Correlation between tumour size and Lymphatic spread in cases of type I endometrial carcinoma

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Abstract

Introduction and Objectives: Endometrial cancer is the most common malignancy of the female genital tract in the world. The lymphatic spread is the most frequent pathway for spread. It primarily involves the pelvic lymph nodes. It was suggested recently that tumour size (TS) may be a risk factor for lymph node (LN) metastases.

The aim of the present study was to assess the relationship between tumour size and pelvic lymph node metastasis in patients undergoing surgical staging for type-1 (endometrioid) endometrial adenocarcinoma, in order to plan for proper surgical approach.

Patients and Method: A total of 29 patients with type I (endometrioid) endometrial adenocarcinoma, were included. TS was obtained through detailed ultrasound (U/S). It was defined as the largest of the three dimensions of the tumour. All cases were subjected to total hysterectomy with bilateral salpingo-oophorectomy & bilateral pelvic lymphadenectomy. TS was re-assessed pathologically. The main outcome was to assess the relation between TS (by ultrasound and by pathologically) and LN metastasis. Correlation between TS and other prognostic factors such as grade, stage, and lympho-vascular space involvement, were also studied as secondary outcomes

Results: Tumour sizes by U/S and by gross pathologic examination were significantly related to LN metastasis (p=0.009 and 0.011 respectively). There was agreement between TS measured by U/S and by pathologic examinations, (ICC) = 0.975 (95% CI 0.946-0.988) (F=39.376, p=0.000*)).

The TS measured by U/S was a statistically significant discriminator of LN metastasis (AUC = 0.867 (95% CI 0.689-0.964) (Z=3.810, p=0.0001)), with a cut off value of 4.50 cm (sensitivity=80.00%, specificity=79.17%, PPV=44.4% and NPV=95.0%). Similarly, the TZ measured by pathology was also statistically significant discriminator of LN metastasis (AUC=0.858 (95% CI 0.679-0.959) (Z=3.346, p=0.0008)), with a cut off value of 5.00 cm (sensitivity=80%, specificity=91.67%, PPV=66.7%, NPV=95.7%).

Conclusions: Assessment of TS by U/S and by pathologic examination are comparable in cases of type I (endometrioid) endometrial adenocarcinoma. Both methods are reliable in predicting pelvic LN metastasis with a cut off value of 4.5 cm and 5 cm respectively. Preoperative assessment by U/S is more practical and useful in planning the extent of surgery and the need for pelvic lymphadenectomy.

Keywords: Endometrial cancer, Endometrioid adenocarcinoma, Pelvic lymph nodes, Lymphadenectomy, Tumour size.

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Introduction

Endometrial cancer is the most common malignancy of the female genital tract in the world, and is the seventh most common cause of death from cancer in women in Western Europe.[1] The incidence has considerably increased during the last three decades and it is currently the fourth most frequent cancer among women, exceeded only by cancer of the breast, lung, and colorectal cancers.[2] More than 90% of cases occur in women older than 50 years of age, with a median age of 63 years.[1]

Multiple risk factors have been identified; patients with endometrial cancer have an identifiable source of excess oestrogen and typically display a characteristic clinical profile comprising a high body mass index (BMI), often with other components of metabolic syndrome (e.g. hypertension, diabetes). The evidence that greater body fatness (reflected by BMI, measures of abdominal girth, and adult weight gain) is a cause of endometrial cancer is convincing. Glycaemic load is probably a cause of endometrial cancer, while the evidence suggesting that sedentary habits (marked by sitting time) and adult attained height as causes of endometrial cancer is limited. Nulliparity and infertility are also classical risk factors for endometrial cancer. Among the causes of infertility, polycystic ovarian syndrome (PCOS) seems to be the most important.[3,4]

Other risk factors are early onset of menstruation, late menopause, hypertension, unopposed oestrogen exposure and tamoxifen. In addition, up to 5% of endometrial cancers are associated with Lynch syndrome type II (known as hereditary non-polyposis colorectal carcinoma syndrome).[3]

Based on histopathology, molecular profile and clinical course, endometrial cancers are divided into two categories. Type I which are typically endometrioid, low-grade (I–II) adenocarcinomas that are usually oestrogen related, they are diagnosed early and have a favourable prognosis. And type II endometrial cancers that are not hormone dependent and are usually grade III endometrioid adenocarcinomas, papillary serous, clear cell

carcinomas and carcinosarcomas (malignant mixed Mullerian tumours). They have p53 mutations and loss of heterozygosity at several chromosomal loci. They are associated with early spread and worse prognosis.[1]

The lymphatic spread is the most frequent pathway occurring three times more than the blood spread, and it allows malignant cells to reach the parametrium, vagina, ovaries, and retroperitoneal pelvic and para-aortic lymph nodes. In general, this type of cancer primarily involves the pelvic lymph nodes: external iliac, internal iliac, common iliac (medial and lateral) and obturator (external and internal in relation with the obturator nerve).[5]

Recent guidelines have divided endometrial cancer patients into two groups based on the biological character of the malignancy. These two groups are, high risk (undifferentiated cancer of any stage or deeply infiltrating cancer besides the stage), here complete intensive surgical staging is required. And low-risk (initially infiltrating cancer, G1–G2) where less invasive approach may be performed.[6]

Risk factors for the recurrence of endometrial carcinoma can be divided into uterine and extrauterine factors. Uterine factors include histologic type, grade, depth of myometrial invasion, cervical involvement, vascular invasion, presence of atypical endometrial hyperplasia, hormone receptor status and DNA ploidy. While extrauterine factors include adnexal involvement, intraperitoneal metastasis, positive peritoneal cytology and pelvic and para-aortic lymph node metastasis.[7,8,9,10,11]

Studies have demonstrated an important association between tumour size (TS) and the risk of lymph node (LN) metastases. Accumulating evidence suggests that the estimation of TS may improve endometrial cancer treatment.[7,12]

The advantage of using TS is based on the fact that it is readily discernible and does not require extra resources or an experienced pathologist. On the other hand, intra-operative evaluation of other prognostic factors such as grade and myometrial invasion requires a well-trained pathologist, which is resource intensive and can vary depending on frozen or paraffin sections.[13,14]

Objectives

The aim of the present study was to assess the relationship between tumour size and pelvic lymph node metastasis in patients undergoing surgical staging for type-1 (endometrioid) endometrial adenocarcinoma, in order to plan for proper surgical approach.

Patients and Method

This study is a prospective observational study. It was conducted between 1st of June 2016, till 31st of December 2016. The study was done after taking the permission from the local ethical committee in accordance with the ethical standards of the responsible committee on human experimentation of Alexandria faculty of medicine in Egypt.

Patient Selection and Procedures: Cases were selected from those attending the Gynae-Oncology Unit of El-Shatby Maternity University Hospital, in Alexandria Egypt.

A total of 29 patients were included. They were diagnosed previously as type I (endometrioid) endometrial adenocarcinoma and were planned for total hysterectomy. Exclusion criteria were type II or stage IV endometrial carcinoma, cases unfit for major surgery and presence of any other concomitant malignancy (genital or extra-genital), and those who received pre-operative radio-therapy or hormonal therapy.

After revision of all patients' clinical data and endometrial biopsies (or sampling) results (previously obtained to confirm diagnosis), Oral and written informed consents were taken.

For all participants, the tumour size (TS) was obtained through a detailed grey-scale 2D trans-vaginal and trans-abdominal ultrasound (U/S). It was defined as the largest of the three dimensions of the tumour.[15] All U/S examinations and assessments of tumour dimensions were performed by a single expert radiologist, within 10 days prior sampling of the endometrial biopsy.

All cases were subjected to total hysterectomy with bilateral salpingo-oophorectomy & bilateral pelvic lymphadenectomy (cases where lymphadenectomy was not done were excluded from the study).

All specimens were then subjected to detailed histopathologic evaluation, according to the protocol for examination of specimens obtained from patients with carcinoma of the endometrium published by the Collage of American Pathologists (CAP) 2016.[16] The largest dimension of each tumour was re-assessed pathologically and patients were staged according to the FIGO (International Federation of Gynaecology and Obstetrics) 2009 staging review.[17]

Lymph nodes (LNs) were studied considering positive or negative nodes independently of their number or percentage.

Outcomes: The main outcome was to assess the relation between TS (measured by ultrasound and by pathological examination) and LN metastasis in cases of type I (endometrioid) endometrial adenocarcinoma.

The correlation between the TS and other prognostic factors such as grade, stage, and lympho-vascular space involvement, were also studied as secondary outcomes.

Statistical Methodology: Data were collected and entered to the computer using SPSS (Statistical Package for Social Science) program for statistical analysis (version 21).[18]

Data were entered as numerical or categorical, as appropriate. Kolmogorov-Smirnov test of normality revealed significance in the distribution of some

variables, so the non-parametric statistics was adopted.[19]

Data were described using minimum, maximum, median and inter-quartile range for not-normally distributed data. Categorical variables were described using frequency and percentage of total. Comparisons were carried out between two studied independent not-normally distributed subgroups using Mann-Whitney U test.[20] Chi-square test was used to test association between qualitative variables. Monte Carlo correction was carried out when indicated (expected cells less than 5).[21]

The intra-class correlation and Bland-Altman plot were used to quantify the degree to agreement (reliability) between U/S and pathological size.[22,23] Box and Whiskers graphs were used. Area under the ROC (AUC) was carried using MedCalc Software version 14.[24,25] An alpha level was set to 5% with a significance level of 95%, and a beta error accepted up to 20% with a power of study of 80%.

Results

After application of inclusion and exclusion criteria, 29 cases with type I (endometrioid) endometrial adeno-carcinoma were recruited and subjected to total hysterectomy with bilateral salpingo-oophorectomy & bilateral pelvic lymphadenectomy. All specimens were subjected to detailed histopathologic evaluation using the CAP system. Data were collected, tabulated and analysed.

Patients' and tumour characteristics are shown in Table 1. The median age of studied cases was 60 years (ranging from 30 to 74), and the median calculated tumour size by U/S was 3.5 cm (ranging from 1.5 to 8 cm).

After pathological examination of the excised specimens, the median pathologically-measured tumour size was 4.0 cm (ranging from 1.5 to 10 cm), the majority of cases were grade II (moderately differentiated); 17 cases (58.6%), and most of them were among stage Ia (tumour involves < half myometrial thickness;[17] 19 cases (65.5%). 19 cases had LVSI (65.5%), and positive LN affection was detected in 5 cases (17.2%).

Table 1: Patients' and tumour characteristic features

	Number	Percent
Patient age (in years)		
- Min-Max	30.0-74.0	
- Mean ± S.D.	57.68 ± 10.93	
- Median	60.0	
Tumour size by ultrasound (in cm)		
- Min-Max	1.5-8.00	
- Mean ± S.D.	3.83 ± 1.98	
- Median.	3.5	
Tumour size by pathology (in cm)		
- Min-Max	1.5-10	
- Mean ± S.D.	4.06 ± 2.59	
- Median.	4.0	
Tumour Grade		
I	8	27.6
II	17	58.6
III	4	13.8
Tumour Stage		
Ia	19	65.5
Ib	7	24.1
IIIa	2	6.9
IIIb	1	3.4
LVSI		
-ve	19	65.5
+ve	10	34.5
LN metastasis		
-ve	24	82.8
+ve	5	17.2

Min: Minimum,
Max: Maximum,
S.D.: Standard deviation,
LVSI: Lympho-Vascular Space Invasion.
L.N.: Lymph Node.

When correlated to LN affection, tumour sizes by US and by gross pathologic examination were significantly related to LN metastasis; (*p*=0.009 and 0.011 respectively), as shown in Table 2, Fig. 1.

Table 2: Relation between tumour size and lymph node metastasis

	Lymph Node Metastasis		Significance (p value)
	Negative (n=24)	Positive (n=5)	
Size (by ultrasound)			
- Min-Max	1.50-6.50	3.50-8.00	$Z_{(MW)}$=2.556
- Mean ± S.D.	3.39±1.429	5.90±1.746	p=0.009*
- Median (IQR)	3.50 (2.00-4.50)	6.00 (4.25-7.50)	
- KS test	D=0.169, p=0.075 NS	D=0.136, p=0.200 NS	
Size (by pathology)			
- Min-Max	1.50-8.00	3.50-10.00	$Z_{(MW)}$=2.505
- Mean ± S.D.	3.52±1.658	6.50±2.345	p=0.011*
- Median (IQR)	3.75 (2.00-4.75)	6.00 (4.75-8.50)	
- KS test	D=0.154, p=0.147 NS	D=0.216, p=0.200 NS	

Min: Minimum,
Max: Maximum,
S.D.: Standard deviation,
IQR: Inter-quartile range,
KS: Kolmogorov-Smirnov test of normality,
MW: Mann-Whitney U test,
MC: Monte Carlo correction of Chi-Square significance
*: statistically significant (p<0.05)
NS: not statistically significant (p>0.05)

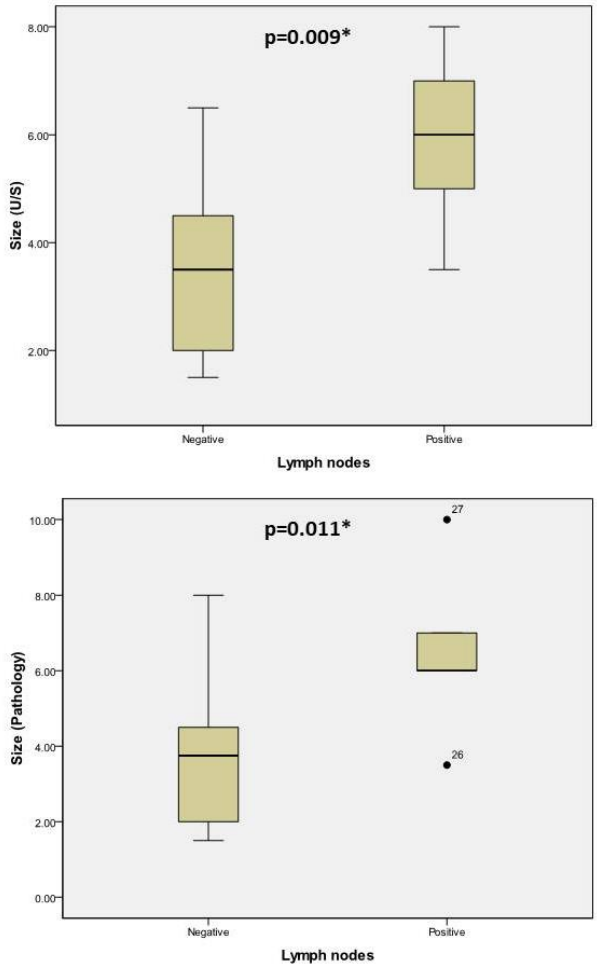

Fig. 2: Relation between tumour size and lymph node metastasis

When the two used methods for assessment of TS were compared, results showed agreement between TS measured by U/S and by pathologic examinations, as shown in Fig. 2. The intra-class correlation coefficient (ICC) = 0.975 (95% CI 0.946-0.988) (F=39.376, p=0.000*)

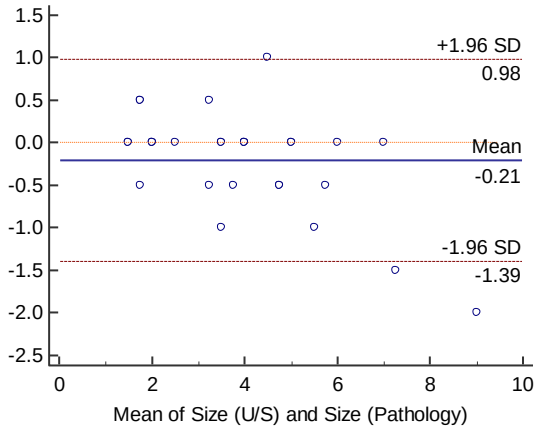

Fig. 2: Bland and Altman plot, showing the agreement between tumour size measured by ultrasound and by pathologic examinations

Diagnostic test accuracy statistics **(Area under the Receiver Operators Characteristics (ROC) curve):** The TS measured by U/S (in cms) was a statistically significant discriminator of LN metastasis with Area Under the ROC Curve (AUC) = 0.867 (95% CI 0.689-0.964) (Z=3.810, p=0.0001). The diagnostic criterion using Youden index is the level of >4.50 cm with a sensitivity of 80.00% (95%CI 28.4-99.5%), specificity

of 79.17% (95%CI 57.8-92.9%), Positive predictive value (PPV) of 44.4% and negative predictive value of 95.0%.

While the TZ measured by pathology (in cms) was also statistically significant discriminator of LN metastasis with Area Under the ROC Curve (AUC) = 0.858 (95% CI 0.679-0.959) (Z=3.346, p=0.0008). The diagnostic criterion using Youden index is the level of >5.00 cm with a sensitivity of 80% (95%CI 28.4-99.5%), specificity of 91.67% (95%CI 73.0-99.0%), Positive predictive value (PPV) of 66.7% and negative predictive value of 95.7%.

Pairwise comparison for the two ROC curves revealed statistically non-significant difference (Z=0.280, p=0.7793) (using Delong method, De long et al., 1988). (Fig. 3 and 4)

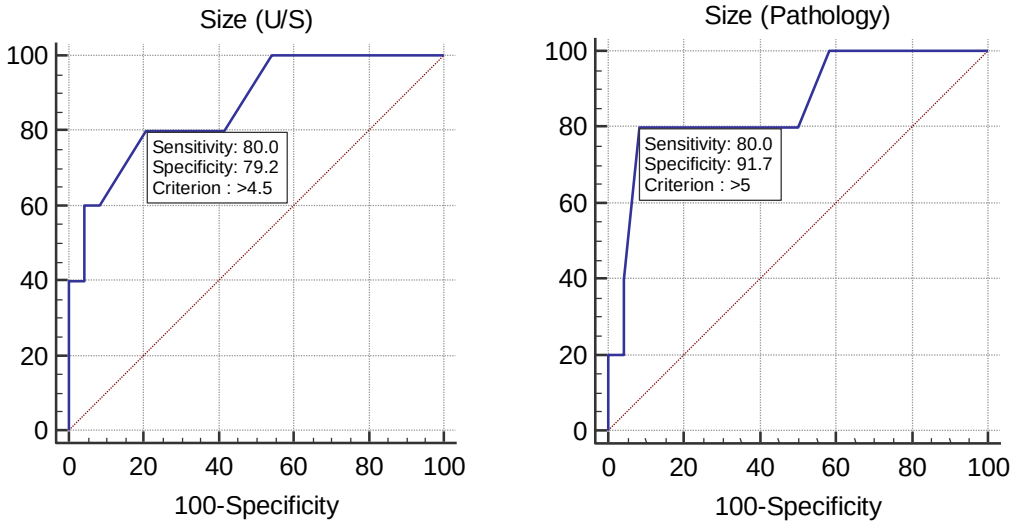

Fig. 3: Detection of lymph node metastasis by tumour size measured by both ultrasound (U/S) and pathology. Area under the ROC curve for lymph node metastasis

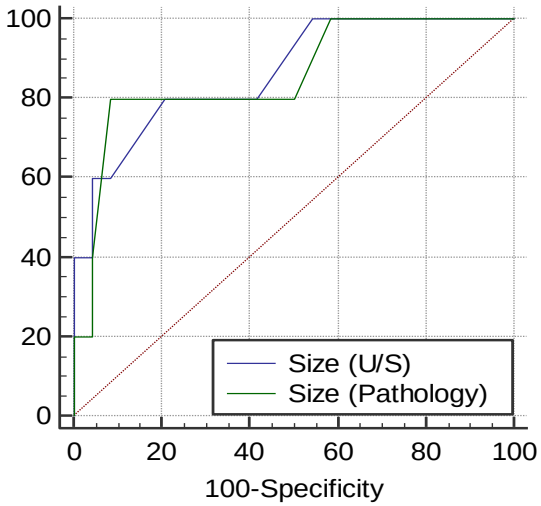

Fig. 4: Pairwise comparison for the two ROC curves for detection of lymph node metastasis by tumour size measured by both ultrasound (U/S) and pathology. Area under the ROC curve for lymph node metastasis

Discussion

Pelvic lymphadenectomy during surgical staging for endometrial cancer is still a controversial issue. Recent recommendations have limited lymphadenectomy to intermediate-high risk cancers; those with more than 50% myometrial invasion, grades II and III endometrioid carcinoma, and type II (non-endometrioid) endometrial cancer.[26]

This prospective study was carried out to assess the relation between TS and pelvic LN metastasis in cases planned for surgical staging for type I endometrial adenocarcinoma, and if this could be considered as a reliable risk factor that may guide for the decision of pelvic lymphadenectomy during surgery.

To our knowledge, all the previous similar researches which related TS to LN metastasis and/or other prognostic factors for endometrial cancer have assessed TS by gross pathologic examination rather than by U/S examination.[7,27,28]

We thought that assessing TZ by U/S will be more reliable, as this tool is available pre-operatively and would guide decision making for proper surgical approach or at least for selecting more qualified surgeons or estimating the possible duration of surgery.

The current study is the first one that utilises U/S (rather than pathology) in assessment of TS in order to relate it to LN metastasis. Not only that, we also detected an agreement between both methods (U/S and pathologic examination) in measuring TS, and thus, could be used for prediction of pelvic LN metastasis, but with a different cut off values (4.5 cm for TS by U/S, and 5 cm for TS by pathology).

Thirty four cases were primary enrolled in the present study, 5 cases were excluded; two were stage IV (and started adjuvant chemotherapy), two others had

only total hysterectomy with bilateral salpingo-oophorectomy without lymphadenectomy due to morbid obesity and operative difficulty. And the last one -82 years- died due to cardiac arrest prior scheduling for laparotomy.

Our results showed that TS can be utilized to verify the presence of pelvic LN metastasis, with cut off value of 4.5 cm for measuring TS by U/S, and of 5 cm for measuring TS by gross pathology.

In 2010, ESMO (European Society for Medical Oncology) guidelines have published that TS and location are to be considered in assessment of endometrial cancer, although not included in the FIGO (International Federation of Gynaecology and Obstetrics) staging.[1] The same was published by the NCCN (National Comprehensive Cancer Network) guidelines, 2013, they stated that patients with stage I endometrial cancer and who are completely surgically staged are stratified by adverse risk factors (i.e. age, positive lympho-vascular space invasion, tumour size, and lower uterine (cervical/glandular) segment involvement.[29] No additional considerations were published in the guidelines of ESMO-ESGO-ESTRO Consensus Conference on Endometrial Cancer in 2016.[12] and the more recent NCCN guidelines in 2017.[30]

In a previous study in 1991, Lurain et al reported decrease in the risk of lymph node metastases and an increase of survival in tumours <2 cm.[31]

In more recent studies, other (higher) cut off values were reported to predict LN metastasis. One hundred forty seven cases of endometrial carcinoma were studied by Berretta et al, they have found that a marked correlation existed between tumour largest diameter and nodal metastases. The average dimension of tumour with nodal metastases was 6.3 cm (±3.1) and the median was 6.5 cm. The correlation coefficient was 0.003 ($p<0.01$).[7] This cut off value was close to the one estimated by pathology in the current study (5 cm).

Senol et al, have stated that tumour diameter was found to be predictor for recurrence with higher values than generally accepted.[32] Similarly, Mahdi et al, reported that TS was an independent predictor of LN metastasis and disease-specific survival in patients with endometrioid endometrial carcinoma grossly confined to the uterus (stage I). Tumour (5 cm) was a predictor of disease-specific survival but no difference in outcome was noted between tumour (2–5 cm) and tumour (<2 cm).[27]

In a more recent study in 2016, Canlorbe et al have stated that TS was an independent prognostic factor of LN involvement in women with low-risk endometrial cancer and could be a valuable additional histological criterion for selecting women at increased risk of LN metastases to better adapt surgical staging. Again they assessed TS pathologically, and reported that TS < 35 mm was emerged as the optimal threshold for a higher rate of nodal involvement and a lower recurrence-free survival in women with low-risk endometrial cancer associated with LN metastases to better adapt surgical staging.[28]

Conclusions and Recommendations

We concluded that preoperative assessment of TS by U/S is comparable to postoperative assessment by pathologic examination of the excised biopsies, in cases of type I (endometrioid) endometrial adenocarcinoma. Both methods are reliable in predicting pelvic LN metastasis with a cut off value of 4.5 cm and 5 cm respectively.

Preoperative assessment by U/S may be considered more practical and useful in planning the extent of surgery and the need for pelvic lymphadenectomy.

However, the relatively small number of cases in the current study may be a limitation. Therefore, we recommend establishment of more studies with larger numbers to confirm the calculated results.

We also recommend assessment of TS by measuring tumour volume (using the three dimensions) rather than the biggest diameter; this may elicit more precise results.

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