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Original Research

Ten-year survival in patients with endometrial adenoacanthoma and endometrial adenocarcinoma with malignant squamous cell differentiation

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Summary

Objectives: It is acknowledged that squamous differentiation in the endometrial adenocarcinoma does not affect the outcome of type I cancer. However, it has been recently reported that the so-called shadow cell differentiation is likely present in endometrial adenoacanthomas. As the shadow cells differentiation suggests a caspase-independent cell death, based on the previous reports it can be hypothesized that the endometrial adenoacanthoma would have a better prognosis than the endometrial adenocarcinoma with squamous differentiation. *Methods:* From a database of 829 endometrial cancer, 34 endometrial adenoacanthomas and 18 endometrial adenocarcinomas with malignant squamous differentiation were assessed. The Kaplan-Meier curves were generated and compared for endometrial adenoacanthomas and endometrial adenocarcinomas with malignant squamous differentiation. *Results:* the 10-year survival in patients with adenocarcinoma with malignant squamous differentiation is significantly lower than the survival in patients with adenoacanthoma. Advanced stage (2009 FIGO II or over) was more likely found in adenocarcinoma with malignant squamous differentiation at the surgery time. Matching groups for the FIGO stage, there were no difference in overall survival. *Conclusion:* patients with endometrial adenoacanthoma have a better prognosis than patients with endometrial adenocarcinoma with malignant squamous differentiation probably because of the earlier stage diagnosis.

Key words: Endometrial adenocarcinoma; Adenoacanthoma; Squamous cell differentiation.

Introduction

In the past, squamous cell differentiation in type I endometrial adenocarcinoma (the endometrial adenoacanthoma and the endometrial adenocarcinoma with malignant squamous cell differentiation) was suspected to be associated in endometrial cancer [1, 2].

Subsequent studies have shown no association between squamous differentiation and outcome in endometrial cancer [3-6]. The survival factors for the endometrial adenocarcinoma were the ones currently acknowledged for the endometrial epithelial cancer [7, 8]. The last paper treating the adenoacanthoma and the endometrial adenocarcinoma with malignant squamous cell differentiation outcome is the Pekin and other article, published in 2001 [9].

In 2015, Nakamura [10] demonstrated that the shadow cell differentiation comes from the squamous elements in endometrial adenoacanthoma, and in 2018 Nakamura [11] reported that the shadow cell differentiation is a form of terminal, caspase-independent apoptosis. This report has led us to hypothesize that squamous cells of adenoacanthoma could die from apoptosis because they are more differentiated than the squamous cells of endometrial adenocarcinoma with malignant squamous differentiation. Therefore, the adenocarcinoma with malignant squamous cells would have a worse prognosis than the adenoacanthoma, as suggested in the past. Based on this hypothesis we reviewed our database on endometrial adenocarcinomas, aiming to compare the outcome between adenoacanthomas and adenocarcinomas with malignant squamous cells differentiation.

Materials and Methods

A large, historical database on endometrial cancer was previously published in 2018 [12]. Those data were collected from a single center (Institute of Obstetrics and Gynecology, University of Ferrara) from 1981 to 2015. Eighty-hundred and twenty nine patients were available. Thirty-four endometrial adenoacanthomas and 18 endometrial adenocarcinomas with malignant squamous differentiation were found in that database. All cancers were restaged according to the 2009 FIGO classification [13]. 10-year survival of patients with adenoacanthoma and adenocarcinoma with malignant squamous differentiation was assessed by comparing the Kaplan-Meier curves. Patient's age, tumour grading, FIGO 2009 stage, surgical radicality, adjuvant chemotherapy, adjuvant radiotherapy were compared between adenoacanthoma and adenocarcinoma with

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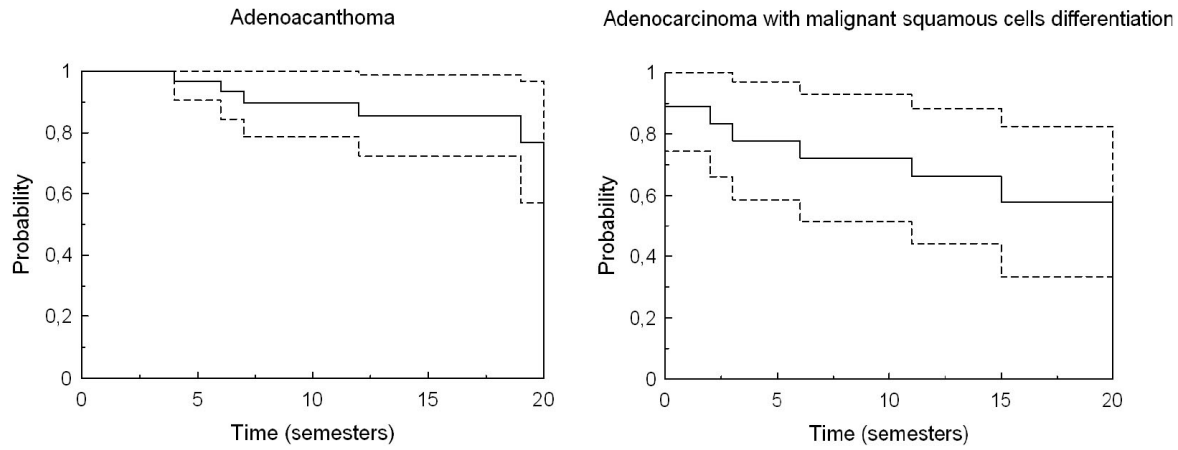

Figure 1. — Survival curves with 95% confidence intervals. Time variable (on x-axis) is expressed in semesters.

malignant squamous differentiation. Time variable is expressed in semesters. The Kaplan-Meier curves were compared in univariate analysis by using the Log-rank sum test, the Breslow test, the Tarone-Ware test. Chi square test, Fisher's exact test and Mann-Whitney test were also used for univariate comparison, for matching groups for significant confounders. A new comparison of Kaplan-Meier curves between groups after the matching was planned. Kyplot 2.0 and SPSS 16.0 were used for statistical analyses. $p \leq 0.05$ was set for significance.

Results

Ten-year survival of patients with adenoacanthoma is 77.0% (Figure 1), while 10-year survival of patients with adenocarcinoma with malignant squamous differentiation is 57.9% (Figure 1). Difference in survival is significant (Log-rank: $p = 0.063$; Breslow: $p = 0.033$; Tarone-Ware: $p = 0.043$).

Table 1 reports mean ages and rates along with univariate comparisons. The FIGO stage II or over is significantly higher in adenocarcinoma with malignant squamous differentiation than in adenoacanthoma. No other differences were found. By matching for the FIGO staging, no differences in overall survival were also found among Kaplan-Meier curves (curves not shown).

Conclusion

The main finding of the current short report is that the adenocarcinoma of the endometrium with malignant squamous differentiation has a worst prognosis than adenoacan-

Table 1. — *Descriptive statistics and univariate comparisons.*

	Adenoacanthoma	Adenocarcinoma with malignant squamous cell differentiation	*p*
Age	61.4	64.5	0.424
FIGO 2009 Stage			
-II+	1 (2.9%)	7 (38.9%)	**0.003**
-Ia	9 (26.5%)	2 (11.1%)	0.351
-Ib	24 (70.6%)	9 (50.0%)	0.244
Grading			
-Grade 1	12 (35.3%)	4 (22.2%)	0.512
-Grade 2	17 (50.0%)	11 (61.1%)	0.637
-Grade 3	5 (14.7%)	3 (16.7%)	0.768
Radicality on parametria			
-Yes	0	1 (5.6%)	0.272
Lymphadenectomy			
-Yes	4 (11.8)	5 (27.8%)	0.143
Adjuvant chemotherapy			
-Yes	15 (44.1%)	8 (44.4%)	0.625
Adjuvant radiotherapy			
-Yes	12 (35.3%)	4 (22.2%)	0.259

Adenocarcinoma with squamous cell differentiation is diagnosed more likely at 2009 FIGO stage II or over [13], as highlighted in bold.

thoma of the endometrium, because it could be diagnosed at more advanced 2009 FIGO stage.

This conclusion has been reached after reviewing an historical cohort of patients with endometrial cancer. The historical bias imposes caution in interpreting the results. However, differences in the overall survival due to more advanced FIGO stage can be supported by recently reported data of Nakamura [11].

As the squamous cell differentiation is uncommon in endometrial adenocarcinoma and therapy for the endometrial carcinoma are improved, the outcome of endometrial cancers with squamous differentiation should be further reassessed, or it should be checked with meta-analysis if adenoacanthoma of the endometrium is diagnosed at an earlier stage in available studies than adenocarcinoma of the endometrium with malignant squamous differentiation.

Author contributions

Indraccolo Ugo has written the article and has performed the statistical analysis. Martinello Ruby and Scutiero Gennaro have performed the bibliographic research on endometrial adenoacanthoma and adenocarcinoma of the endometrium with malignant squamous cell differentiation. Bernardi Giulia, Borghi Chiara and Brasile Orsola have reviewed the database of 829 endometrial cancer, restaged it according to the 2009 FIGO staging [13] and encoded cases for the analysis. Greco Pantaleo has reviewed the article, its background, its conclusions.

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Conflict of interest

The authors affirm that there is no conflict of interest.

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