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Management of Complex Pelvic Masses Using a Multivariate Index Assay: A Decision Analysis

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Abstract

Objective—To develop a cost-minimization analysis of a multivariate index assay (MIA) used for women with complex pelvic masses.

Methods—A decision analysis model was used to evaluate 81,000 hypothetical patients with a complex pelvic mass requiring surgery. Three strategies were evaluated: (1) referral to a gynecologic oncologist (GO) based on clinical assessment including physical exam, ultrasonography, and CA125 (CLINICAL); (2) utilization of a multivariate index assay (MIA); or (3) referral of all patients to a GO (REFER ALL). Various reoperation rates were evaluated with sensitivity analyses. Actual payer costs were compared between each strategy.

Results—The CLINICAL strategy cost \$933.9 million (M) and resulted in 72% of patients receiving appropriate initial surgical staging. The REFER ALL strategy cost \$939.7M and all patients were appropriately staged. The MIA strategy cost \$976.7M and resulted in 91% of patients having appropriate initial staging. Using conservative reoperation rates (10-20%), 461 patients required reoperation using CLINICAL strategy compared to 142 patients in MIA strategy. Using aggressive reoperation rates (40-50%), 1715 patients required reoperation using CLINICAL strategy resulting in an incremental cost of \$15.2M compared to 529 patients at \$4.7M in MIA strategy. The increased costs associated with an aggressive reoperation rate resulted in the REFER ALL strategy being the least expensive alternative, with the highest rates of appropriate initial surgery.

Conclusions—Utilizing an MIA resulted in more ovarian cancer patients receiving appropriate initial surgery, but at increased costs. Referring all patients with complex masses avoids the most reoperations at reduced cost compared to using an MIA.

Keywords

Ovarian cancer; decision analysis; pelvic mass; multivariate index assay

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Conflict of Interest Statement

The authors declare that there are no conflicts of interest.

Introduction

With an estimated 21,880 new cases and 13,850 deaths in the United States in 2010, ovarian cancer is the deadliest gynecologic malignancy [1]. If diagnosed at an early stage, 5-year survival reaches 94%; however, 75% of ovarian cancer cases are advanced at diagnosis [1, 2]. Early detection and optimal surgical debulking are the cornerstones in the management of ovarian cancer and have been shown to improve survival [3]. The American Congress of Obstetricians and Gynecologists (ACOG) currently recommends that a woman with clinical risk factors of having ovarian cancer should be managed by a gynecologic oncologist (GO) who is trained to perform surgical staging and cytoreductive surgery [2]. In women in whom there is a concern for ovarian cancer based on symptoms, ACOG recommends a pelvic exam with transvaginal ultrasound and CA125. Unfortunately, a normal CA125 does not rule out cancer and up to 50% of patients with early stage ovarian cancer are associated with normal CA125 values [2]. The low accuracy of available tests makes it difficult to predict which patients with a complex pelvic mass will have ovarian cancer discovered at operation. As many as 65% of women with ovarian cancer are initially managed by a non-GO [4].

Recently, a multivariate index assay (MIA) was FDA-approved to assess the likelihood of malignancy in women who have adnexal masses and are planning to undergo surgery. This test combines the results of five serum immunoassays (CA 125, transthyretin, apolipoprotein A1, b2-microglobulin, and transferrin) into a single numerical result [5, 6]. When the MIA test is combined with clinical suspicion, it has a reported 94% sensitivity and negative predictive value of 93%, which are improvements over clinical judgment and CA125 alone (77% sensitivity, 87% negative predictive value [5, 6]. Notably, the positive predictive value of this MIA is less than that of presurgical clinical judgment (37% vs 60%) [6]. It is unknown whether this improved predictability would ultimately result in more favorable outcomes, justifying the increased cost associated with performing the test. ACOG recommendations regarding this new test state that the “clinical utility of the test is not yet established [2].” However, the increased accuracy of the MIA test would result in fewer reoperations thereby avoiding additional costs and morbidity of misdiagnosis. Referral of all patients with a complex mass to a GO for initial surgery may increase costs but presumably have the most beneficial clinical outcome. The objective of this study was to develop a cost-minimization analysis which evaluated the MIA test for the evaluation of women planning to undergo surgery for a complex pelvic mass compared to current strategies of using clinical information alone, or referring all patients to a GO.

Methods

Overall Model

Based on an estimated annual incidence of 21,880 cases of ovarian cancer, and approximately 27% overall rate of malignancy among all pelvic masses [6], a hypothetical total of 81,037 pelvic masses was calculated ($81,037 \times 27\% = 21,880$) and rounded to 81,000 for this study. A decision analysis model evaluated this hypothetical cohort of 81,000 patients who presented to their gynecologist with a complex pelvic mass necessitating surgery (TreeAge Software, Inc. (version 2009), Williamstown, MA) (Figure 1). This was the clinical scenario included in the MIA trial for which sensitivity, specificity, and positive and negative predictive values are available. Three strategies of managing patients with complex pelvic masses were evaluated in the model. The CLINICAL strategy involves using patient history, physical exam findings, imaging, and a CA125 to determine the likelihood of malignancy. This strategy is the current standard of care, and the Society of Gynecologic Oncologists (SGO) and ACOG have previously published guidelines on when to refer patients to a GO [2]. The MIA strategy involves performing the MIA test on all patients planning surgery. All patients with a positive MIA test would be referred to a GO. In the last

strategy, the REFER ALL strategy, all patients with a complex pelvic ovarian mass needing surgery are referred to a GO at the time of diagnosis for primary surgical management.

Clinical Estimates

We used the reported test characteristics from a prospective, double-blind MIA clinical study to create our decision model [5, 6]. Rates of malignancy and histopathology were also determined from the MIA trial, so that rates of malignancy were consistent with the positive and negative predictive values (Table 1). Using this data, 32% of patients in the CLINICAL strategy would be referred due to a high suspicion for malignancy. In the MIA strategy, 67% of patients had a positive MIA test and would be referred to a GO. The PPV of clinical assessment was 60% compared to 37% with the addition of the MIA test. The NPV of clinical assessment was 89% compared to 93% with the MIA test.

In our baseline analysis, we used conservative reoperation rates of 10% for epithelial ovarian cancers and 20% for stromal or germ cell cancers. Because a reoperation is a significant factor in both cost and patient morbidity, and is highly variable among practitioners, we also performed a sensitivity analysis evaluating more aggressive reoperation rates of 40% for epithelial cancers and 50% for stromal or germ cell cancers. Patients with low malignant potential tumors or non-gynecologic cancers did not receive a reoperation.

Cost Estimates

Analysis was conducted from the perspective of a third-party payer and conservative estimates were used, based on the state of Alabama; actual payer costs of surgery were estimated for each strategy using a 50% cost-to-charge ratio (Table 2). Assignment of surgical costs assumed that patients under the care of a benign gynecologist underwent a hysterectomy and bilateral salpingo-oophorectomy (CPT 58150) regardless of surgical findings and pathology. A GO used the same charges as benign gynecologists when pathology was benign, and performed appropriate surgical staging including omentectomy and debulking (CPT 58951) when the mass was malignant. Surgery by a benign gynecologist assumed a total abdominal hysterectomy and bilateral salpingo-oophorectomy would be performed and patients would have a two-day hospital stay. The total cost was estimated to be \$11,196. A staging procedure with a GO was assumed to include a three-day hospital stay, and with the added consultation fee was estimated at \$12,425. A reoperation was designated as an exploratory laparotomy with lymph node dissection and omentectomy (CPT 38780). The total cost of a reoperation with consultation and a two-day hospital stay was \$12,396.

Results

In our baseline model using conservative estimates for reoperation, the MIA strategy was the most expensive strategy at \$976.7 M (Figure 2). The REFER ALL strategy was less expensive at \$939.7 M. The CLINICAL strategy was least expensive at \$933.9 M. Based on rates of finding cancer in this population, 72% of patients in the CLINICAL strategy would have benign disease and have appropriate surgery by a benign gynecologist (Table 3). Adding the MIA test would increase referrals to GOs and result in 91% of patients having the appropriate initial surgery. Assuming these conservative reoperation rates, use of the CLINICAL strategy would lead to approximately 461 reoperations. This number was reduced to 142 by using the MIA test.

We performed a sensitivity analysis to evaluate more aggressive reoperation rates. These assumed reoperation rates of 40% for epithelial ovarian cancer and 50% for germ cell and

stromal cancers (versus 10% and 20%, respectively, for conservative rates). In this model, 1715 patients would require a reoperation using the CLINICAL strategy, resulting in an incremental cost of \$15.2 M above the conservative operation rates for this strategy. Using the MIA strategy, 529 patients would require a reoperation, at an incremental cost of \$4.7 M in this strategy (Figure 2). With these more aggressive reoperation rates, the REFER ALL strategy is both least expensive and allows the highest percent of patients to receive the appropriate primary surgery. Addition of the MIA test is more expensive than use of CLINICAL information alone, but at just a 3.4% increase in cost, while preventing 1,186 women from requiring a second operation and its associated morbidity (Table 4).

Discussion

We demonstrated in a decision analysis model that the MIA test adds costs to the management of women with pelvic masses. We also showed that the number of patients with a benign mass referred to a GO would be increased with the use of the MIA test. Overall, the MIA strategy results in more patients being appropriately referred to a GO for staging and debulking compared to the CLINICAL strategy (72% vs. 91%). The REFER ALL strategy is the least expensive management strategy and provides the highest rates of appropriate initial surgery.

There is a clear need for better diagnostic tools to facilitate early referral and appropriate treatment of women with ovarian cancer. Using current recommendations, a significant number of women are not referred to a GO for management, particularly premenopausal women in whom CA125 is less sensitive [4]. Studies have shown that outcomes are improved when surgical debulking operations can remove all gross disease, and that these procedures are more successful when performed by experienced surgeons [3, 7-12]. Additionally, many women who do not receive their initial surgery with a specialist ultimately require a reoperation, which contributes to increased costs and morbidity. A multicenter trial showed that 33% of patients with apparent stage 1 or 2 disease who underwent a surgical restaging had more advanced stage noted at the second surgery [13]. Initial management by a GO translates to improved survival by virtue of increased frequency of receiving chemotherapy, and increased rates of optimal surgical debulking [4]. This cost minimization analysis assumes that there are no further reoperations after referral to a GO. It has been shown that intraoperative frozen section reporting benign pathologies correlate with final pathology 98-99% of the time [14]; consequently, the possibility of reoperation even after referral to a GO is small. This small reoperation risk after GO referral was not included in the model since the scope of this particular analysis was to evaluate the impact of the MIA on the initial referral pattern and associated costs at that level. Including this small reoperation cost would not impact the model and the overall results of the study.

Recently, the MIA test was developed and FDA-approved for use in women with pelvic masses planning to undergo surgery [6]. It was designed to be a triage test to assist gynecologists in determining whether a GO should be consulted for patients with a complex pelvic mass. Such consultations are hypothesized to improve survival and reduce second operations, though these endpoints have not yet been specifically tested. This test has been shown to improve the sensitivity of detecting malignancy and negative predictive value when compared with clinical suspicion alone in both early-stage and advanced ovarian cancers as well as in both pre- and postmenopausal women. It has not been tested as a screening test in any population of patients. It is also important to note that this test should not be used in the presence of factors that place the patient at a high risk of having ovarian cancer, such as patients with pelvic masses that also have an elevated CA125, evidence of metastasis on imaging studies, or ascites. MIA has not been evaluated in this setting and these patients should be referred to a GO for initial management. The exact algorithm of the

MIA is unknown, but notably, CA125 is a component of this MIA; the sensitivity of the MIA is reportedly better than that of CA125, while specificity is reportedly worse. Though beyond the scope of the current analysis, it may be interesting to explore a cost-effectiveness comparison between CA125 and MIA employing a lower CA125 threshold, thereby improving sensitivity and lowering specificity.

This study has several limitations. First, we were not able to create a true cost-effectiveness analysis since it must evaluate and compare the cost of a strategy to a measure of effectiveness, typically in overall survival and/or quality-adjusted life year (QALY). As there is no data regarding the overall survival with a MIA test, a cost-minimization analysis was performed with respect to costs and reoperation rates rather than with incremental cost-effectiveness ratios (ICERs). Potentially, if there were no difference in survival between the strategies, then the least expensive strategy would be the most cost-effective. With rising health care costs and financial constraints, it may be difficult for third party payers to cover a treatment strategy that is more expensive with no improvement in survival. Second, the model has been simplified to include the most dominant drivers of cost, and cannot represent all the potential scenarios that gynecologists encounter when treating women with pelvic masses. Although a range of reoperation rates in the sensitivity analysis was estimated, the actual reoperation rates are not known and conclusions may differ regarding overall expense (though to a minor extent), especially when comparing the CLINICAL and REFER ALL strategies. The additional morbidities associated with a second reoperation such as deep venous thromboses, infections, and potentially higher rates of injuries to other abdominal organs, are not considered because of the absence of accurate data. If these complications are higher with second operations, as one might assume, the importance of referral would be even greater. Finally, costs vary widely across the country based on insurance provider. This analysis also does not include societal cost, such as cost of transportation to see a specialist or lost productivity for patients and caregivers, which could potentially alter the costs of such a test. Certainly, under the REFER ALL strategy, while this may avoid the most reoperations, many of the costs are carried by the patients and their caregivers, such as transportation to a GO, and lost productivity from potential travel to see a specialist. In addition, there is no data regarding the impact on quality of life in any of these strategies, which may affect patient preferences and referral patterns.

The most appropriate management of a patient with a complex pelvic mass, in terms of avoiding the most reoperations with the lowest costs, as well as improvements in overall survival [4], is to refer all patients to a GO for initial surgical management. Frequently this is not adopted due to issues of access, and tests to stratify women into those at highest risk of a malignancy are needed. Performing the MIA test in the defined population would result in more referrals to a GO, higher rates of appropriate initial surgery, and lower rates of reoperation compared to using clinical information alone, at the sacrifice of increased costs. Further studies should be prospectively performed, with particular attention to the impact on survival and associated morbidities. Ultimately, the MIA test may be helpful in evaluating patients with a pelvic masses but it is critical for the test to be used with good clinical judgment.

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Research Highlights

- A decision analysis was created to evaluate strategies for management of complex pelvic masses.
- 3 strategies were studied: conventional, referring all patients, and use of an MIA.
- MIA increases cost, but also increases rates of appropriate initial surgery.

Figure 1. Decision Analysis Model employing three different management strategies. (MIA: multivariate index assay; LMP: low malignant potential)

Figure 2. Estimated costs associated with each management strategy, and incremental costs of reoperation utilizing more aggressive reoperation rates.

Table 1

Model Outcomes.

Outcome	%
% of clinically assessed patients referred	32
% of patients with a positive MIA test	67
% of patients with a malignancy	27
PPV of clinical assessment	60
NPV of clinical assessment	89
PPV of clinical plus MIA test	37
NPV of clinical plus MIA test	93
% of epithelial patients with reoperation	10
% of LMP patients with reoperation	0
% of germ cell/stromal patients with reoperation	20

MIA – Multivariate Index Assay;

NPV – negative predictive value;

PPV – positive predictive value;

LMP – low malignant potential

Table 2

Model Costs.

Intervention	Cost
TAH/BSO by gynecologist	\$11,196
TAH/BSO by GO	\$11,296
TAH/BSO/Staging by GO	\$12,425
Reoperation by GO	\$12,396
Office consult	\$200
MIA test	\$650

TAH – total abdominal hysterectomy;

BSO – bilateral salpingo-oophorectomy;

GO – gynecologic oncologist

Table 3

Results using conservative reoperation rate.

Strategy [^]	Costs ⁺	Incremental Costs ⁺	Reoperations	Reoperations Avoided
Clinical	\$933.9 M	--	461	--
Refer All	\$939.7 M	\$5.8 M	--	461
MIA	\$976.7 M	\$42.8 M	142	319

⁺M – million[^]MIA – Multivariate Index Assay

Table 4

Results using aggressive reoperation rate.

Strategy [^]	Costs ⁺	Incremental Costs ⁺	Reoperations	Reoperations Avoided
Refer All	\$939.7 M	--	--	--
Clinical	\$949.1 M	\$9.4 M	1715	--
MIA	\$981.4 M	\$32.3 M	529	--

⁺M – million[^]MIA – Multivariate Index Assay