



**Oncological outcome after completing or abandoning (radical) hysterectomy in patients with cervical cancer and intraoperative detection of LN positivity**

## **ABRAX (ABandoning RAd hyst in cerviX cancer)**

Retrospective cohort study

<b>Protocol ID:</b>	CEEGOG CX2 ENGOT-Cx3/CEEGOG/ABRAX
<b>Version:</b>	v1.0
<b>Date:</b>	14-May-2017
<b>Author:</b>	David Cibula

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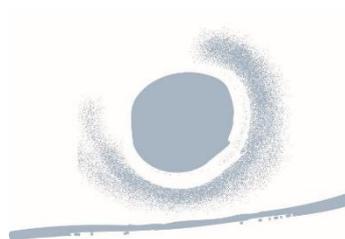
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**STUDY DESIGN:**

**International, Multicentric, Retrospective Cohort**

<b>NAME</b>	David Cibula, M.D., Ph.D., Professor
<b>DATE OF SIGNATURE</b>	14 / May / 2017
<b>TRIAL CHAIRMAN SIGNATURE</b>	

# 1. Protocol Synopsis

Acronym	ABRAX (ABandoning RAD hyst in cerviX cancer)
ID	CEEGOG CX2 ENGOT-Cx3/CEEGOG/ABRAX
Full Title	Oncological outcome after completing or abandoning (radical) hysterectomy in patients with cervical cancer and intraoperative detection of LN positivity
Primary end point	Progression free survival (PFS)
Secondary end points	<ol style="list-style-type: none"> <li>1) Prevalence of <math>\geq</math> G2 treatment related morbidity (CTCAE)</li> <li>2) Overall survival (OS)</li> <li>3) Pelvic PFS</li> <li>4) Oncological outcome after stratification according to the prognostic parameters such as tumour size, number of involved LN, type of metastases, presence of LVSI, histological type</li> </ol>
Objectives	<ol style="list-style-type: none"> <li>1) To determine if the performance of radical hysterectomy improves oncological outcome in patients with intraoperative detection of LN involvement (comparing to radio(chemo)therapy alone)</li> <li>2) Compare the prevalence of <math>\geq</math> G2 treatment-related morbidity between the group with or without radical hysterectomy</li> <li>3) Evaluate if the survival benefit of radical hysterectomy is modified by prognostic parameters (tumour size, histological type, type of metastases, presence of LVSI, number of involved LN)</li> </ol>
Inclusion criteria	<ul style="list-style-type: none"> <li>✓ Histologically confirmed squamous cell carcinoma, adenocarcinoma, adenosquamous carcinoma</li> <li>✓ Stage pT1a – pT2b</li> <li>✓ Patient referred for primary surgical treatment (neoadjuvant chemotherapy is not an exclusion criteria) intended to perform LN staging followed by radical / simple hysterectomy or fertility-sparing procedure (FST)</li> <li>✓ <b>Intraoperative detection of LN involvement (any type of metastasis):</b> <ul style="list-style-type: none"> <li>○ <b>Macroscopic involvement = grossly involved lymph nodes (if confirmed by final pathology)</b></li> <li><b>OR</b></li> <li>○ <b>Microscopic involvement = SLN / LN intraoperative pathologic evaluation (frozen section)</b></li> </ul> </li> <li>✓ Follow-up data available for <math>\geq</math> 2 years</li> <li>✓ Surgery performed between January 2005 and December 2015</li> </ul>

<p>Eligibility for the study (the following cases can be included)</p>	<ul style="list-style-type: none"> <li>✓ Neoadjuvant chemotherapy</li> <li>✓ Any surgical approach (laparoscopy, laparotomy, robotic surgery)</li> <li>✓ SLN biopsy performed or not – with or without SLN pathologic ultrastaging</li> <li>✓ Paraaortic lymphadenectomy performed or not</li> <li>✓ Positive paraaortic lymph nodes</li> <li>✓ Pelvic lymphadenectomy completed or not</li> <li>✓ Any type of uterine procedure (simple hysterectomy, radical hysterectomy, fertility sparing procedure)</li> <li>✓ Any type of adjuvant treatment</li> <li>✓ Any preoperative staging strategy</li> <li>✓ Any surveillance strategy</li> </ul>
<p>Exclusion criteria</p>	<ul style="list-style-type: none"> <li>✓ <b>Preoperative evidence of grossly involved LN</b></li> <li>✓ Histologic subtypes other than those noted in the Inclusion criteria</li> <li>✓ <b>Negative pelvic LN</b></li> <li>✓ <b>LN involvement reported by the final histology but not detected during the surgery</b></li> <li>✓ Unavailability of follow-up data</li> </ul>

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## 2. Background

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The management of patients with intraoperative detection of LN involvement currently varies widely. Management options include completing or abandoning radical hysterectomy, performing or abandoning pelvic lymph node dissection (PLND) and even continuing with inframesenteric or infrarenal paraaortic lymph node dissection (PALND). The most significant aspect is the decision

regarding the performance of radical hysterectomy, due to the high morbidity caused by combined treatment composed of radical surgery and adjuvant radiotherapy in these patients<sup>1-2</sup>.

Thanks to the broader use of modern imaging technologies in pre-treatment work-up, the number of patients with an intraoperative finding of grossly involved LN has decreased. At the same time though, as an increasing number of institutions routinely perform SLN biopsy and submit SLNs for frozen section, microscopic LN positivity is more often detected intraoperatively.

Data on the oncologic outcome of patients with LN involvement after radical hysterectomy and adjuvant radiotherapy are broadly available. Recent figures show five-year survival in stage IB at around 70–85 %<sup>3-5</sup>. In contrast, the data on patients in whom radical hysterectomy was abandoned due to intraoperative detection of LN involvement are scarce. Available literature mostly refers to small groups of cases with grossly involved LN detected during surgery<sup>6-10</sup>. In the majority of papers, there is a trend towards longer PFI in patients with completed radical hysterectomy, while overall survival does not differ<sup>8-10</sup>. The results are, however, severely biased because retrospective groups in whom radical hysterectomy was abandoned had worse prognostic factors. The largest analysed series obtained data from the US-based SEER database (Surveillance, Epidemiology, and End Results)<sup>5</sup>. Even in such a robust national dataset of more than 3,100 patients, only a small subset of 50 cases in whom radical hysterectomy was abandoned intraoperatively was found. Overall, the five-year survival was identical to patients with completed radical hysterectomy (69% vs. 71%). However, the reliability of data is limited by its source, which is a retrospective national cancer database.

Current clinical practice remains divided. The main arguments used by supporters and opponents of both types of management are summarized in Table 1. The goal of this retrospective cohort study is to obtain the best data available from an adequate number of patients treated by both types of management in the same period of time and to analyse the risks and benefits of the performance of radical hysterectomy if LN involvement is detected intraoperatively in spite of non-suspicious preoperative radiological assessment. Another objective is to assess how the presence of selected factors with potential impact on the response to radiotherapy (histological type, size of tumour, number of positive LNs, size of LN metastases) can determine the benefit of the radical hysterectomy on oncological outcome.

Table 1: Arguments supporting either the performance of or abandoning radical hysterectomy after intraoperative detection of LN involvement

Reasons to abandon	Reasons to complete
<ul style="list-style-type: none"> <li>➤ Avoidance of morbidity related to radical hysterectomy itself</li> <li>➤ Lower morbidity related to radiotherapy if previous radical hysterectomy is avoided</li> <li>➤ Better oncological outcome due to the possibility of using brachytherapy</li> </ul>	<ul style="list-style-type: none"> <li>➤ Lower risk of central pelvis recurrence (especially in larger tumours or adenocarcinomas)</li> <li>➤ Lower morbidity due to the avoidance of brachytherapy</li> </ul>

### 3. Study limitations

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The retrospective nature is the major trial limitation. Taking into account a limited number of patients with intraoperative detection of LN involvement, a prospective design would be demanding if not undoable. Moreover, randomisation of patients would be difficult to conduct because individual institutions usually strongly prefer one of the two types of management tested in this trial.

A potential limitation is the selection of higher-risk patients for one preferred management. However, it can be hypothesized that no other prognostic risk factors are used in the majority of institutions for triaging these patients, and all cases with positive LN are managed by one preferred algorithm. Moreover, the oncological outcome will be adjusted to the presence of main prognostic factors in each group.

Due to a long-term study period, incomplete data might become another limitation, especially concerning radiotherapy or treatment-related morbidity. Mandatory variables have been identified in the database, a clinical monitor will review data, and cases with missing mandatory type of data will be excluded. One of the inclusion criteria is the requirement for availability of at least two-year follow-up data.

The assessment of treatment-related morbidity is one of the biggest challenges. The classification and evaluation of post-operative and post-radiation complications is, however, a difficult task even in prospective trials. The main reasons are the following: a) lack of a uniform classification system, b) a broad spectrum of complications, c) subjective evaluation of its causality. Due to the above-mentioned reasons, only more severe complications with a higher probability of reporting in medical charts will be documented in the study (see Chapter 7).

## 4. Study aims

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### Primary End-Point

Progression free survival (PFS)

### Secondary End-Point

1. Prevalence of  $\geq$  G2 treatment related morbidity (CTCAE)
2. Overall survival (OS)
3. Pelvic PFS
4. Oncological outcome after stratification according to the prognostic parameters such as tumour size, number of involved LN, type of metastases, presence of LVSI, histological type, neoadjuvant chemotherapy

### Objectives

1. To determine if the performance of radical hysterectomy improves oncological outcome in patients with intraoperative detection of LN involvement (compared to radio(chemo)therapy alone)
2. Compare the prevalence of  $\geq$  G2 treatment-related morbidity between the group with or without radical hysterectomy
3. Evaluate if the survival benefit of radical hysterectomy is modified by prognostic parameters (tumour size, histological type, type of metastases, presence of LVSI, number of involved LN)

## 5. Study description

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Patients with early stage (pT1a – pT2b) cervical cancer (squamous, adeno or adenosquamous), who did not have positive lymph nodes on preoperative imaging, who were scheduled for primary surgical treatment, and in whom metastatic involvement of pelvic LN was found during surgery either as a grossly (macroscopically) involved LN or on intraoperative pathology assessment (any type of metastasis), will be enrolled. Patients can be included irrespective of surgical approach (laparoscopy, robotic surgery, laparotomy) and surgical procedure performed (SLN biopsy yes or no, performance of PLND or PALND, type of (radical) hysterectomy). Figure 1 shows the algorithm of the selection of eligible candidates.

Data on patients' characteristics, disease characteristics at diagnosis, primary treatment, adjuvant treatment, serious treatment-related complications, and survival will be collected.

## Inclusion criteria

- ✓ Histologically confirmed squamous cell carcinoma, adenocarcinoma, adenosquamous carcinoma
- ✓ Stage pT1a – pT2b
- ✓ Patient referred for primary surgical treatment intended to perform LN staging followed by radical / simple hysterectomy or fertility-sparing procedure (FST)
- ✓ **Intraoperative detection of LN involvement (any type of metastasis):**
  - **Macroscopic involvement = grossly involved lymph nodes (if confirmed by final pathology)**
  - OR**
  - **Microscopic involvement = SLN / LN intraoperative pathologic evaluation (frozen section)**
- ✓ Follow-up data available for  $\geq 2$  years
- ✓ Surgery performed between January 2005 and December 2015

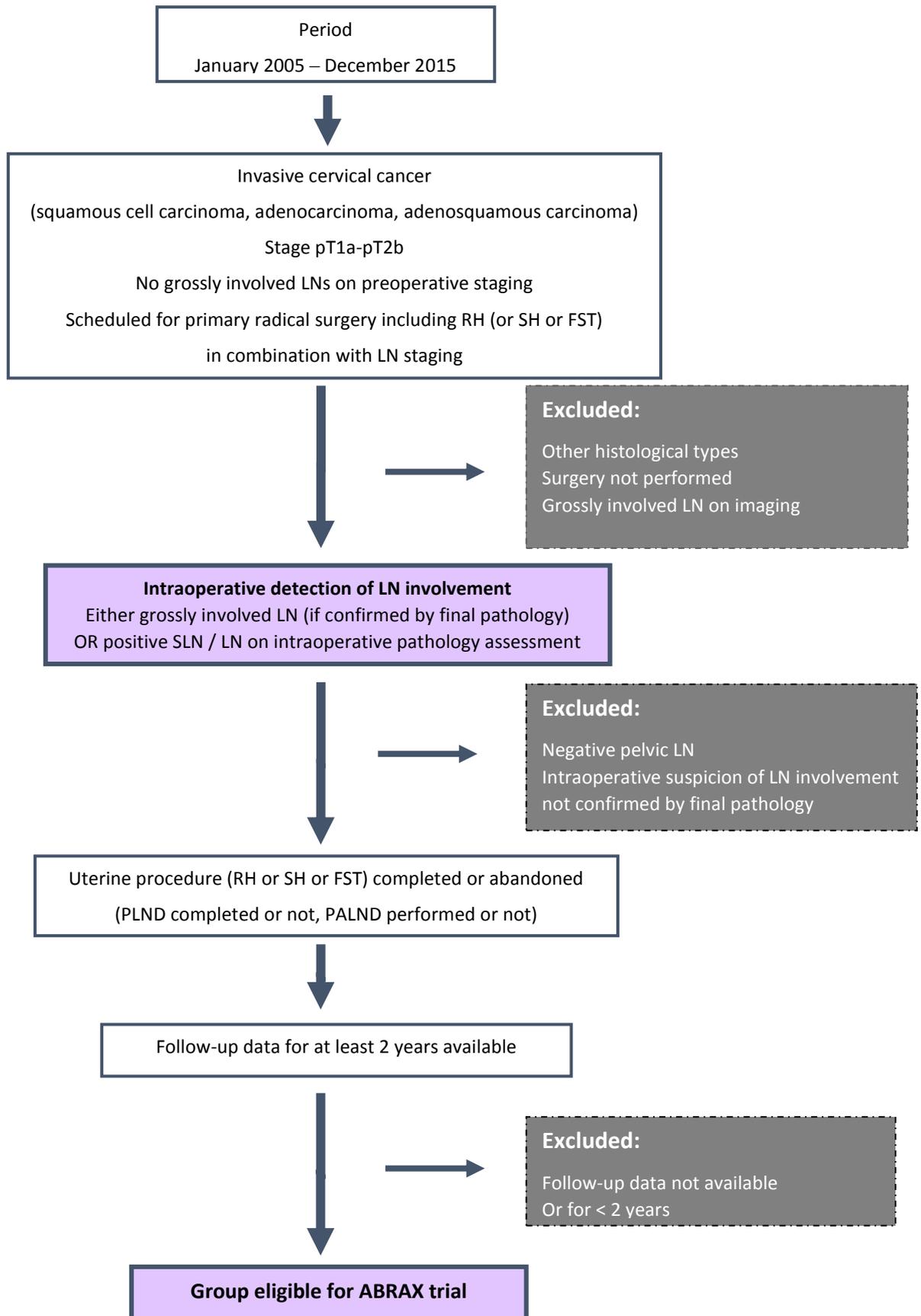
## Exclusion criteria

- ✓ **Preoperative evidence of grossly involved LN**
- ✓ Histologic subtypes other than those noted in the Inclusion criteria
- ✓ **Negative pelvic LN**
- ✓ **LN involvement reported by the final histology but not detected during the surgery**
- ✓ Unavailability of follow-up data

## Patients who are also eligible for the study

- ✓ Neoadjuvant chemotherapy given before surgery
- ✓ Any surgical approach (laparoscopy, laparotomy, robotic surgery)
- ✓ SLN biopsy performed or not – with or without SLN pathologic ultrastaging
- ✓ Paraaortic lymphadenectomy performed or not
- ✓ Pelvic lymphadenectomy completed or not
- ✓ Any type of uterine procedure (simple hysterectomy, radical hysterectomy, fertility sparing procedure)
- ✓ Any type of adjuvant treatment
- Any preoperative staging strategy
- ✓ Any surveillance strategy

## 6. Study setting



## 7. Reporting of treatment-related complications

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Only those complications that, in the investigator's opinion, are related to the cervical cancer treatment should be documented. Complications (adverse events) will be classified according to the NCI Common Terminology Criteria for Adverse Events Version 4.0 ([http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE\\_4.03\\_2010-06-14\\_QuickReference\\_5x7.pdf](http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf)). Comments were included for each category (Appendix 3) in order to make it more easily applicable to the assessment of late complications with an impact on the quality of life. Taking into account the limited reliability of retrospective evaluation of less serious adverse events, only complications of grade 2–5 will be retrospectively reported.

## 8. Type of metastases

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The type of metastases will be classified according to the TNM system. Macrometastases are defined as metastasis  $> 2$  mm in diameter, micrometastases are metastases  $> 0.2$  and  $\leq 2$  mm, and isolated tumour cells (ITCs) as individual tumour cells or small clusters of cells up to 0.2 mm in diameter or  $< 200$  cells.

## 9. Ethical committee approval

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It is the responsibility of participating institutions to receive the approval from the institutional ethical committee. Patients' consent is not required.

The study will be performed in accordance with the terms of the protocol, generally accepted standards of Good Clinical Practice and the investigators will adhere to all applicable laws and regulations governing the conduct of clinical trials, including but not limited to the ICH Harmonized Tripartite Guidelines for Good Clinical Practice and the Declaration of Helsinki.

The Investigator shall treat all information and data relating to the study as confidential and shall not disclose such information to any third parties or use such information for any purpose other than the performance of the study.

## 10. Minimum requirements for centre participation

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- Local ethical committee approval
- Adequate administrative support available

## 11. Study supervision

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Central supervision: the Steering Committee is responsible for the protocol, quality control, interim analyses of the data and final analysis and reporting of the study.

Local supervision: the Principal Investigators are responsible for the data collection in their centres.

## 12. Data handling

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**The trial will use a web-based electronic data capture ABRAX Information System (AIS) for all data collection.** Users will be able to access the AIS through major web browsers without a need to install any additional software. Access to AIS will be restricted to only authorized users and communication between the server and users will be secured by an encrypted protocol HTTPS. Only non-identifiable data will be collected and a local identifier will be provided by the system for all patients. Each centre will obtain unique username and password for AIS after the submission of signed "Application to Join the ABRAX Trial" form to the Trial centre (ceegog@ceegog.eu).

## 13. Monitoring

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Monitoring will be provided by the Trial office, which is responsible for checking the accuracy, completeness, and plausibility of all data and its compliance with the protocol and GCP requirements.

## 14. Funding

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The ABRAX trial is a non-commercial retrospective trial that does not receive any support from the industry. **Participating institutions will not receive any financial compensation for participation in the study.** All expenses related to the trial (administrative centre, statistics, electronic data capture system, monitoring) will be covered by research grants.

## 15. Publication rules (adopted from ENGOT publication rules)

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### 15.1 General

- a) All calculations regarding the number and position of co-authors will be based on the numbers of patients recruited by institutions / groups with positions guaranteed by the institution / group leading the specific project.
- b) Each institution / group is independent and free to fill in individual names according to its number and position of co-authorships.

### Number of co-authors per group

- a) An institution / group receives a co-authorship position if it has recruited / submitted at least 5 % of the total number of patients / cases. Every additional 5 % = 1 additional co-author.
- b) Institutions that recruit < 5 % of patients can be co-authors of secondary publications.

### 15.2 Additional publications of sub-projects or subgroup / institutional data

- a) Each participating institution / group can receive a dataset of patients recruited by the respective study institution / group after the final analysis.
- b) Separate analyses by one participating institution / group on their included patients should not include primary or secondary end points, and the leading institution (Trial Chair) must be informed about any such project.
- c) All sub-publications or meta-analyses can only be published after the main manuscript of the study has been published.

- d) Any additional subgroup analysis of the whole population (usage of other institutions' data) done by a participating institution / group should be prospectively discussed among the whole group and agreed upon.
- e) Co-authors' number and position in sub-publications follows the same rules as for main publication.

## 16. Abbreviations

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AIS – ABRAX Information System

BMI – Body Mass Index

CEEGOG – Central and Eastern European Gynecologic Oncology Group

CTCAE – Common Terminology Criteria for Adverse Events

ENGOT – European Network for Gynaecological Oncological Trial groups

FST – Fertility-sparing treatment

G – Grade

GCP – Good clinical practice

HTTPS – Hypertext Transfer Protocol Secure

ICH – International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use

ICT – Isolated tumour cell

LN – Lymph nodes

LVSİ – Lymphovascular space invasion

MAC – Macrometastases

MIC – Micrometastases

NCI – National Cancer Institute

OS – Overall survival

PALND – Paraaortic lymph node dissection

PFI – Progression free interval

PFS – Progression free survival

PLND – Pelvic lymph node dissection

RH – Radical hysterectomy

SH – Simple hysterectomy

SLN – Sentinel lymph node

TNM – TNM Classification of Malignant Tumours

## 17. References

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- 2) Sedlis A, Bundy BN, Rotman MZ, Lentz SS, Muderspach LI, Zaino RJ. A randomized trial of pelvic radiation therapy versus no further therapy in selected patients with stage IB carcinoma of the cervix after radical hysterectomy and pelvic lymphadenectomy: A Gynecologic Oncology Group Study. *Gynecol Oncol*. 1999 May;73(2):177-83.
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## 18. List of Appendices

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Appendix 1 Ethical committee approval

Appendix 2 Application to join the ABRAX trial

Appendix 3 Common Terminology Criteria for Adverse Events v4.0 (CTCAE)

## APPENDIX 1 Ethical committee approval

**Etická komise**  
**Všeobecné fakultní nemocnice v Praze**  
**ETHICS COMMITTEE**  
**of the General University Hospital, Prague**

Na Bojišti 1  
 128 08 Praha 2  
 tel.: 224964131  
 e-mail: eticka.komise@vfn.cz

Vážený pan  
 prof. MUDr. David Cibula, CSc.  
 Onkogynekologické centrum,  
 Gynekologicko-porodnická klinika I.LF UK a VFN v Praze,  
 Apolinářská 18, 128 51 Praha 2

20.07.2017  
 č.j.: 998/17 S-IV

Etická komise VFN projednala na svém zasedání dne 20.7.2017 Vámi předložený projekt – ind.výzkum, č.j.: 998/17 S-IV.

**Název studie/Title of CT:** Porovnání doby přežití bez progresu a celkového přežití či odstoupení od radikální hysterektomie u pacientek s karcinomem děložního hrdla, u kterých bylo peroperačně diagnostikováno nádorové postižení lymfatických uzlin.

**Žadatel/Applicant:** prof. MUDr. David Cibula, CSc; Onkogynekologické centrum, Gynekologicko-porodnická klinika I.LF UK a VFN v Praze, Apolinářská 18, 128 51 Praha 2

**Lhůta pro podání písemné zprávy o průběhu KH od jeho zahájení/ Time schedule for submission of the written Annual Report from the CT commencement:**  1x ročně/Once a year  Jiná lhůta/Other

**Úhrada nákladů spojených s posouzením žádosti a vydáním stanoviska /Reimbursement of costs related to assessment and issue of the EC opinion:**  Ano/Yes  Ne, zdůvodnění/ No, reasons: Nesponzorovaný projekt

**Datum doručení žádosti / Date of submission of the Application Form:** 29.6.2017

**Datum jednání EK + čas/Date and time of Ethics Committee's session:** 20.7.2017 (15,30 –17,30 hod.)

**Seznam míst hodnocení s označením míst, ke kterým se EK vyjádřila jako místní EK a kde vykonává dohled**

Místo hodnocení / Jméno zkoušejícího Trial Site / Name of Investigator	Místní EK Local EC	Adresa místní EK Address
prof. MUDr. David Cibula, CSc; Onkogynekologické centrum, Gynekologicko-porodnická klinika I.LF UK a VFN v Praze, Apolinářská 18, Praha 2, 128 51	<input checked="" type="checkbox"/>	EK při VFN, Na Bojišti 1, 128 08 Praha 2

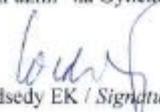
**Seznam hodnocených dokumentů / List of all submitted documents:**

Název dokumentu, verze, datum Document title, version, date	Schváleno /Approved		Vzato na vědomí / Taken into account	
	ANO Yes	NE No	ANO Yes	NE No
Průvodní dopis z 15.6.2017	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>
Dotazník k předkládaným dokumentům – Víceúčelový formulář EK VFN, z 13.6.2017	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>
Protokol ID: CEEGOG CX2, anglická verze 1.0 z 14.5.2017	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Protokol Synopsis v anglickém jazyce, verze 1.0 z 14.5.2017	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Synopse protokolu v českém jazyce, nedatované verze	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Čestná prohlášení z 20.6.2017	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>
Souhlas přednosty kliniky prof. MUDr. Aloise Martana, DrSc, 20.6.2017	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>
Životopis hlavního zkoušejícího prof. MUDr. Davida Cibuly, CSc. z 15.6.2017	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>

**Stanovisko etické komise:**

EK VFN vydává **souhlasné** stanovisko k provedení individuálního výzkumu – “Porovnání doby přežití bez progresu a celkového přežití či odstoupení od radikální hysterektomie u pacientek s karcinomem děložního hrdla, u kterých bylo peroperačně diagnostikováno nádorové postižení lymfatických uzlin” na Gynekologicko-porodnické klinice I.LF UK a VFN v Praze.

Etická komise  
 Všeobecná fakultní nemocnice  
 v Praze  
 Na Bojišti 1  
 128 08 Praha 2

  
 Podpis předsedy EK / Signature of Chairperson

MUDr. Josef ŠEDIVÝ, CSc.

## Seznam členů etické komise/ List of the Ethics Committee Members:

	Muž/ Žena Male/ Female	Odbornost Specialist	Zaměstnanec zřizovatele EK*		Funkce v EK Role in EC	Přítomen Attendance		Hlasoval Voted	
			Ano Yes	Ne No		Ano Yes	Ne No	Ano Yes	Ne No
MUDr. Josef Šedivý, CSc.	M/M	Clinical Pharmacologist	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Předseda/ Chairperson	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>
MUDr. Magda Šišková, CSc.	Ž/F	Haematologist	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Místopředseda/ Vice-chairperson	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>
JUDr. Milada Džupinková, MBA	Ž/F	Lawyer	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Člen/Member	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>
Jana Farkačová	Ž/F	Lab. Technician	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Člen/Member	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>
Doc. MUDr. Pavel Freitag, CSc.	M/M	Gynaecologist	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Člen/Member	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>
Ing. Antonín Grošpic, CSc.	M/M	Engineer	<input type="checkbox"/>	<input checked="" type="checkbox"/>	Člen/Member	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>
Prof. MUDr. Eva Kubala Havrdová, CSc.	Ž/F	Neurologist	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Člen/Member	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>
MUDr. Hana Honová	M/M	Oncologist	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Člen/Member	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>
MUDr. Anna Jedličková	Ž/F	Microbiologist	<input type="checkbox"/>	<input checked="" type="checkbox"/>	Člen/Member	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>
MUDr. Jiří Kolář	M/M	Cardiologist	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Člen/Member	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>
MUDr. Ladislav Korábek, CSc., MBA	M/M	Dental surgeon	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Člen/Member	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>
Prof. MUDr. František Perlík, DrSc.	M/M	Pharmacologist	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Člen/Member	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>
Prof. MUDr. Jan Roth, CSc.	M/M	Neurologist	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Člen/Member	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>
Mgr. Libuše Roytová Mgr. ThLic. of Theologie	Ž/F	Member of clergy	<input type="checkbox"/>	<input checked="" type="checkbox"/>	Člen/Member	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>
MUDr. Kateřina Rusinová, MgA., Ph.D.	Ž/F	Anesthesiologist- Intensive Med.	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Člen/Member	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>
JUDr. Šárka Špeciánová	Ž/F	Lawyer	<input type="checkbox"/>	<input checked="" type="checkbox"/>	Člen/Member	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>
MUDr. Marcela Trojánková	Ž/F	Privat Nefrologist	<input type="checkbox"/>	<input checked="" type="checkbox"/>	Člen/Member	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>
Prof. MUDr. Jiří Zeman, DrSc.	M/M	Paediatricist – Adolescent Med	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Člen/Member	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>

pozn: \*Zaměstnanec zřizovatele EK/ Employee of EC appointing authority)

Etická komise prohlašuje, že byla ustavena a pracuje v souladu se správnou klinickou praxí (GCP) a platnými právními předpisy. Poslední sloupec udává, zda členové EK byli přítomni hlasování, ale nikoli jak hlasovali ve věci./The Ethics Committee hereby declares that it was established and operates in accordance with its Rules of Procedure in compliance with GCP and valid legal regulations. EC members personally presented the voting procedure (and NOT their individual voting result to or against the cause) are indicated in the last column:

 Ano/Yes     Ne/No

Komentář/Comments:

Datum/Date: 20.07.2017

 Podpis předsedy EK nebo zástupce  
Signature of Chairperson or Vice-Chairperson

MUDr. Josef ŠEDIVÝ, CSc.

 Etická komise  
Všeobecná fakultní nemocnice  
v Praze  
Na Bojišti 1  
128 08 Praha 2

## APPENDIX 2 Application to join the ABRAX trial

**APPLICATION TO JOIN THE ABRAX TRIAL****OFFICIAL NAME OF THE DEPARTMENT / INSTITUTION:**

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Official address: \_\_\_\_\_

Name of the department chair: \_\_\_\_\_

**STUDY INVESTIGATOR:**

Name: \_\_\_\_\_

Email address: \_\_\_\_\_

Contact phone number: \_\_\_\_\_

**STUDY COORDINATOR OR STUDY NURSE (OPTIONAL):**

Name: \_\_\_\_\_

Email address: \_\_\_\_\_

Contact phone number: \_\_\_\_\_

**I hereby confirm that:**

- I have received the trial protocol
- I have obtained the approval from the Local Ethical Committee
- I understand the protocol and my institution fulfils criteria for joining the trial

**Minimum requirements for centre participation**

- Local ethical committee approval

DATE:

NAME OF STUDY INVESTIGATOR:

SIGNATURE:

APPENDIX 3 Common Terminology Criteria for Adverse Events v4.0 (CTCAE)
 

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Grade	CTCAE description	Comments
Grade 2	Moderate; minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental ADL.	Complications that had a long-term negative impact on daily activities, such as shopping, or cooking.
Grade 3	Severe or medically significant but not immediately life threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.	Complications that required hospitalisation, re-operation or which had a long-term negative impact on patients' self-care (bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden).
Grade 4	Life-threatening consequences; urgent intervention indicated.	Life-threatening complications or those with long-term debilitating consequences for the quality of life of the patient.
Grade 5	Death related to AE.	