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Normal Risk Ovarian Screening Study: 21-Year Update

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ABSTRACT

Clinical trials frequently include multiple end points that mature at different times. The initial report, typically based on the primary end point, may be published when key planned co-primary or secondary analyses are not yet available. Clinical Trial Updates provide an opportunity to disseminate additional results from studies, published in JCO or elsewhere, for which the primary end point has already been reported.

PURPOSE The Normal Risk Ovarian Screening Study (NROSS) tested a two-stage screening strategy in postmenopausal women at conventional hereditary risk where significantly rising cancer antigen (CA)-125 prompted transvaginal sonography (TVS) and abnormal TVS prompted surgery to detect ovarian cancer.

METHODS A total of 7,856 healthy postmenopausal women were screened annually for a total of 50,596 woman-years in a single-arm study (ClinicalTrials.gov identifier: NCT00539162). Serum CA125 was analyzed with the Risk of Ovarian Cancer Algorithm (ROCA) each year. If risk was unchanged and <1:2,000, women returned in a year. If risk increased above 1:500, TVS was undertaken immediately, and if risk was intermediate, CA125 was repeated in 3 months with a further increase in risk above 1:500 prompting referral for TVS. An average of 2% of participants were referred to TVS annually.

RESULTS Thirty-four patients were referred for operations detecting 15 ovarian cancers and two borderline tumors with 12 in early stage (I-II). In addition, seven endometrial cancers were detected with six in stage I. As four ovarian cancers and two borderline tumors were diagnosed with a normal ROCA, the sensitivity for detecting ovarian and borderline cancer was 74% (17 of 23), and 70% of ROCA-detected cases (12 of 17) were in stage I-II. NROSS screening reduced late-stage (III-IV) disease by 34% compared with UKCTOCS controls and by 30% compared with US SEER values. The positive predictive value (PPV) was 50% (17 of 34) for detecting ovarian cancer and 74% (25 of 34) for any cancer, far exceeding the minimum acceptable study end point of 10% PPV.

CONCLUSION While the NROSS trial was not powered to detect reduced mortality, the high specificity, PPV, and marked stage shift support further development of this strategy.

ACCOMPANYING CONTENT

Data Supplement

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INTRODUCTION

Poor outcomes in ovarian cancer relate to late detection with 70%-75% of cases diagnosed in advanced stage (III or IV) where the cure rate is less than 30%.[1] Although computer algorithms suggest that mortality could be reduced by 10%-30% if ovarian cancers were detected at an earlier stage,[2] only 25%-30% of patients are currently diagnosed in stage I or II. Neither serum biomarkers nor transvaginal sonography (TVS) alone are sufficiently specific nor sensitive to detect early-stage ovarian cancer.[3] A two-stage strategy with rising cancer antigen (CA)-125 followed by TVS has shown more promise.

To assess the risk associated with a rising CA125, the Bayesian Risk of Ovarian Cancer Algorithm (ROCA) was developed.[4-6] ROCA supports a two-stage strategy, where significantly rising CA125 prompts TVS and abnormal imaging prompts surgery.[7,8] Using ROCA to trigger TVS, the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS) and the Normal Risk Ovarian Cancer Screening Study (NROSS) in the United States had sufficient specificity to achieve only two

to four operations required to detect each case of ovarian cancer.[7,9-11]

The UKCTOCS randomly assigned 202,638 postmenopausal women[10,11] to a control group (101,314), annual TVS group (50,623), and a multimodal group (50,625) screened with annual CA125 analyzed with the ROCA followed by TVS in a small fraction of participants,[11] producing a stage shift of 14%, but no improvement in mortality.[11] The NROSS is a single-arm study, identical to the multimodal arm of the UKCTOCS. In contrast to the UKCTOCS, a much greater stage shift has been observed. Here, we update an earlier report of results from the NROSS.[7]

METHODS

Study Sites and Organization

Since the initial report in 2013,[7] this study has been conducted at 11 sites described in the Data Supplement.

Protocol eligibility, enrollment in the trial, blood drawing and processing, and statistical analysis are described in the study by Lu et al.[7]

ROCA Analysis

Each patient's individual CA125 profile over time provided the basis for the ROCA calculation that determined a woman's risk for having ovarian cancer. If a patient's ROCA risk of ovarian cancer was <1 in 2,000 (normal risk), the woman was asked to return for a repeat CA125 in 1 year, and ROCA was recalculated. For a ROCA risk between 1 in 2,000 and 1 in 500 (intermediate risk), CA125 was repeated in 3 months, and ROCA was recalculated. For a ROCA risk of >1 in 500 (elevated risk), transvaginal ultrasound was performed using standard criteria,[12] and the participant was referred to a gynecologic oncologist. When surgery was performed, pathology was evaluated using standard criteria.[13]

RESULTS

The NROSS trial included 7,856 apparently healthy postmenopausal women at average hereditary risk for ovarian cancer who were screened annually for a total of 50,596 woman-years in a single-arm study (ClinicalTrials.gov identifier: NCT00539162) over 21 years from 2001 to 2022. The average number of years screened per participant was

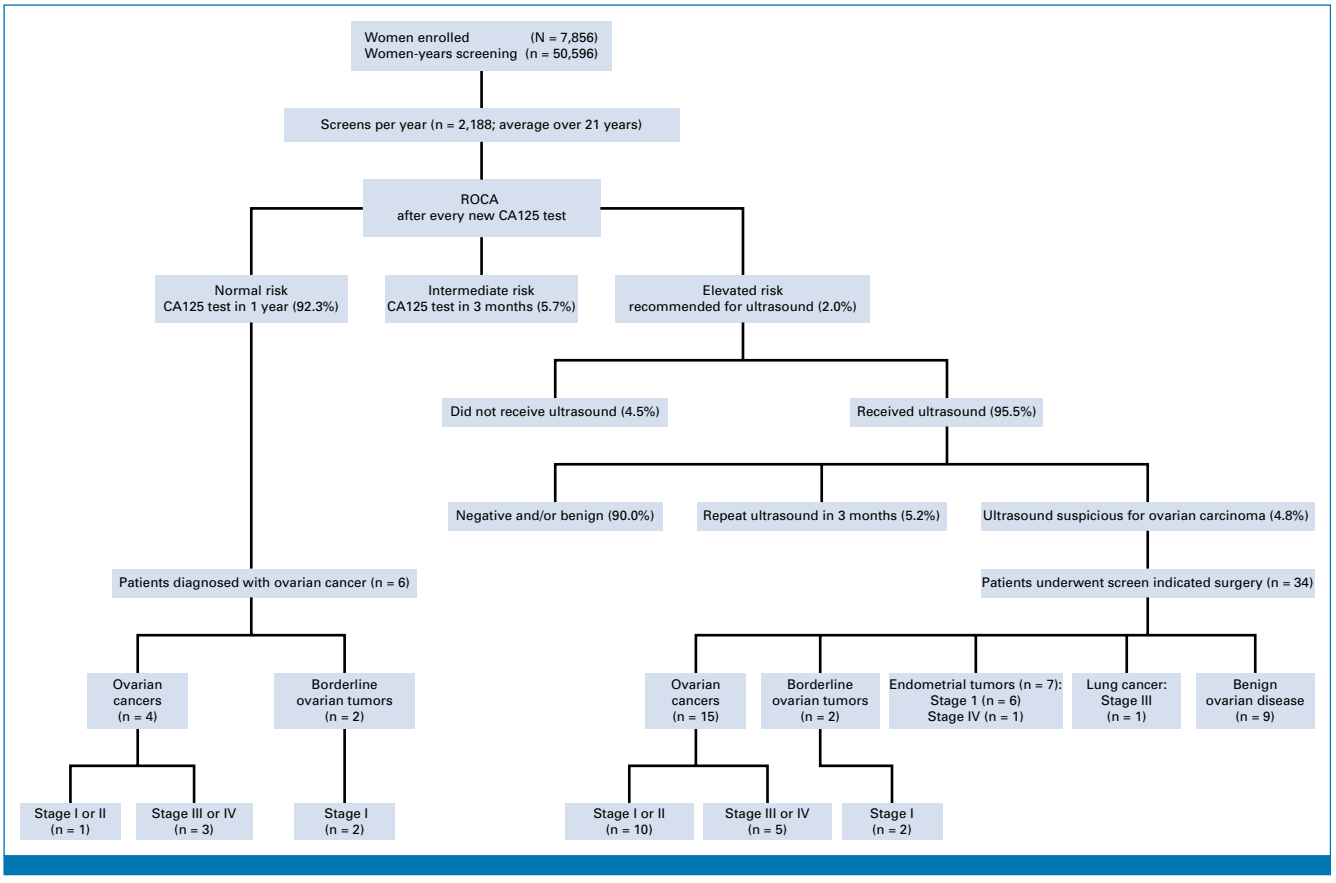

FIG 1. Flow diagram of participant flow including referral to TVS, study indicated surgeries, and outcomes of study indicated surgeries and clinically detected ovarian cancers and borderline tumors. Averages per year over 21 years are provided for screening encounters—CA125 tests and TVSs. The average number of CA125 tests per year was the total CA125 blood draws performed in the study divided by 21 years, percentage ROCA recommendations are the number of recommendations for each category divided by the total number of CA125 blood draws, and percentage ultrasound recommendations computed by combining a physician ultrasound impression and a final physician recommendation. CA125, cancer antigen-125; ROCA, Risk of Ovarian Cancer Algorithm; TVS, transvaginal sonography.

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6.5 years (standard deviation, 5.4; median, 4.7; IQR, 2.0-10.2). The median age at informed consent was 60 years with an IQR of 56-65 years, and detailed information regarding race and ethnicity are described in the Data Supplement (Table S1).

On the basis of the ROCA, an average of 2.0% of women per year were referred for TVS after each annual screen (Fig 1), and 95.5% underwent TVS. Of the patients undergoing TVS, 4.8% raised suspicion for cancer, and a fraction of these patients went to surgery on the basis of evaluation by a gynecologic oncologist.

The annual false-positive rate for women without ovarian cancer to have an additional CA125 test (intermediate risk) was 5.7%, to have TVS (elevated risk) 2%, and to undergo surgery 0.2%. Thus, the specificity for intermediate and elevated risk ROCA was 92.3%, the specificity for elevated risk ROCA prompting TVS was 98%, and the specificity of the combined ROCA and TVS prompting surgery was 99.8% (Fig 1).

Of 34 operations prompted by the study (Table 1, Figs 1 and 2), 15 invasive ovarian cancers and two borderline tumors were detected, providing a positive predictive value (PPV) of 50% (17 of 34 [95% CI, 32.4 to 67.6]), and 12 of the 17 (70%)

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TABLE 1. Findings at Operations Prompted by the ROCA

Participant No.	Stage	Histology	Overall Time to Diagnosis, Years	ROCA+ to Surgery, Days
1	IA	High-grade serous ovarian carcinoma	6 years/6 months	42
2	IC	High-grade serous ovarian carcinoma	1 year/2 months	10
3	IC	Ovarian clear cell carcinoma	17 years/3 months	326
4	IC	Moderately differentiated mixed endometrioid and mucinous with <5% clear cell ovarian carcinoma	3 years/2 months	19
5	IC	High-grade endometrioid ovarian carcinoma	1 month	42
6	IC	High-grade mixed endometrioid and clear cell ovarian carcinoma	5 years/5 months	81
7	IIA	High-grade serous ovarian carcinoma	6 years/9 months	19
8	IIB	High grade serous ovarian carcinoma	11 years/6 months	34
9	IIB	High-grade serous with focal endometrioid ovarian carcinoma	3 years/10 months	25
10	IIC	High-grade endometrioid ovarian carcinoma	9 years/3 months	16
11	IIIC	High-grade serous and endometrioid ovarian carcinoma	11 years/1 months	14
12	IIIC	High grade serous ovarian adenocarcinoma	10 years/3 months	50
13	IIIC	High-grade carcinoma consistent with Mullerian origin	8 years/2 months	32
14	IIIC	High-grade serous ovarian carcinoma	5 years/2 months	54
15	IV	Clear cell ovarian carcinoma	1 year/3 months	14
16	I	LMP serous ovarian tumor	2 years/4 months	240
17	I	LMP serous ovarian tumor	7 years/10 months	15
18	IB	Endometrial adenocarcinoma	5 months	36
19	IA	Endometrial adenocarcinoma	14 years/6 months	65
20	IA	Endometrial adenocarcinoma	14 years/11 months	2
21	IA	Endometrial adenocarcinoma	2 years/8 months	90
22	I	Endometrial adenocarcinoma	2 years/5 months	75
23	I	Endometrial adenocarcinoma	9 years/1 month	6
24	IV	Endometrial clear cell carcinoma	4 years/3 months	32
25	IIIB	Lung adenocarcinoma	11 years/10 months	166
26	Benign	Serous cystadenofibroma and endosalpingiosis	8 years/2 months	14
27	Benign	Serous cystadenoma	1 month	24
28	Benign	Serous cysts	2 years/3 months	22
29	Benign	Cystadenoma with mixed mucinous and serous components	4 years/1 month	44
30	Benign	Serous cystadenoma, cellular fibroma, struma ovarii, and benign cyst	5 years	50
31	Benign	Foreign body type giant cell reaction to refractile material	2 years/4 months	43
32	Benign	Serous cystadenoma	8 years	15
33	Benign	Tubal adenomyoma	8 years	7
34	Benign	Stromal hyperthecosis	9 years/11 months	20

Abbreviations: LMP, low malignant potential (borderline); ROCA, Risk of Ovarian Cancer Algorithm.

were in early stage (I or II). Five of the 12 early-stage cases were detected by ROCA with CA125 <35 U/mL (Fig 2A). If the two serous borderline tumors are excluded, 10 of 15 (67%) of the ovarian cancers were detected in early stage, including eight high-grade, one moderately differentiated, and one clear cell carcinoma. Of the five late-stage (III-IV) cancers detected, three were high-grade serous, one high grade of Mullerian origin, and one clear cell. Overall, no more than two operations were required to detect each ovarian cancer.

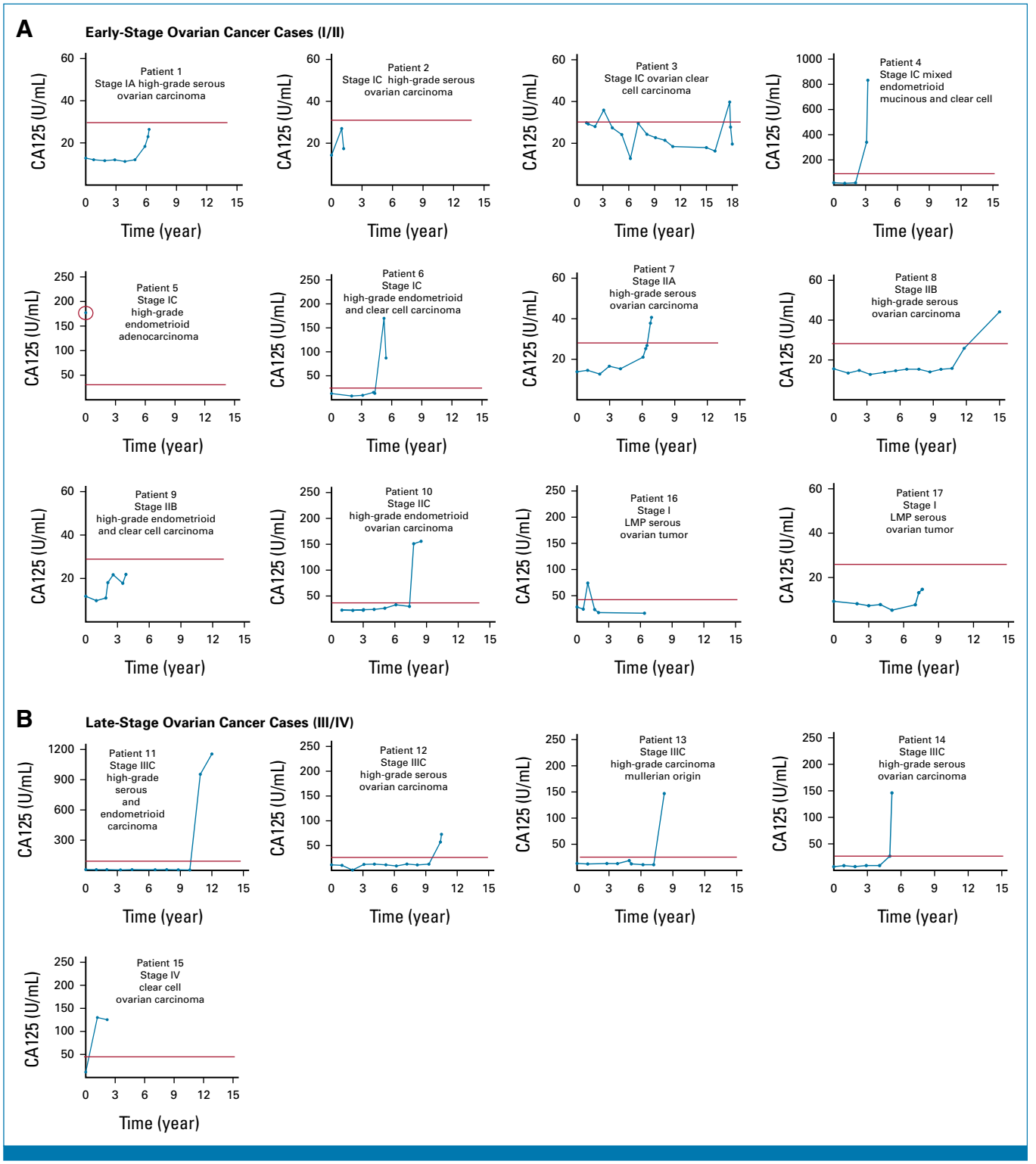

FIG 2. CA125 values over time before operations prompted by the ROCA. (A) Early-stage cases. (B) Late-stage cases. (C) Other cancers. (D) Benign pelvic masses (the red line indicates conventional cutoff of CA125 measurement as >35 U/mL). CA125, cancer antigen-125; ROCA, Risk of Ovarian Cancer Algorithm. (continued on following page)

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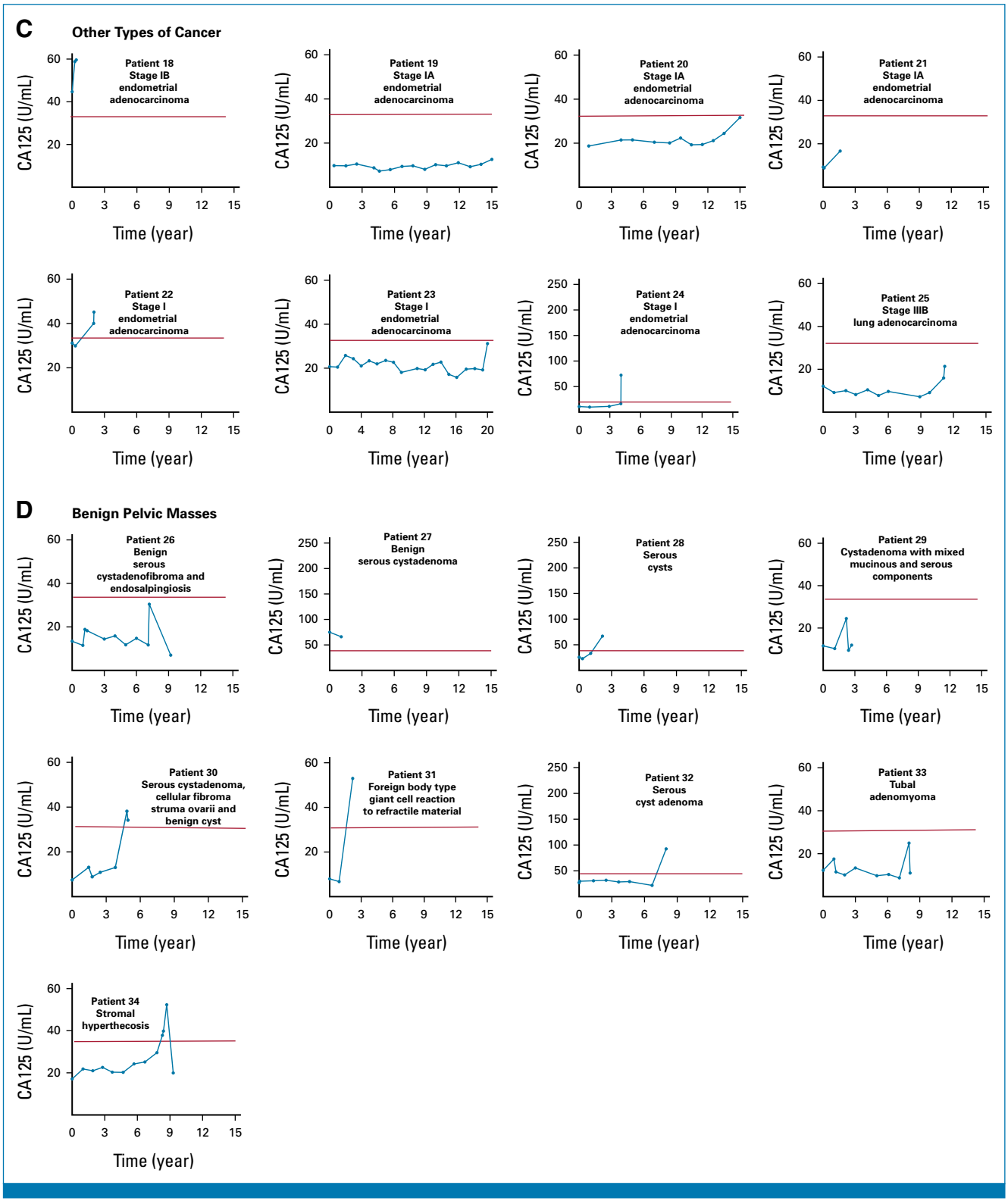

FIG 2. (Continued).

In addition, seven cases of uterine endometrial cancer were detected with an abnormal ROCA followed by TVS, with six endometrial cancers in early-stage I and a clear cell cancer in stage IV (Table 1). Overall 25 cancers and borderline tumors were diagnosed with 34 operations yielding a PPV for detecting any malignancy of 74%. Nine lesions were found to be benign at surgery (Table 1). Importantly, all ROCA operations were associated with pathological findings predicted by TVS.

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Six ovarian cancers and borderline tumors were missed by the ROCA (Data Supplement, Table S2) with surgery performed <1 year since last screen. Of these, two were borderline and four were high-grade serous ovarian cancers with one in stage I and three in stage IIIC. Consequently, the overall sensitivity for detecting ovarian and borderline cancer was 74% (17 of 23) and 79% for ovarian cancer (15 of 19). Compared with the UKCTOCS control arm, NROSS reduced late-stage (III-IV) ovarian cancer by 34%, from 76% to 42% (8 of 19, $P = .0016$).[11] Using US SEER data from 2004 to 2019 that includes both ovarian cancers and serous borderline tumors, NROSS reduced distant stage from 60.5% to 30.4% (7/23; $P = .005$), a stage shift of 30%.

The interval from the ROCA prompting ultrasound to surgery could affect the stage at detection and success of treatment. Among the 17 ovarian or borderline cancer cases detected, TVS and primary surgery were performed within a median of 32 days (IQR, 15-50).

DISCUSSION

NROSS has found that a two-stage screening strategy with CA125 followed by TVS has adequate specificity to achieve a PPV of 50%. Only two operations were required to detect each case of ovarian cancer, consistent with the three to four operations required in the UKCTOCS using a similar strategy (11). Remarkably, 70% of ovarian cancers detected by the ROCA in the NROSS were in early stage (I-II). Recognition that a fraction of high-grade serous ovarian cancers can arise from the fallopian tubes, where there are no anatomic barriers to transperitoneal spread, has raised concern that small early-stage tubal cancers may be particularly difficult to detect. The fraction of cancers arising from the fallopian tube in women at conventional genetic risk is not known, but our data suggest that the majority of ovarian cancers can be detected in early stage regardless of their site of origin.

In the original report of the UKCTOCS (11), multimodal screening produced a net stage shift of 14%. Using the same UKCTOCS control, the NROSS increased early-stage disease and reduced late-stage disease by 34%. Using US SEER data as a control, the NROSS reduced late-stage disease by 30%. Reasons underlying the differences in stage shifts between the two studies are not clear but could relate to statistical variation, quality control of TVS, or delays in blood processing.[14,15]

The magnitude of late-stage reduction, with a related shift to early stage (I-II), is likely to be an important factor for reducing mortality. An association has been observed between stage shift and mortality in screening trials for non–small-cell lung and breast cancers.[16-19] A 20% or greater magnitude reduction in late stage has been associated with a significant decrease in mortality in randomized trials of mammography,[18] and stage shift is an integral component of models that predicts the mortality advantage of mammographic screening.[19] While the UKCTOCS had a <20% stage shift, it remains to be determined whether a higher stage shift, as occurred in NROSS, would significantly reduce mortality.

An even greater stage shift and reduction in time to diagnosis might be achieved by improving both phases of two-stage screening.[20,21] As only 80% of ovarian cancers express CA125, we have found that the sensitivity for early-stage (I-II) ovarian cancer can be significantly increased when CA125 is used in combination with HE4, HE4 antigen-autoantibody complexes, and osteopontin.[22] Values of these four biomarkers have been combined to create a second-generation ROCA2 with substantially greater sensitivity and lead time than the first-generation ROCA. Improved sensitivity of the initial phase has been shown critical in cost-effectiveness studies.[23]

The specificity of ROCA2 can be evaluated in future studies with the current NROSS cohort. If sufficient specificity is observed and the late-stage reduction observed in this study can be maintained at 30% or more and potential cost-effectiveness demonstrated, a randomized trial powered to observe a mortality advantage could be considered.

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CLINICAL TRIAL INFORMATION

NCT00539162 (NROSS Trial)

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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DATA SHARING STATEMENT

The biomarker data and deidentified participant data may be made available at the request of investigators whose proposed use of the data and objective are appropriate. Upon request and subject to review, data access may be granted under conditions upon approval and permissions from each data provider. Proposals should be directed to rbast@mdanderson.org. To gain access, data requesters will need to sign a data access agreement.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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