Clinical Oncology xxx (2018) 1–9

Contents lists available at ScienceDirect

Clinical Oncology

journal homepage: www.clinicaloncologyonline.net

Overview

Outcome and Prognostic Impact of Surgical Staging in Serous Tubal Intraepithelial Carcinoma: A Cohort Study and Systematic Review

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Received 28 February 2018; accepted 21 March 2018

Abstract

The optimal management of breast cancer susceptibility gene (BRCA)1/2 carriers with isolated serous tubal intraepithelial carcinoma (STIC) found at risk-reducing salpingo-oophorectomy (RRSO) is unclear. The prevalence of occult carcinoma and STIC in a consecutive series of BRCA1/2 carriers undergoing RRSO is reported. The outcome of staging procedures in BRCA1/2 carriers with isolated STIC at RRSO as well as the relationship between staging, chemotherapy treatment and risk of recurrence was assessed via a systematic review of the literature. Our series included 235 BRCA1/2 carriers who underwent RRSO. Federation of Gynaecology and Obstetrics stage IA carcinoma or STIC was found at RRSO in three (1.3%) and two (0.9%) patients, respectively. A systematic review of the literature included 82 BRCA1/2 carriers with isolated STIC found at RRSO. In 13/82 (16%) cases with STIC, staging was reported. In none of these cases staging revealed more advanced disease. Recurrent disease was found in four of 36 patients with reported follow-up. The estimated risk of recurrence in patients with isolated STIC at RRSO was about 11% (95% confidence interval 3–26%) after a median follow-up of 42 months (range 7–138). No recurrences were reported in those patients with STIC at RRSO who underwent staging or received chemotherapy. We found 1.3% occult carcinoma and 0.9% STIC at RRSO in our cohort of BRCA1/2 carriers. A systematic review of the literature suggests that additional treatment after RRSO, i.e. staging and/or chemotherapy, is associated with a lower risk of recurrence. However, data on staging and follow-up are limited.

Key words: BRCA; recurrence; RRSO; staging; STIC; systematic review

Statement of Search Strategies Used and Sources of Information

We searched studies written in English in Pubmed, Embase, World of Science and Cochrane Library using relevant search terms for the systematic review. The last search was carried out in April 2017. All studies were reviewed against the inclusion and exclusion criteria. Citation lists of eligible articles were hand-searched for additional relevant articles.

Introduction

In about 10–15% of all ovarian cancer cases, a breast cancer susceptibility gene (BRCA) 1 or 2 germline mutation can be found [1,2]. The cumulative risk of developing ovarian carcinoma by the age of 70 years for BRCA1 and BRCA2 carriers is about 40% and 15%, respectively [3,4].

Risk-reducing salpingo-oophorectomy (RRSO) is estimated to reduce the risk of developing ovarian carcinoma in BRCA1/2 carriers by about 80% [5,6]. Therefore, a RRSO is recommended in women with a BRCA1 or BRCA2 mutation between the ages of 35 and 40 years or 40 and 45 years, respectively, or as soon as childbearing has been completed after this age [7].

More than a decade ago, precursor lesions of serous ovarian carcinoma, i.e. dysplasia and serous tubular intraepithelial carcinoma (STIC), were first described in RRSO specimens of BRCA1/2 carriers [8–10]. In the literature,

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https://doi.org/10.1016/j.clon.2018.03.036
0936-6555/

isolated STIC has been described in 0.7–4.0% of BRCA1/2 carriers undergoing RRSO and occult carcinoma in 1–4% of these cases [11–15]. As these precursor lesions are predominantly found in the distal fimbriated end of the fallopian tube, the Sectioning and Extensively Examining the Fimbriated End (SEE-FIM) protocol was introduced in 2006 [9]. This protocol ensures a detailed examination of the fallopian tube [9,16].

The reported number of BRCA1/2 carriers with isolated STIC at RRSO is limited in the literature. There is no consensus regarding the optimal management of BRCA1/2 carriers with isolated STIC at RRSO. Staging procedures in BRCA1/2 carriers with isolated STIC have been described in only a few studies [13,17,18]. Recurrent disease after isolated STIC at RRSO has been reported in BRCA1/2 carriers [14,17]. However, whether the risk of recurrence depends on the outcome of staging procedures and/or given chemotherapy is not clear.

In the present study, we report on the prevalence and outcome of occult ovarian carcinoma or STIC found at RRSO in our own cohort of BRCA1/2 carriers. Furthermore, we assessed the outcome of surgical staging and prognosis of BRCA1/2 carriers with isolated STIC at RRSO in a systematic review.

Materials and Methods

Cohort Study

Between May 2003 and December 2016, 468 women considered at high risk of hereditary ovarian cancer were referred to the outpatient clinic of hereditary cancer of the Department of Gynecology at the Leiden University Medical Center (LUMC).

Women with not (yet) performed RRSO ($n = 153$), no confirmed pathogenic BRCA1/2 mutation ($n = 71$), no ultrasound documented ($n = 6$) or suspicion of malignancy prior to RRSO based on CA125 and suspicious findings on ultrasound ($n = 3$) were excluded from the current study. Finally, 235 BRCA1/2 carriers undergoing RRSO, without suspicion of malignant disease based on ultrasound findings and CA125 serum levels, were included in the current study.

Follow-up was calculated from the date of surgery until the last date of follow-up visit or date of death. Because most women also underwent breast cancer surveillance at the Department of Surgery, the last date of follow-up could also be obtained from these records. Patient-specific information, including mutation status, age at RRSO, gynaecological examinations and breast carcinoma history, was prospectively collected. The study was approved by the Medical Ethical Committee of the LUMC.

The RRSO was preferably carried out by laparoscopy. Both adnexa including the fallopian tube were removed up to the uterine cornua. Specimens were removed within an endobag in order to prevent tumour spill in case of occult malignancy. Cytology washings of the pelvis and abdomen were not routinely collected at RRSO. Whether RRSO included a hysterectomy was at the discretion of the patient and the gynaecologist, but was not routinely carried out.

RRSO specimens were submitted entirely for histological examination. The adnexa were fixed, transversely sectioned at 3 mm intervals, stained with haematoxylin and eosin and examined microscopically. RRSO specimens have been examined according to the SEE-FIM protocol since 2011 [9,16]. Occult carcinoma was classified according to the International Federation of Gynaecology and Obstetrics (FIGO) criteria [19]. STIC was defined as an intraepithelial carcinoma, characterised by disorganised cellular crowding and nuclear stratification consisting of secretory cells in the absence of ciliated cells. Furthermore, it includes mitotic activity, a high nuclear/cytoplasm ratio, nuclear pleomorphism with loss of polarity and nuclear enlargement [20].

The primary outcome of the cohort study was the prevalence of occult carcinoma or STIC in the collected RRSO specimens. Descriptive values of variables were displayed as frequencies or percentages for discrete variables and as median and range for continuous variables. Differences between groups were compared using the chi-squared test for discrete variables and the Kruskall–Wallis *H*-test for continuous variables. The statistical analysis was carried out using SPPS version 23 (SPSS, Chicago, IL, USA) and $P < 0.05$ was considered significant.

Systematic Review

Eligibility Criteria, Literature Search and Data Collection

We searched Pubmed (1950 to April 2017), Embase (1974 to April 2017), World of Science (1945 to April 2017) and Cochrane Library for studies describing STIC at RRSO. Electronic search strategies for Pubmed, Embase, World of Science and Cochrane Library are summarised in the Supplementary Data. The previously mentioned databases were last searched in April 2017. Titles and/or available abstracts of all articles found were scanned and full-text reports of potentially eligible articles were assessed. Studies were included when written in English, with an available full text and describing any case of isolated STIC at RRSO in BRCA1/2 carriers. Conference abstracts, case reports and reviews not describing own cases were excluded. When articles proved to be an update of previously published data, only the most recent article was included. Citation lists of eligible articles were hand-searched for additional relevant articles. Data were reported using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist, as shown in Supplementary Table S1.

Data Extraction

Data extracted from articles, when available, included: cohort size and mutation status of the cohort undergoing RRSO, surgical procedures at RRSO and prevalence of isolated STIC at RRSO. For cases with isolated STIC at RRSO, mutation status, age at RRSO, cytology outcome at RRSO, staging surgery and/or adjuvant treatment, follow-up and recurrent disease were assessed. A literature search, title/abstract screening, full-text review and data extraction

Please cite this article in press as: Van der Hoeven NMA, et al., Outcome and Prognostic Impact of Surgical Staging in Serous Tubal Intraepithelial Carcinoma: A Cohort Study and Systematic Review, Clinical Oncology (2018), https://doi.org/10.1016/j.clon.2018.03.036