



The Prognostic Value of DNA Ploidy Determination in Endometrial Cancer

Massimo Origoni^{1*}, Patrizia De Marzi¹, Giada Almirante¹, Jessica Ottolina¹, Luigi Frigerio², Marco Carnelli², Chiara Gelardi¹ and Massimo Candiani¹

Abstract

Aneuploidy, defined as an abnormal quantity of DNA in cells nuclei, is the most frequently observed genetic abnormality in cancer cells. Alterations in cell cycle control and chromosomal missegregation very often result in the accumulation of excess genetic material. These genetic reassortments simultaneously imbalance lots of structural and regulatory proteins. This chromosomal instability may be associated with mutations in tumor suppressor genes or loss of function of mismatch repair genes. These are common pathways of cancerogenesis in endometrial cancer. Endometrial cancer represents the most common female genital tract malignancy and is generally associated with favourable outcomes for affected patients. Despite this, recurrence rates and disease-related deaths are consistently reported in published series, also in so-defined low-risk groups of patients. Hence, is reasonable to believe that traditional prognostic factors—surgical stage, histologic type, tumor grading, myometrial deep of invasion, involvement of vascular spaces—do not definitely respond to the clinical needs of a comprehensive management. The determination of DNA ploidy in endometrial cancer has been widely investigated in the last decades and clear evidence is available of its direct correlation with prognosis. Despite this, poor acceptance and skepticism are common believes in the scientific community. Aim of the paper has been the attempt to underline, upon scientific strength, the importance and clinical potential usefulness of this determination in gynecological oncological practice.

Keywords

DNA ploidy; DNA content; DNA index; Endometrial cancer; Prognosis; Survival

Background

Endometrial cancer (EC) is the most common gynecologic malignancy and is generally considered a poorly aggressive gynaecological tumor, with a 5-year overall survival rate of 80-85%. Seventy-five percent of women with EC are classified stage I at the time of diagnosis, with an 89% 5-year survival rate reported for these patients; of note, out of the 15-20% of women who die of endometrial cancer, almost half of the cases were early stages of the disease. Thus, although accounting for the great minority of cases,

*Corresponding author: Massimo Origoni, Department of Gynecology & Obstetrics, Vita Salute San Raffaele University School of Medicine, Ospedale San Raffaele Scientific Institute, Via Olgettina 60, 20132 Milano, Italy, Tel: +390226432579; Fax: +390226432759; E-mail: massimo.origoni@hsr.it

Received: October 22, 2012 Accepted: January 04, 2013 Published: January 10, 2013

EC-related deaths are significantly reported in this apparently low-risk population. This probably not only reflects the limitations of current prognostic assessment but also the inherent variability in the tumor biology. Surgery, including total abdominal hysterectomy with bilateral salpingo-oophorectomy is considered as the gold standard treatment, although the extent of surgery may vary [1,2]. Adjuvant therapy is reserved to high-risk patients. However, according to this management, survival rates did not substantially improve over the last decades [3]. Several factors such as depth of myometrial invasion, tumor grading, histologic subtype and vascular space invasion have been identified as predictors of relapse. In particular, histological heterogeneity plays a relevant role, determining significant differences in prognosis: the most common histotype, the endometrioid subtype (Type I), accounting for almost 80% of all endometrial cancers, is correlated with a better long-term prognosis and survival than serous and/or clear cell histological type (Type II). However, only few women with disease confined to the uterine corpus will show these traditional high-risk features, and a small proportion of them will ultimately relapse. Therefore it is necessary to define adjunctive prognostic and predictive factors to stratify low and high-risk groups of patients, especially for early stages EC of the endometrioid subtype. In recent years several studies have tried to define new prognostic predictors for identifying those patients at higher risk for extrauterine disease spread and recurrence after primary treatment. More accurate stratification of patients would allow clinicians to improve patients' selection for radical surgery and adjuvant therapy, avoiding overtreatments and morbidities for those patients with good prognosis.

DNA Ploidy in Endometrial Cancer

Normal human somatic cells with 46 chromosomes (23 pairs) are defined as diploid, whereas cells with fewer or more than 46 chromosomes as considered as aneuploid. Diploidy of tumor cells is correlated with well differentiated cell clones and, for most human neoplasm's including EC, patients' outcome is better for diploid tumors [4]. Aneuploidy implies an abnormal quantity of genomic material in the cell, being this presumably a consequence of inherited and somatic alterations in proto-oncogenes and tumor-suppressor genes, which play a key role in regulating cell growth, differentiation, angiogenesis, invasion and metastasis.

Flow cytometry and image cytometry

DNA analysis with flow cytometry (FCM) or image cytometry (ICM) quantifies nuclear DNA in cancer cells and classifies the tumor on the basis of its DNA ploidy. Each technique presents both advantages and disadvantages. In most studies DNA analysis is performed by FCM on either frozen or formalin-fixed, paraffin embedded tissues, essentially following the procedures originally described by Hedley [5] with modification according to Schutte [6]. Flow cytometry allows 20,000-50,000 cells to be analyzed; however, tumor cells cannot be separated from normal cells and this may bias the distribution of abnormal cells in DNA histogram. In contrast, ICM visually selects each cancer cell, thus excluding surrounding cells from the analysis. However, because of the small number of cells

analyzed, rare non-diploid cells may be missed. Anyway, there is a good correlation (>80%) between DNA ploidy results obtained from both FCM and ICM [7,8], even if FCM has been more frequently performed.

Prognostic role of DNA ploidy in EC

In several studies flow cytometric analysis of DNA ploidy has been shown to provide stronger and independent prognostic information in comparison to standard pathologic parameters both in univariate (UA) and multivariate analysis (MA) [9-35]. Britton [14] analyzed DNA ploidy patterns of 256 EC patients; non-diploid patterns were detected only in 22% of cases, but accounted for 52% of the relapses. The 4-year overall survival rate for non-diploid EC patients was 57% compared to 88% of those with diploid DNA pattern ($p<0,001$). At multivariate survival analysis, the two most cogent independent prognostic factors were histologic type and DNA ploidy.

Ikedo [19] demonstrated an association between aneuploidy and advanced stage, tumor grade, myometrial invasion, nodal metastasis and positive peritoneal cytology in a study of 76 surgically staged EC patients. Moreover, the authors reported a fivefold (33 versus 6.9%) higher prevalence of lymph nodes metastases in patients with aneuploid tumors compared to patients with diploid tumors. Iversen [11] studied both the DNA ploidy and steroid receptor status as outcome predictors in EC patients. UA showed significant prognostic value for ploidy, surgical stage, grade and depth of myometrial invasion; however, in the stepwise analysis only ploidy and surgical stage were finally significant. Larson [36] reported in a study of 208 EC patients that aneuploid tumors had a significantly higher prevalence of metastases to the cervix, adnexa and omentum, malignant pelvic cytology and advanced surgical stages. Moreover, they found a fivefold higher risk of pelvic lymph nodes metastases and a six fold higher risk of para-aortic lymph nodes metastases in patients with aneuploid tumors compared to those with diploid tumors.

Lundgren [27], in a study of 376 stage I-IV patients with EC, reported that beside stage and histological subtype, DNA ploidy was the strongest outcome predictor and was reliable in predicting the risk of relapse. Mangili [28], in a multivariate analysis study of 203 consecutive cases of EC, reported that among all prognostic factors (including age at diagnosis, grade, peritoneal cytology, node involvement, vascular invasion, myometrial invasion and ploidy) only DNA ploidy performed as an independent prognostic variable.

More interestingly, some investigators studied the prognostic role of ploidy in early stage EC patients. Friberg [33] evaluated patients with stage I-II EC, demonstrating a 5-year survival rate of 92% in patients with diploid lesions and 36% in aneuploid tumors. Britton [34] determined ploidy in 203 patients with surgical stage I EC: non-diploid specimens were observed only in 16% of patients but accounted for 50% of all recurrences. Moreover the Authors reported that ploidy effectively stratified the endometrioid tumors according to their risk of recurrence: diploid and non-diploid endometrioid tumors had a 5-year survival rate of 93% and 74% respectively ($p=0.01$). Von Minckwitz [22] reported that, in patients with stage I disease, DNA ploidy and S phase fraction were found to be independent and the most significant outcome predictive factors at MA, also including grade, histological type and estrogen receptor status. Mangili [35], in a study of 222 stage I endometrioid EC patients reported that only

DNA ploidy and age at diagnosis resulted independent prognostic factors (Cox, $p=0.01$ and $p<0.0001$ respectively); furthermore DNA ploidy was the only prognostic factor related to recurrence risk (log rank, $p<0,05$). The effective role of ploidy as prognostic factor in early stages of EC is still matter of debate [36-43]. Several authors reported a prognostic value of ploidy in terms of survival rates in UA but not in MA. Ørbo [39], in a study involving 123 women with EC stage I-IV found that FIGO stage, histologic grade, myometrial infiltration depth, ploidy, vessel invasion and progesterone receptor status were significantly related to survival in the UA. However in the multivariate regression analysis only FIGO stage, vessel infiltration and nuclear perimeter were independently related to survival. Similarly, Lundgren [40], in a small cohort of patients with EC ($n=80$) found that DNA ploidy loses its significant prognostic value when submitted to MA; the authors speculated that DNA ploidy was unexpectedly not significant at MA probably due to the small number of patients. Terada [41] reviewed ploidy in 100 patients with stage IB and IC EC; results of this study indicate that aneuploidy affects the overall survival rate but does not increase the risk of recurrence if patients are adequately staged at the time of initial surgery. However, given the small number of relapses, the Authors suggested a prognostic role of ploidy in patients who were not appropriately surgically staged. Mariani [38], in a case-cohort study on histopathologic and molecular predictors of distant failure in EC, reported that aneuploidy significantly predicted distant relapses but lost any significance when a logistic regression was performed. Osmanağaoğlu [42] similarly found that ploidy was an independent prognostic indicator in MA and was correlated with tumor recurrence in UA, however it did not result significant for tumor recurrence in MA.

Conversely, Pfisterer [43] reported that ploidy status did not correlate either with recurrence-free survival or with overall survival in UA. In particular, they found an increased risk of reduced overall survival at UA; however, given the small number of events ($n=26$), no statistically significant differences were observed. Moreover, Kanski [37] reported in a study on 171 stage I EC patients, that patients with diploid tumors had a slightly increased (but not significant) survival rate compared to patients with non-diploid tumors ($p=0.12$). Recently, a Korean study further confirmed that DNA aneuploidy is an independent prognostic factors and it is useful to identify "high-risk" patients among those usually considered at "low risk", as stage I endometrial cancer [44]. In large series of consecutive patients with early stage endometrial cancer, DNA ploidy was studied in order to evaluate its reliability as a prognostic factor. Data confirmed that patients with non-diploid tumors have a significant higher risk of relapse and disease-related death, but the superiority of ploidy over the traditional prognostic factors was not demonstrated [45-47]. Pradhan [48] considered DNA Index (DI) of the aneuploid tumor in DNA ploidy results in about 900 cases of endometrioid adenocarcinoma; patients with aneuploid tumor with $DI >1.20$ had higher recurrence rates, higher distant failures rate and poorer disease-free and overall survival, while patients with aneuploid tumors with $DI <1.20$ mainly relapsed locally and had higher recurrence rates than patients with diploid tumor. These results may suggest that patients with aneuploid tumor with $DI \leq 1.20$ can be clinically followed up or be considered for adjuvant vaginal brachytherapy. It must be however underlined that, in this experience, DNA ploidy was not found to be an independent prognostic factor when traditional ones were taken into account. In

our experience [35], patients with aneuploid tumor and $DI \leq 1.20$ were included in the same group of those with diploid tumor in order to decide whether to give adjuvant therapy. In contrast to the aneuploid tumors with $DI \leq 1.20$, the aneuploid tumors with $DI > 1.20$ are more clinically aggressive and relapse mainly outside the pelvis in the same fashion as serous and clear-cell adenocarcinomas, indicating that these patients can be potential candidates for adjuvant chemotherapy. The same authors [49] performed a DNA ploidy analysis in cases of stage I and II serous adenocarcinoma of the endometrium and demonstrated a prognostic significance of these parameters: patients with diploid ($n=19$), aneuploid ($n=29$), and tetraploid ($n=8$) tumor had 5-year recurrence rates of 10, 38, and 53%, respectively ($p=0.09$). A DNA ploidy parameter, 5c exceeding rate, was found to be a prognostic marker for recurrence ($p=0.03$), progression-free survival ($p<0.01$), and overall survival ($p=0.02$). These results seem to be particularly interesting, as it has been reported that DNA ploidy closely correlates with histopathologic subtypes of endometrial cancer [50].

Ploidy and postoperative management of EC

There is still no consensus on the evidence-based optimal treatment of patients with early stage EC. Surveys by Maggino have shown that the clinical management of the same tumor may vary according to different oncological referral centres in Europe [1] and in the United States [2]. Naumann [44] analyzed the current standards of care for early stage EC adopted by the members of the Society of Gynecologic Oncologists and reported that for stage IB grade 3 and all stage IC most gynaecologic oncologist would recommend some type of adjuvant radiation therapy. Almost all the studies reported in the literature clearly identify DNA ploidy as a strong prognostic factor in EC patients; however, a very recently published editorial by Terada [51] is not consistent with this and did not support the use of DNA ploidy as a replacement of traditional prognostic factors for treatment decision; interestingly the author stated that "...obviously, such a strategy will include some 'low-risk' patients who ultimately recur and some 'high-risk' patients who will survive without adjunctive therapy". Unexpectedly, DNA content in EC cases is not routinely screened in clinical practice worldwide. Generally, aneuploid endometrial neoplasms are usually either G3 endometrioid adenocarcinomas, clear-cell carcinomas or uterine papillary-serous adenocarcinomas. Non-endometrioid and high-grade (G3) endometrioid histotypes are consistently accepted to be high-risk features. In clinical practice, the real challenge is to identify high-risk cases among the heterogeneous group of endometrioid EC, accounting for 85% of all endometrial neoplasms. DNA ploidy may play a key role in the subset of patients for whom adjuvant therapy after hysterectomy is still a controversial issue, i.e. moderately differentiated (G2) endometrioid carcinomas stage IB-IC. Susini [31] reported the 10-year results of a prospective study on the prognostic role of ploidy in EC; by multivariate analysis DNA aneuploid pattern was demonstrated to be the strongest independent predictor of poor outcome, followed by age and surgical stage; aneuploidy tumors had a significantly higher risk ratio for recurrence (5.03) and death due to the disease (6.50) compared to diploid tumors. These results suggest that even in the subgroup of well-differentiated (G1) tumors it is possible to distinguish patients with excellent prognosis bearing a DNA diploid tumor and patients with less favourable outcome correlated to a DNA aneuploid tumor. More interestingly, in patients

with G2 endometrioid tumors, representing a group for which prognosis and need for adjuvant therapy are still unclear, DNA ploidy allows the identification of a subset of more aggressive tumors that definitely requires adjuvant therapy. Other authors recently proposed multiple factor analysis, including DNA content evaluation, to overcome the limits of traditional pathological risk assessment. Lim [45] prospectively assigned 406 consecutive stage I "low-risk" patients (endometrioid EC limited to $<50\%$ myometrial infiltration and no vascular space invasion or grade 3) to treatment groups based on tumor ploidy. Patients with aneuploid tumors were submitted to vaginal vault radiotherapy (RT), while those with diploid tumors were followed and treated only at relapse. The authors reported that patients with aneuploid tumors treated with RT have the same risk of relapse as untreated patients with diploid tumors, suggesting a useful role of this ploidy-based treatment policy in clinical practice. In addition, Hogberg [46] proposed treating patients according to new risk criteria, including DNA ploidy. In this large study on 335 stage I-II endometrioid EC patients, high-risk cases were defined by the sum of those with grade 3 and/or deep myometrial infiltration and the cases with aneuploid tumors: highly significant differences were reported between the "low risk" and the "high risk" groups regarding overall survival, disease-specific survival and failure rates, despite the administration of adjuvant vaginal brachytherapy to the high risk group. Mangili [35] reported preliminary results of postoperative risk assessment by means of DNA ploidy in stage I endometrioid EC patients. The authors reported that, since ploidy was introduced as a "decision-making" factor, 69.4% of patients in stage IC were spared adjuvant therapy. Neither increase in tumor related mortality in this group nor any statistically significant increase in recurrence rate was observed between patients submitted to adjuvant therapy according to traditional prognostic factors stratification and those managed according to ploidy evaluation. Inconsistently, Lindahl [52] reported that a treatment programme in endometrioid EC based upon DNA ploidy alone, for which adjuvant vaginal brachytherapy was performed in non-diploid tumors, was not the optimal treatment option, suggesting more research towards cytostatics.

Summarized results of the most significant studies regarding the prognostic role of DNA ploidy in endometrial cancer are reported in Table 1.

Conclusions

Considering the large number of studies reported in literature, DNA ploidy appears to be with no doubt very relevant in the prognostic assessment of early stages endometrioid EC patients, allowing the identification of cases at increased risk for disease recurrence and/or cancer-related death; this would signify the recognition of patients who would benefit from adjuvant strategies despite the apparent low-risk. However, it is actually neglected or poorly considered by the large majority of gynaecological oncologists in clinical practice. It must be underlined that, and we strongly support this concept, DNA ploidy determination should not replace the use of traditional and evidence-based validated prognostic indicators, rather, they should complement each other to optimize the clinical workout. Since DNA ploidy has not been positively considered in clinical practice for more than 20 years, the hypothesis of gaining a real clinical value nowadays seems to be quite unrealistic. Chromosomal instability leading to structural and numerical abnormalities of chromosomes has a

Table 1: Summarized results of the principal studies dealing with prognostic relevance of DNA ploidy in endometrial cancer.

Author	n° Cases	Stage	Type	Technique	Statistics	Prognostic Value
Ambros [18]	57	I	EN	ICM	UA+MA	$p=0.002^*$ $p=0.03^{**}$
Britton [14]	256	I-IV	EN+CC+SP	FCM	MA	$p<0.001$
Dyas [17]	121	I-II	n.a.	FCM	UA	$p<0.01$
Friberg [33]	103	I-II	EN	FCM	UA	$p<0.001$
Hogberg [46]	335	I-II	EN	FCM	UA	$p<0.0001$
Ikeda [19]	76	I-III	EN	FCM	MA	$p<0.01$
Lindahl [9]	166	I-II	EN	FCM	MA	$p=0.015$
Lindahl [16]	245	I-II	EN	FCM	UA	$p=0.0001$
Lundgren [40]	80	I-IV	EN+CC+SP	ICM	UA	$p<0.001$
Mangili [28]	203	I-III	EN	FCM	UA+MA	$p=0.001^*$ $p=0.012^{**}$
Mangili [35]	222	I	EN	FCM	UA+MA	$p=0.003^*$ $p=0.01^{**}$
Newbury [15]	233	I-IV	EN+CC+SP	FCM	MA	$p<0.001$
Ørbo [39]	123	I-IV	EN+CC+SP	FCM	UA+MA	$P=0.008^*$ n.s.**
Pfisterer [43]	202	I	EN	FCM	UA+MA	n.s.* n.s.**
Pradhan [48]	937	I-II	EN	ICM	UA+MA	$p=0.02^*$ n.s.**
Song [47]	217	I	EN+NEN	FCM	UA+MA	$p=0.001^*$ $p=0.017^{**}$
Sorbe [21]	227	I-IV	EN+NEN	FCM	UA+MA	$P<0.0001^*$ n.s.**
Suehiro [32]	106	n.a.	EN	ICM	UA+MA	$p=0.012^*$ $p=0.016^{**}$
Susini [23]	74	I-IV	EN+CC+SP	FCM	UA+MA	$p<0.001^*$ $p=0.03^{**}$
Susini [26]	50	I-IV	EN+CC+SP	FCM	UA	$p=0.002$
Susini [31]	174	I-IV	EN+CC+SP	FCM	UA+MA	$p<0.0001^*$ $p<0.0001^{**}$
Terada [41]	100	I	EN	FCM	UA+MA	$P=0.04^*$ n.s.**
Van der Putten [13]	38	I	EN	FCM	UA+MA	$p<0.01^*$ $p<0.00001^{**}$
Zaino [25]	254	I-II	EN+NEN	FCM	UA+MA	$p=0.001^*$ $p<0.001^{**}$

n.a.: Not Available; EN: Endometrioid; CC: Clear Cell; SP: Serous Papillary; NEN: Non Endometrioid; FCM: Flow Cytometry; ICM: Image Cytometry; UA: Univariate Analysis; MA: Multivariate Analysis; *: at univariate analysis; **: at multivariate analysis.

primary role in the malignant alteration of tumors. Chromosomal aneuploidy is found in 20–35% of cases of endometrial cancer and is associated with advanced cancers, high-grade non-endometrioid cancer and deep myometrial invasion in the FIGO staging of carcinoma. We believe that the ever growing need to identify positive prognostic factors in female genital malignancies, together with the increasing importance of fertility-sparing strategies of treatment, will hopefully lead to a greater consideration of this interesting biological aspect of endometrial cancer.

References

- Maggino T, Romagnolo C, Zola P, Sartori E, Landoni F, et al. (1995) An analysis of approaches to the treatment of endometrial cancer in Western Europe: a CTF study. *Eur J Cancer* 31A: 1993-1997.
- Maggino T, Romagnolo C, Landoni F, Sartori E, Zola P, et al. (1998) An analysis of approaches to the management of endometrial cancer in North America: a CTF study. *Gynecol Oncol* 68: 274-279.
- Pecorelli S, Benedict JL, Creasman WT (1998) FIGO annual report on the

- results of treatment in gynaecological cancer. *J Epidemiol Biostat* 3: 35-61.
- Salvesen HB, Akslen LA (2002) Molecular pathogenesis and prognostic factors in endometrial carcinoma. *APMIS* 110: 673-689.
- Hedley DW, Friedlander ML, Taylor IW, Rugg CA, Musgrove EA (1983) Method for analysis of cellular DNA content of paraffin-embedded pathological material using flow cytometry. *J Histochem Cytochem* 31: 1333-1335.
- Schutte B, Reynders MM, Bosman FT, Blijham GH (1985) Flow cytometric determination of DNA ploidy level in nuclei isolated from paraffin-embedded tissue. *Cytometry* 6: 26-30.
- Bauer TW, Tubbs RR, Edinger MG, Suit PF, Gephart GN, et al. (1990) A prospective comparison of DNA quantitation by image and flow cytometry. *Am J Clin Pathol* 93: 322-326.
- Kaern J, Wetteland J, Tropé CG, Farrants GW, Juhng SW, et al. (1992) Comparison between flow cytometry and image cytometry in ploidy distribution assessments in gynaecologic cancer. *Cytometry* 13: 314-321.
- Lindahl B, Alm P, Killander D, Långström E, Tropé C (1987) Flow cytometric DNA analysis of normal and cancerous human endometrium and cytological-histopathological correlations. *Anticancer Res* 7: 781-789.

10. Lindahl B, Alm P, Fernö M, Killander D, Långström E, et al. (1987) Prognostic value of flow cytometrical DNA measurements in stage I-II endometrial carcinoma: correlations with steroid receptor concentration, tumor myometrial invasion, and degree of differentiation. *Anticancer Res* 7: 791-797.
11. Iversen OE, Utaaker E, Skaarland E (1988) DNA ploidy and steroid receptors as predictors of disease course in patients with endometrial carcinoma. *Acta Obstet Gynecol Scand* 67: 531-537.
12. Rosenberg P, Wingren S, Simonsen E, Stål O, Risberg B, et al. (1989) Flow cytometric measurements of DNA index and S-phase on paraffin-embedded early stage endometrial cancer: an important prognostic indicator. *Gynecol Oncol* 35: 50-54.
13. van der Putten HW, Baak JP, Koenders TJ, Kurver PH, Stolk HG, et al. (1989) Prognostic value of quantitative pathological features and DNA content in individual patients with stage I endometrial carcinoma. *Cancer* 63: 1378-1387.
14. Britton LC, Wilson TO, Gaffey TA, Cha SS, Wieand HS, et al. (1990) DNA ploidy in endometrial carcinoma: major objective prognostic factor. *Mayo Clin Proc* 65: 643-650.
15. Newbury R, Schuerch C, Goodspeed N, Fanning J, Glidewell O, et al. (1990) DNA content as a prognostic factor in endometrial carcinoma. *Obstet Gynecol* 76: 251-257.
16. Lindahl B, Gullberg B (1991) Flow cytometrical DNA-ploidy and clinical parameters in the prediction of prognosis in stage I-II endometrial cancer. *Anticancer Res* 11: 397-401.
17. Dyas CH, Simmons TK, Ellis CN, Austin JM Jr, Partridge EE Jr, et al. (1992) Effect of deoxyribonucleic acid ploidy status on survival of patients with carcinoma of the endometrium. *Surg Gynecol Obstet* 174: 133-136.
18. Ambros RA, Kurman RJ (1992) Identification of patients with stage I uterine endometrial adenocarcinoma at high risk of recurrence by DNA ploidy, myometrial invasion, and vascular invasion. *Gynecol Oncol* 45: 235-239.
19. Ikeda M, Watanabe Y, Nanjoh T, Noda K (1993) Evaluation of DNA ploidy in endometrial cancer. *Gynecol Oncol* 50: 25-29.
20. Melchiorri C, Chieco P, Lisignoli G, Marabini A, Orlandi C (1993) Ploidy disturbances as an early indicator of intrinsic malignancy in endometrial carcinoma. *Cancer* 72: 165-172.
21. Sorbe B, Risberg B, Thornthwaite J (1994) Nuclear morphometry and DNA flow cytometry as prognostic methods for endometrial carcinoma. *Int J Gynecol Cancer* 4: 94-100.
22. Von Minckwitz G, Kühn W, Kaufmann M, Feichter GE, Heep J, et al. (1994) Prognostic importance of DNA-ploidy and S-phase fraction in endometrial cancer. *Int J Gynecol Cancer* 4: 250-256.
23. Susini T, Rapi S, Savino L, Boddi V, Berti P, et al. (1994) Prognostic value of flow cytometric deoxyribonucleic acid index in endometrial cancer: comparison with other clinical-pathologic parameters. *Am J Obstet Gynecol* 170: 527-534.
24. Nordström B, Strang P, Lindgren A, Bergström R, Tribukait B (1996) Carcinoma of the endometrium: do the nuclear grade and DNA ploidy provide more prognostic information than do the FIGO and WHO classifications? *Int J Gynecol Pathol* 15: 191-201.
25. Zaino RJ, Davis AT, Ohlsson-Wilhelm BM, Brunetto VL (1998) DNA content is an independent prognostic indicator in endometrial adenocarcinoma: a Gynecologic Oncology Group study. *Int J Gynecol Pathol* 17: 312-319.
26. Susini T, Rapi S, Massi D, Savino L, Amunni G, et al. (1999) Preoperative evaluation of tumor ploidy in endometrial carcinoma: an accurate tool to identify patients at risk for extrauterine disease and recurrence. *Cancer* 86: 1005-1012.
27. Lundgren C, Auer G, Frankendal B, Moberger B, Nilsson B, et al. (2002) Nuclear DNA content, proliferative activity, and p53 expression related to clinical and histopathologic features in endometrial carcinoma. *Int J Gynecol Cancer* 12: 110-118.
28. Mangili G, De Marzi P, Viganò R, Rabaiotti E, Sassi I, et al. (2002) Identification of high risk patients with endometrial carcinoma: prognostic assessment of endometrial cancer. *Eur J Gynaecol Oncol* 23: 216-220.
29. Santala M, Talvensaaari-Mattila A (2003) DNA ploidy is an independent prognostic indicator of overall survival in stage I endometrial endometrioid carcinoma. *Anticancer Res* 23: 5191-5196.
30. Lundgren C, Auer G, Frankendal B, Nilsson B, Nordström B (2004) Prognostic factors in surgical stage I endometrial carcinoma. *Acta Oncol* 43: 49-56.
31. Susini T, Amunni G, Molino C, Carriero C, Rapi S, et al. (2007) Ten-year results of a prospective study on the prognostic role of ploidy in endometrial carcinoma. *Cancer* 109: 882-890.
32. Suehiro Y, Okada T, Okada T, Anno K, Okayama N, et al. (2008) Aneuploidy predicts outcome in patients with endometrial carcinoma and is related to lack of CDH13 hypermethylation. *Clin Cancer Res* 14: 3354-3361.
33. Friberg LG, Norén H, Delle U (1994) Prognostic value of DNA ploidy and S-phase fraction in endometrial cancer stage I and II: a prospective 5 year survival study. *Gynecol Oncol* 53: 64-69.
34. Britton LC, Wilson TO, Gaffey TA, Lieber MM, Wieand HS, et al. (1989) Flow cytometric DNA analysis of stage I endometrial carcinoma. *Gynecol Oncol* 34: 317-322.
35. Mangili G, Montoli S, De Marzi P, Sassi I, Aletti G, et al. (2008) The role of DNA ploidy in postoperative management of stage I endometrial cancer. *Ann Oncol* 19: 1278-1283.
36. Larson DM, Berg R, Shaw G, Krawisz BR (1999) Prognostic significance of DNA ploidy in endometrial cancer. *Gynecol Oncol* 74: 356-360.
37. Konski A, Domenico D, Tyrkus M, Irving D, Neisler J, et al. (1996) Prognostic characteristics of surgical stage I endometrial adenocarcinoma. *Int J Radiat Oncol Biol Phys* 35: 935-940.
38. Mariani A, Sebo TJ, Webb MJ, Riehle D, Katzmann JA, et al. (2003) Molecular and histopathologic predictors of distant failure in endometrial cancer. *Cancer Detect Prev* 27: 434-441.
39. Ørbo A, Rydningren M, Straume B, Lysne S (2002) Significance of morphometric, DNA cytometric features, and other prognostic markers on survival of endometrial cancer patients in northern Norway. *Int J Gynecol Cancer* 12: 49-56.
40. Lundgren C, Frankendal B, Silfverswärd C, Nilsson B, Tryggvason K, et al. (2003) Laminin-5 γ 2-chain expression and DNA ploidy as predictors of prognosis in endometrial carcinoma. *Med Oncol* 20: 147-155.
41. Terada K, Mattson D, Goo D, Shimizu D (2004) DNA aneuploidy is associated with increased mortality for stage I endometrial cancer. *Gynecol Oncol* 95: 483-487.
42. Osmanağaoğlu MA, Kadioğlu S, Osmanağaoğlu S, Bozkaya H, Reis A, et al. (2005) The relationship between mutant p53 gene, DNA contents and conventional clinicopathological prognostic variables in cases with endometrial carcinoma. *Eur J Gynaecol Oncol* 26: 64-70.
43. Pfisterer J, Kommos F, Sauerbrei W, Rendl I, Kiechle M, et al. (1995) Prognostic value of DNA ploidy and S-phase fraction in stage I endometrial carcinoma. *Gynecol Oncol* 58: 149-156.
44. Naumann RW, Coleman RL (2007). The use of adjuvant radiation therapy in early endometrial cancer by members of the Society of Gynecologic Oncologists in 2005. *Gynecol Oncol* 105: 7-12.
45. Lim P, Aquino-Parsons CF, Wong F, Dupuis B, Phillips D, et al. (1999) Low-risk endometrial carcinoma: assessment of a treatment policy based on tumor ploidy and identification of additional prognostic indicators. *Gynecol Oncol* 73: 191-195.
46. Hogberg T, Fredstorp-Lidebring M, Alm P, Baldetorp B, Larsson G, et al. (2004) Southern Swedish Gynecologic Oncology Group. A prospective population-based management program including primary surgery and postoperative risk assessment by means of DNA ploidy and histopathology. Adjuvant radiotherapy is not necessary for the majority of patients with FIGO stage I-II endometrial cancer. *Int J Gynecol Cancer* 14: 437-450.
47. Song T, Lee JW, Kim HJ, Kim MK, Choi CH, et al. (2011) Prognostic significance of DNA ploidy in stage I endometrial cancer. *Gynecol Oncol* 122: 79-82.
48. Pradhan M, Abeler VM, Danielsen HE, Sandstad B, Tropé CG, et al. (2012) Prognostic importance of DNA ploidy and DNA index in stage I and II

endometrioid adenocarcinoma of the endometrium. *Ann Oncol* 23: 1178–1184.

49. Pradham M, Davidson B, Abeler VM, Danielsen HE, Tropé CG, et al. (2012) DNA ploidy may be a prognostic marker in stage I and II serous adenocarcinoma of the endometrium. *Virchows Arch* 461: 291-298.

50. Pradhan M, Abeler VM, Danielsen HE, Tropé CG, Risberg BA (2006) Image cytometry DNA ploidy correlates with histological subtypes in endometrial carcinomas. *Mod Pathol* 19: 1227-1235.

51. Terada K (2012) DNA ploidy in endometrial cancer: unfinished business? *Ann Oncol* 23: 1083-1084.


52. Lindahl B, Måsbäck A, Persson J, Ranstam J, Willén R (2009) Adenocarcinoma corpus uteri stage I-II: results of a treatment programme based upon cytometry. *Anticancer Res* 29: 4731-4735.

Author Affiliations

[Top](#)

¹Department of Gynecology & Obstetrics, Vita Salute San Raffaele University School of Medicine, Ospedale San Raffaele Scientific Institute, Milano, Italy
²Obstetrics and Gynecology Unit, Ospedali Riuniti di Bergamo, Italy

Submit your next manuscript and get advantages of SciTechnol submissions

- ❖ 50 Journals
- ❖ 21 Day rapid review process
- ❖ 1000 Editorial team
- ❖ 2 Million readers
- ❖ More than 5000 
- ❖ Publication immediately after acceptance
- ❖ Quality and quick editorial, review processing

Submit your next manuscript at • www.scitechnol.com/submission