Liquid biopsies for improving the pre-operative diagnosis of ovarian cancer

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Ethical review	Approved WMO
Status	Recruiting
Health condition type	Reproductive neoplasms female malignant and unspecified
Study type	Observational non invasive

Summary

ID

NL-OMON51106

Source
ToetsingOnline

Brief title
OVI-DETECT

Condition

- Reproductive neoplasms female malignant and unspecified
- Obstetric and gynaecological therapeutic procedures

Synonym
cancer of the ovary, ovarian cancer

Research involving
Human

Sponsors and support

Primary sponsor: Antoni van Leeuwenhoek Ziekenhuis
Source(s) of monetary or material Support: KWF Kanker bestrijding

Intervention

Keyword: circulating tumor DNA, diagnostics, Ovarian cancer, tumor educated platelets

Outcome measures

Primary outcome

The sensitivity and specificity of a new diagnostic algorithm including liquid biopsies, to differentiate patients with ovarian cancer from patients with a benign ovarian tumor.

Secondary outcome

1. Calculation of cost-effectiveness of addition of plasma liquid biopsy measurement in the triage of patients with an ovarian tumor.

2. Psychological burden of the uncertainty of having cancer or not before surgical treatment.

Study description

Background summary

In the Netherlands, 7,600 women are diagnosed with an ovarian tumor annually. Only 5% of these tumors are malignant upon definitive histological assessment. This means that a general gynecologist encounters a patient with early-stage ovarian cancer less than once a year. It is, therefore, a challenge to diagnose preoperative ovarian carcinoma. Accurate preoperative diagnosis is crucial because patients with ovarian carcinoma need to undergo surgery in an oncology center, performed by a gynecologic oncologist.

Current preoperative methods to distinguish between benign and malignant ovarian tumors are based on classification systems containing clinical, biochemical, and ultrasound features. For instance, predictive ultrasound models developed by the International Ovarian Tumor Analysis (IOTA) consortium are commonly used. However, they require training and expertise, making them challenging to implement.
The predictive value of current serum biomarkers like CA-125 is limited, as it does not increase in approximately 50% of early-stage ovarian carcinomas and

can also be elevated in benign gynecological conditions such as endometriosis.

Dutch guidelines use the Risk of Malignancy Index (RMI) to determine if the risk of ovarian carcinoma is increased. This score is based on CA125 concentration, specific ultrasound features, and menopausal status. According to Dutch guidelines, patients with an ovarian tumor are referred to oncology centers if the RMI is elevated (>200). The published sensitivity and specificity of the RMI in an unselected population of patients with ovarian tumors are 72% and 92%, respectively. However, in the enriched population treated in oncology centers, a pilot study among 366 patients revealed a sensitivity of 84% for the RMI and a specificity of only 51%. This implies an incidence of malignancy within this population of 40%, which is unacceptably low, suggesting that half of the patients referred to oncology centers with benign tumors undergo unnecessary extensive surgery and unnecessary emotional distress about the possibility of cancer.

Tissue biopsies are crucial in treating ovarian carcinoma as they can confirm or exclude malignancy preoperatively. However, in early stages, tissue biopsy is considered an unwanted invasive procedure as it can cause the spread of tumor cells. In summary, despite the development of various predictive models, making an accurate preoperative diagnosis of early-stage ovarian carcinoma remains challenging. There is an urgent need to develop predictive models with a high degree of accuracy that are easy to implement in clinical practice to maximize the number of malignant tumors treated in oncology centers. Blood-based 'liquid' biopsies, or liquid biopsies, are emerging as an alternative to traditional tissue biopsies, as they can provide accurate and comprehensive information about tumors. Examples include circulating tumor DNA (ctDNA), circulating tumor cells (CTC), and tumor-educated blood platelets (TEPs). TEPs, responsible for hemostasis, can also absorb tumor signals in the form of micro-tumor RNA. By using sequencing techniques such as DNA methylation, low-coverage whole genome sequencing, and whole genome sequencing, as well as detecting structural DNA and RNA changes in ctDNA and TEPs, malignancies can be detected or excluded.

These DNA changes were first discovered incidentally through the non-invasive prenatal test (NIPT). Besides assessing potential errors in fetal DNA, it was found to detect DNA changes in maternal DNA; in asymptomatic pregnant women, DNA changes were found in maternal DNA consistent with the presence of malignancy. In a study of patients with early-stage ovarian carcinoma (stages I and II), ctDNA analysis showed a sensitivity of 69% and a specificity of >99%. Furthermore, it has been shown that the amount of ctDNA correlates with tumor size. Other studies, albeit conducted within small patient populations, show that when ctDNA is combined with existing tumor markers like CA-125, both sensitivity and specificity increase.

In our small pilot study on TEPs, a sensitivity of 76% and specificity of 98% were found for high-grade ovarian carcinoma, and a sensitivity of 81% and

specificity of 80% for low-grade carcinoma. Due to the limited size of this pilot study on TEPs, a validation series will follow to determine if TEPs can be added to the developing algorithm. Due to the small size of this pilot study on TEP performance, the OVI-DETECT study will conduct a validation of TEPs as a potential biomarker.

Study objective

The primary objective of this study is to develop an diagnostic algorithm using ct-DNA, and TEPs as liquid biomarkers in combination with the existing ultrasound models (RMI and IOTA-models) and biomarkers (CA125 and HE4) to differentiate between early ovarian cancer and benign ovarian tumors in pre-operative setting.
Where we will first assess the TEPs in a validation series whether they will become part of the algorithm.

Study design

Investigator-initiated, prospective case-control study.

Study burden and risks

There is no extra burden/risk for the patients in this study. Five extra blood tubes are drawn at one time point during a standard pre-operative blood sampling and 2 questionnaires have to be filled out.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. Age >=18 years
2. Presence of a ovarian tumor and referred to specialized center for surgery based on:
a. Any ultrasound model
b. Subjective assessment of the referring gynecologist
c. Normal Glomerular Filtration Rate (GFR): >60ml/min/1,73m2
3.General criteria:
a. Understanding of Dutch language
b. Fit for surgery (WHO 1-2)
c. Written informed consent

Exclusion criteria

1. Suspicion of advanced-stage of disease, e.g. ascites or peritoneal depositions
2. History of cancer (excl. BCC) within 5 years prior to inclusion
3. Multiple malignancies at the same time

Study design

Design

Study type: Observational non invasive
Masking: Open (masking not used)

Control:	Uncontrolled
Primary purpose:	Diagnostic

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	02-07-2021
Enrollment:	450
Type:	Actual

Medical products/devices used

Registration:	No

Ethics review

Approved WMO Date:	21-01-2021
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	16-04-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	27-08-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	03-04-2024
Application type:	Amendment
Review commission:	METC NedMec

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
CCMO	NL75690.031.20