Treatment of patients with endometrial cancer

In patients with endometrial cancer, knowledge of tumor extension determines prognosis and appropriate treatment. Ultrasound, CT, and MRI are effective in predicting local tumor extension and presence of nodal disease. However, imaging exams are seldom used in everyday gynecology practice. Instead, tumor extension and subsequent treatment planning including specialty referral are mostly based on clinical examination and tumor grade. At presentation, 80% of patients with endometrial cancer have stage-I disease, for which initial treatment is simple hysterectomy and bilateral salpingo-oophorectomy [1]. The remaining 20% of patients require either extended hysterectomy and pelvic lymph node dissection or are not surgical candidates and would benefit from primary radiation [1]. Thus, whereas most patients are treatable by a general gynecologist, as many as 20% require the skills of a gynecologic oncologist [2].

Using tumor grade as a triage for specialty referral, patients with grade-1 tumor are usually treated by general gynecologists. These patients are referred to gynecologic oncologists only after advanced tumor extension is discovered at their initial surgery. This is estimated to occur in 13% of patients [3]. Patients with grade-3 tumor are referred directly to gynecologic oncologists, but it is estimated that 46% of this patient cohort will have stage-1 disease and therefore do not need specialist care. There is no clear consensus for triage of patients with grade-2 tumor [4].

If all patients are referred to a gynecologic oncologist for their initial care, then many patients will be referred unnecessarily. Unnecessary referral results in patient inconvenience and increased expense. Furthermore, it may result in overly aggressive initial treatment, such

as lymph node sampling, with consequent worsened morbidity. On the other hand, if all patients are treated initially by a general gynecologist, then some patients will receive sub-optimal first treatment. This runs counter to the adage in oncologic medicine that "the first treatment should be the best possible, since it has the greatest chance for curing the patient" [5].

Value of imaging tests for endometrial cancer

Imaging tests, whether US, CT, or MRI, provide information that can complement the prediction of tumor extension, particularly assessment of the depth of myometrial invasion [6, 7, 8, 9]. The dissemination of these imaging tests into clinical practice is, however, hampered by uncertainty as to whether the added information is worth the added diagnostic costs. Controversy regarding clinical utility is particularly true for MRI which is the most accurate but also the most expensive test.

In order to determine the optimal triage strategy for patients with endometrial cancer, the value of imaging tests can be evaluated on several levels of complexity and clinical relevance. Most simply, value may be evaluated in terms of the test's discriminatory power for predicting tumor extension. This level of analysis defines value according to test sensitivity and specificity – variables that are independent of clinical context.

Alternatively, value of the test can be analyzed in terms of the test's effect on the probability for tumor extension. This level of analysis defines value according to pre-test and post-test probabilities – variables that are dependent on prevalence of disease. Disease prevalence defines clinical context from an epidemiological (or global) perspective.

In order to evaluate the value of imaging tests for making patient-specific management decisions, the analysis must account for the patient's specific clinical circumstances and preferences. This level of analysis defines value according to its utility in day-to-day clinical practice. It combines variables of test sensitivity, test specificity, test cost, disease prevalence, and the value of information to the patient.

Value defined by ROC analysis

During the past 15 years the discriminatory power of the diagnostic tests for predicting tumor extension has been reported extensively. These studies generally focus on a single modality and often involve relatively small numbers of patients. Consequently, a meta-analysis is required to achieve adequate statistical power to determine the relative test performance [10]. As described by Kinkle et al., contrast MRI has discriminatory power for predicting deep myometrial invasion, cervical extension, or lymph node involvement [11]. Computed tomography has discriminatory power for deep myometrial invasion or lymph node involvement. Ultrasound has discriminatory power for deep myometrial invasion.

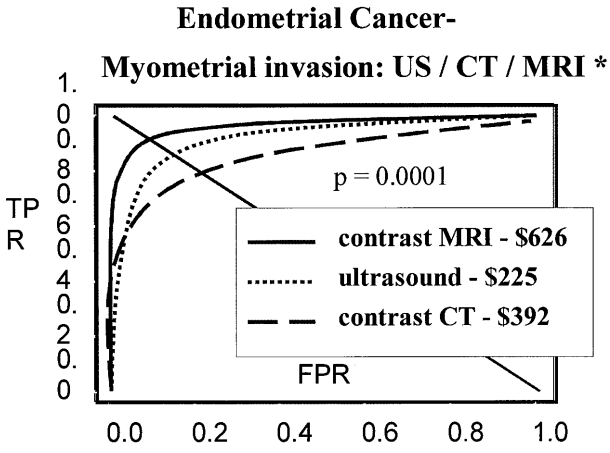

Fig. 1. Summary of receiver operating characteristics (ROC) curves from meta-analysis of CT, US, and MRI test performance for predicting myometrial invasion. The MRI curve demonstrates improved discriminatory power over US which demonstrates improved discriminatory power over CT. Q* values occur where the respective ROC curves intersect the *diagonal line*. (From [12])

When imaging tests are compared, MRI has the greatest and CT has the least discriminatory power for predicting deep myometrial invasion (Fig. 1).

Once summary ROC are determined, it is possible to define relative test performance using Q* values. A Q* value corresponds to the point on an SROC curve where sensitivity and specificity are equal [12]. Using Q* values the relative test performance of the alternative tests are illustrated in Table 1. For deep myometrial invasion, the estimated sensitivity/specificity for MRI is 92 %, for US is 85 % and for CT is 79 %.

Of note, Q* values represent a statistical tool rather than an empiric measurement of the most likely performance threshold of the test in clinical practice. Indeed, it is implausible that an interpreter could actually operate at the precise threshold where sensitivity and specificity are equal. Instead, Q* values are tools to compare the discriminatory power of the alternative tests in a manner akin to area under the curve analysis. As indicated by the Q* values, US has more discriminatory power than CT, and MRI has more discriminatory power than either US or CT.

Table 1. Test performance (Q* values) for MRI, CT, and US for predicting endometrial cancer extension. Q* values represent predicted point on the test's summary receiver operating characteristics curve where sensitivity and specificity are equal. (From [12])

Test performance	Q* values (95 % CI)
Predicting deep myometrial invasion	
MRI	0.91 (0.89–0.92)
CT	0.79 (0.61–0.96)
US	0.85 (0.81–0.88)
Predicting lymph node invasion	
MRI	0.85 (0.81–0.93)
CT	0.78 (0.73–0.83)
Predicting cervical invasion	
MRI	0.92 (0.87–0.95)

This information, in combination with test cost, is sufficient for determining cost-effectiveness in some but not all circumstances. For instance, using 1999 Medicare reimbursement rates, the cost of pelvic US, CT, and MRI are $229, $392, and $625, respectively. Since US provides more discriminatory power at less cost than CT, it is "paredo dominant" over CT. This means that there are no clinical circumstances in which CT is cost-effective relative to US or MRI.

Whereas MRI provides more discriminatory power than US, it also costs more to perform. Consequently, further analysis is required to determine whether the added information provided by MRI is worth the added costs.

In order to determine whether MRI is cost-effective relative to US, the analysis must incorporate not only test sensitivity, specificity, and cost, but also to account for the clinical context in which the test is used.

Value defined by Bayesian analysis

Bayesian analysis can be used to incorporate disease prevalence into the analysis, determining the pre-test and post-test probabilities of tumor extension for patients with grades 1, 2, and 3 tumor, respectively. As reported by Frei et al. [14], for grade-1 tumor the post-test probabilities for deep myometrial invasion are: positive MRI 60%, positive US 45%; negative MRI 1%, negative US 3%. As indicated, when the test is negative, there is only 2% difference in post-test probability for tumor invasion following MRI relative to US, and for grade-1 tumor most patients will have negative test results.

For grade-3 tumor the post-test probabilities for deep myometrial invasion are: positive MRI 92%, positive US 87%; negative MRI 10%, negative US17% (Table 2) [13]. In this clinical context approximately 50% of patients have a negative and 50% a positive test. As indicated, a negative MRI is 7% more definitive than a negative US, and a positive MRI is 5% more definitive than a positive US.

In other words, the added discriminatory power of MRI compared with US has little clinical consequence within the context of grade-1 tumor, and greater consequence within the context of grade-3 tumor. This analysis indicates that MRI is unlikely to be cost-effective for grade-1 tumor, but may be cost-effective relative to US for grade-3 tumor. Ultimately, the most cost-effective alternative depends on the precise value to the patient of the information provided by the imaging exams.

Table 2. The pre-test and post-test (US or MRI) probability determined by Bayesian analysis for deep endometrial invasion, stratified by tumor grade. (From [14])

Endometrial cancer probability deep myometrial invasion					
	Pre-test probability	Post-test probability			
		US	MRI	US	MRI
Grade 1	0.13	0.45	0.60	0.03	0.01
Grade 2	0.35	0.75	0.85	0.09	0.05
Grade 3	0.54	0.87	0.92	0.17	0.10

Value of information depends on clinical context

It is impossible to determine the value of this information to a specific patient a priori, since it depends on the patient's unique circumstances and preferences. Indeed, the value of diagnostic information is in many ways intangible. It becomes tangible only to the extent that the information leads to consequences through its influence on subsequent clinical management decisions. For endometrial cancer, the value of information can be represented in terms of monetary value for subsequent surgery or referral to the gynecologic oncologist.

It is important to distinguish the value of information quantified in terms of its clinical consequences from the direct costs actually associated with surgery or referral. The latter are actual direct costs of care that can be estimated from Medicare reimbursement rates. These costs are included implicitly in the analysis. Assigning a monetary denomination to the value of information for the patient is a statistical device (similar to Q* values) that makes it possible to quantitatively compare the cost-effectiveness of the alternative tests within the patient's specific clinical context.

This does not indicate that the value of information for patients is definable abstractly. Instead, a range of plausible values is selected to serve as the basis for the cost-effectiveness analysis. It is necessary for the physician and patient to determine in approximate terms where their circumstances lie within this range of possible values, and once the value of information is approximated the analysis indicates the most cost-effective triage strategy.

To illustrate how the value of information depends on the patient's circumstance and preference, consider the "costs" to the patient associated with referral to a gynecologic oncologist. Referral for a patient from a major metropolitan area is less "costly" than referral for a patient from a rural area; the former faces the inconvenience of travel to a local and unfamiliar specialist clinic, but the latter requires a plane trip, hotel accommodations, and the prospect of undergoing treatment without immediate access to family and friends.

Similarly, surgery is less "costly" for a patient who is a good surgical risk with a quick expected recuperation than for a patient who is a poor surgical risk with a slow expected recuperation. These "costs" include not only monetary costs to the patient, but in many cases more significant psychological "costs" related to risk and suffering. They also include "costs" for lost time or convenience. While these "costs" are multidimensional, their representation in monetary terms is necessary to make quantitative analysis possible.

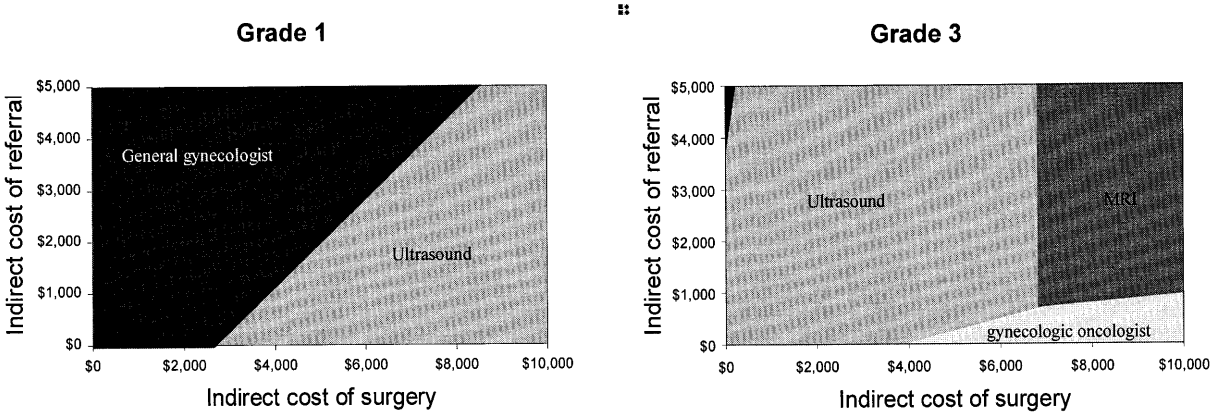

Fig. 2. The most cost-effective triage strategy is indicated for ranges of possible "costs" for referral or surgery for grade-1 or grade-3 tumor, respectively. The "costs" represent plausible circumstances and preferences for patients in monetary terms. For example, if referral "costs" $800 and surgery "costs" $8000, then the patient should be triaged with US for grade-1 tumor or referred directly to the gynecologic oncologist for grade-3 tumor. If referral "costs" $5000 and surgery "costs" $8000, then the patient should be treated by the general gynecologist for grade-1 tumor or triaged with MRI for grade-3 tumor

Value defined by patient-specific cost-effectiveness analysis

In this analysis a mathematical model is constructed that defines value in terms of test sensitivity, specificity, and cost, as well as treatment cost, and disease prevalence, over an estimated plausible range for "cost" to the patient for referral or surgery. Once this model is constructed and the variables are estimated, the most cost-effective strategy is defined as illustrated in Fig. 2.

Figure 2a demonstrates that the optimal triage strategy for patients with grade-1 tumor is either treatment by the general gynecologist or US over a plausible range of clinical contexts, for "cost" of referral between $0 and $5000 and "cost" of surgery between $0 and $10,000. Treatment by the general gynecologist is optimal when the "cost" of surgery is low and "cost" of referral is high. Ultrasound is optimal when the "cost" of surgery is high and "cost" of referral is low.

Figure 2b demonstrates that the optimal triage strategy for patients with grade-3 tumor depends on the patient's specific clinical context. Direct referral to the gynecologic oncologist is optimal if the "cost" for surgery is greater than approximately $7000 when the "cost" of referral is less than approximately $800. Magnetic resonance imaging is optimal if the "cost" of surgery is greater than $7000 when the "cost" of referral is greater than $800. In general, US is optimal when the "cost" of surgery is less than $7000. However, at the upper portion of this range, referral to the gynecologic oncologist is optimal if the "cost" of referral is very low. At the lower portion of this range, treatment by the general gynecologist is optimal if the "cost" of referral is very high.

This analysis demonstrates that patients with grade-1 tumor are optimally triaged either directly to the general gynecologist or that triage can be based on US; MRI is not cost-effective for this patient cohort. In contrast, MRI is cost-effective for patients with grade-3 tumor in many clinical contexts, specifically when the "costs" of surgery and referral are high. Direct referral to the gynecologic oncologist is cost-effective for grades 2 or 3 tumor when the "cost" of surgery is high and "cost" of referral is low.

Technology assessment requires patient-specific cost-effectiveness analysis

In summary, radiologists can define value on multiple levels. On one level, value can be defined in terms of test sensitivity and specificity using ROC analysis. Alternatively, value can be defined in terms of pre-test and post-test probability using Bayesian analysis (likelihood ratios). But ultimately, to definitively determine whether the information provided by an imaging exam is worth its additional cost, the analysis must account for the patient's specific clinical circumstances.

This paper illustrates a method to determine the value of imaging tests for clinical management decisions that are "patient specific." The methodology is still in its infancy compared with ROC or Bayesian analysis. As the "chokepoint" for the evolution of radiological practice becomes technology dissemination instead of technology development, a critical challenge will be the maturation of techniques for cost-effectiveness analysis to determine the value of imaging exams and to develop patient-specific evidence-based diagnostic algorithms.

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