

Aspects of Therapy for Cervical Cancer in Germany 2012 – Results from a Survey of German Gynaecological Hospitals

Aspekte der Therapie des Zervixkarzinoms in Deutschland 2012 – Ergebnisse einer Umfrage unter den deutschen Kliniken für Gynäkologie

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Key words

- staging of cervical cancer
- radiochemotherapy for cervical cancer
- radical hysterectomy
- questionnaire on treatment situation
- therapeutic concepts
- stage-dependent therapy

Schlüsselwörter

- Staging bei Zervixkarzinom
- Radiochemotherapie bei Zervixkarzinom
- radikale Hysterektomie
- Umfrage zur Behandlungssituation
- Therapiekonzepte
- stadienabhängige Therapie

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Bibliography

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Abstract

Introduction: In spite of the existence of guidelines and international recommendations, many aspects in the diagnosis, therapy and follow-up of patients with cervical cancer are not based on validated data. A broad spectrum of different opinions and procedures concerning the therapy for patients with cervical cancer is under controversial discussion by the responsible gynaecologists in German hospitals.

Methods: The present study is intended to picture the current treatment situation for cervical cancer in Germany. For this purpose a specially developed questionnaire with questions divided into 19 subsections was sent to all 688 gynaecological hospitals in Germany.

Results: The response rate to the questionnaire was 34%. 91% of the hospitals treated between 0 and 25 patients with cervical cancer per year. 7.5% treated between 26 and 50 and 1.4% of the hospitals more than 50 patients per year. The bimanual examination was the most frequently used staging method (98%); PET-CT was the least used staging method (2.3%). Interestingly 48% of the hospitals used surgical staging. The great majority of the hospitals (71%) used abdominal radical hysterectomy (Wertheim-Meigs operation) to treat their patients. TMMR via laparotomy was used by 13%. 16% of the hospitals performed laparoscopic or robot-assisted radical hysterectomies. The sentinel concept was hardly used even in the early stages. It must be emphasised that in 74% of the hospitals radical hysterectomies were performed even in cases with positive pelvic lymph nodes and in 43% also in cases with positive paraaortic lymph nodes. The therapy of choice for FIGO IIB cancers is primary radiochemotherapy (RCTX) in 21% of the hospitals; operative staging followed by radiochemotherapy in 24% and treatment by radical hysterectomy followed by adjuvant RCTX was employed in this sit-

Zusammenfassung

Einleitung: Trotz der vorhandenen Leitlinien und internationalen Empfehlungen fußen viele Aspekte der Diagnostik, Therapie und der Nachsorge von Patientinnen mit Zervixkarzinomen nicht auf validen Daten. Von den behandelnden Gynäkologen in den deutschen Kliniken wird ein breites Spektrum an verschiedenen Meinungen und Herangehensweisen an die Therapie der Zervixkarzinompatientinnen kontrovers diskutiert.

Methoden: Die vorliegende Studie sollte die derzeitige Behandlungssituation des Zervixkarzinoms in Deutschland abbilden. Dazu wurde ein speziell dafür entwickelter Fragebogen, der Fragen zu 19 Teilbereichen abdeckte, an alle 688 deutschen Kliniken für Gynäkologie versandt.

Resultate: Die Rücklaufquote der Fragebögen war 34%. 91% der Kliniken behandelten zwischen 0 und 25 Patientinnen mit Zervixkarzinomen pro Jahr. 7,5% zwischen 26 und 50 und 1,4% der Kliniken mehr als 50 Patientinnen/Jahr. Die bimanuelle Untersuchung war die am häufigsten eingesetzte Stagingmethode (98%), das PET-CT wurde zum Staging am seltensten beansprucht (2,3%). Interessanterweise setzten 48% der Kliniken ein operatives Staging um. Die große Mehrheit der Kliniken (71%) therapierte die Patientinnen per abdominaler radikaler Hysterektomie (Wertheim-Meigs-Operation). Die TMMR per Laparotomie wurde von 13% eingesetzt, 16% der Kliniken operierten laparoskopisch oder roboterassistiert per radikaler Hysterektomie. Das Sentinel-Konzept wurde auch bei Frühstadien kaum verwendet. Hervorzuheben ist, dass in 74% der Kliniken radikale Hysterektomien auch bei positiven pelvinen Lymphknoten und in 43% auch bei positiven paraaortalen Lymphknoten durchgeführt wurden. Die Therapie der Wahl bei FIGO-IIB-Karzinomen war die primäre Radiochemotherapie (RCTX) in 21% der Kliniken, ein operatives Staging folgte von einer Radiochemotherapie in 24% und

uation by 46% of the hospitals. In 15–97% of the hospitals for node-negative and in sano resected patients in stage pT1B1/1B2 after radical hysterectomy, an adjuvant RCTX is recommended when further risk factors exist (LVSI, tumour >4 cm, age <40 years, adenocarcinoma, S3).

Conclusion: A broad spectrum of differing staging and therapy concepts is in use for patients with cervical cancer in Germany. A standardisation of therapy is needed. An update of national guidelines could help to achieve more transparency and a standardisation of treatment for patients with cervical cancer.

Abbreviations

FIGO	Fédération Internationale de Gynécologie et d'Obstétrique
GOG	Gynecologic Oncology Group
NCCN	National Comprehensive Cancer Network
OS	Overall survival
PFS	Progression-free survival
RCTX	Radiochemotherapy
RH	Radical hysterectomy
TMMR	Total mesometrial resection
VALRH	Vaginal-assisted laparoscopic radical hysterectomy
LARVH	laparoscopic assisted radical vaginal hysterectomy

Introduction

The treatment of patients with invasive cervical cancer in Germany should be oriented on the currently valid AGO guidelines [1]. These guidelines, as well as international recommendations (e.g., NCCN) are based on prospective and retrospective mono- and multicentric data, since only few prospective randomised studies are available [2]. Even for the radical hysterectomy (RH) which has been practiced for more than one hundred years there are today still no randomised studies comparing the various surgical techniques [99]. Also the classification of radicality by various groups has not led to a standardisation of the surgical methods [3,4]. In addition, because of the declining incidence of invasive cervical cancer – with 4880 newly diagnosed cases and 1600 deaths in Germany, fewer and fewer patients per hospital are being treated which will lead to appreciable problems with regard to experience and training [5].

On the other hand novel diagnostic [100], surgical and radiooncological procedures are being introduced and need to be evaluated [101]. The staging system for cervical cancer according to FIGO is today based solely on gynaecological examinations and cystoscopy/rectoscopy. Although MRI and CT have clear limitations for the staging of women with cervical cancer they are being employed more and more [6]. Whether or not PET-CT can provide improved data for staging is currently not clear [7–10]. Also the oncological relevance of surgical staging is still being discussed controversially and is being checked in the Uterus-11 study of AGO [11–13]. The sentinel concept appears to be applicable with high sensitivity and detection rates for tumours <2 cm; even so there are reservations due to the low prevalence of positive lymph nodes in cases of tumours in stages IA1–IB1 [14,15]. Beside the classical abdominal RH, in recent years other procedures such

die Behandlung per radikaler Hysterektomie gefolgt von adjuvanter RCTX wurde in dieser Situation von 46% der Kliniken umgesetzt. In 15–97% der Kliniken wurde bei nodalnegativen und in sano resezierten Patientinnen nach radikaler Hysterektomie im Stadium pT1B1/1B2 eine adjuvante RCTX empfohlen, wenn weitere Risikofaktoren auftraten (LVSI, Tumor >4 cm, Alter <40 Jahre, Adenokarzinome, G3).

Zusammenfassung: Ein breites Spektrum an verschiedenen Staging- und Therapiekonzepten bei Patientinnen mit Zervixkarzinom wird in Deutschland eingesetzt. Es bedarf einer Standardisierung der Therapie. Ein Update der nationalen Leitlinien kann helfen, mehr Klarheit und eine Standardisierung in die Behandlung von Patientinnen mit Zervixkarzinom zu bringen.

as total laparoscopic RH [16–20], laparoscope-assisted radical vaginal RH [21–24] or vaginal-assisted laparoscopic RH [25], robot-assisted RH [26–28] and TMMR [29] have been developed and provided highly promising oncological results. Nerve-sparing operations also help to markedly reduce the postoperative morbidity. Also from the radiotherapy side, considerable improvements in the treatment of patients with cervical cancer have been achieved. Beside the usual combination of chemotherapy and radiation (radiochemotherapy = RCTX), which achieves a significant improvement in survival for the patient [30–34], it is above all the use of innovative techniques of radiation that clearly reduces the rate of side effects caused by the therapy [35,36]. The sole randomised study to compare radical hysterectomy with radiotherapy alone by Landoni in 1997 must now be considered as outdated with regard to the radiotherapy-associated side effects [37].

Also in the most recent publications on RH more than 50% of the patients receive a postoperative adjuvant radiochemotherapy, which is often associated with an increased morbidity [38,39]. The criteria for an adjuvant therapy are applied in widely different ways in spite of the GOG-109 data [40–43]. Furthermore, different algorithms are used in the follow-up [44–46].

The large number of open and controversial topics prompted our group to develop a questionnaire to assess the current status in the treatment of women with cervical cancer, even though we do not make any claims to completeness for this compilation.

Material and Methods

Between February 2012 and June 2012 a questionnaire comprising 19 topic complexes was sent to the heads of all gynaecological hospitals nationwide in Germany (Questionnaire – **Fig. 1**). The data were evaluated using SPSS. Percentage values each refer to the number of usable replies to the particular topic.

Results

General

From 688 hospitals to which the questionnaire was sent 234 (34%) answered, of these 26 were university hospitals (11%), 113 were medical centres (49%) and 93 were regional and general hospitals (40%). 28% (n = 63) of these hospitals are certified as centres for gynaecological oncology. All hospitals were subdivided into 3 groups according to the number of patients with cervical cancer treated per year: 1: 0–25 patients, 2: 26–50, 3: more than 50. The university hospitals could be assigned as fol-

Questionnaire on therapy for cervical cancer 2012

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(It should not take more than 15 minutes to answer all questions; solely question 13 is somewhat more extensive but concerns an extremely important and controversially discussed topic.)

General	Surgical therapy																
<p>1. What type of hospital do you work in?</p> <p><input type="checkbox"/> University hospital <input type="checkbox"/> Medical centre/specialist hospital <input type="checkbox"/> General regional hospital</p>	<p>7. Which type of radical hysterectomy do you perform mainly? Please check only <i>one or two</i> boxes, if two please give percentages for each of the two methods.</p> <table border="0" style="width: 100%;"> <thead> <tr> <th></th> <th style="text-align: right;">Percent</th> </tr> </thead> <tbody> <tr> <td><input type="checkbox"/> Classic Wertheim operation (open surgery)</td> <td style="text-align: right;">_____</td> </tr> <tr> <td><input type="checkbox"/> TMMR (open surgery)</td> <td style="text-align: right;">_____</td> </tr> <tr> <td><input type="checkbox"/> Laparoscopic-assisted radical vaginal (LARVH) or vaginal-assisted laparoscopic radical hysterectomy (VALRH)</td> <td style="text-align: right;">_____</td> </tr> <tr> <td><input type="checkbox"/> Total laparoscopic radical hysterectomy (TLRH)</td> <td style="text-align: right;">_____</td> </tr> <tr> <td><input type="checkbox"/> Robot-assisted radical hysterectomy (RRH)</td> <td style="text-align: right;">_____</td> </tr> <tr> <td><input type="checkbox"/> Robot-assisted TMMR</td> <td style="text-align: right;">_____</td> </tr> <tr> <td><input type="checkbox"/> Others (please name them)</td> <td style="text-align: right;">_____</td> </tr> </tbody> </table>		Percent	<input type="checkbox"/> Classic Wertheim operation (open surgery)	_____	<input type="checkbox"/> TMMR (open surgery)	_____	<input type="checkbox"/> Laparoscopic-assisted radical vaginal (LARVH) or vaginal-assisted laparoscopic radical hysterectomy (VALRH)	_____	<input type="checkbox"/> Total laparoscopic radical hysterectomy (TLRH)	_____	<input type="checkbox"/> Robot-assisted radical hysterectomy (RRH)	_____	<input type="checkbox"/> Robot-assisted TMMR	_____	<input type="checkbox"/> Others (please name them)	_____
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<input type="checkbox"/> Others (please name them)	_____																
<p>2. Is your department certified as a centre for gynaecological oncology?</p> <p><input type="checkbox"/> Yes <input type="checkbox"/> No</p>	<p>8. Do you <i>as a general rule</i> perform an intraoperative immediate section for microscopy of the resected lymph nodes (please check only one box)?</p> <p><input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Only for suspicious enlargement of individual lymph nodes <input type="checkbox"/> As a rule two-stage procedure (1st OP lymphonodectomy, radical hysterectomy as 2nd OP only when free of tumour)</p>																
<p>3. How many patients with invasive cervical cancer of the following FIGO stages did you treat last year (2011)?</p> <p>IA1 _____ IA2 _____ IB1 _____ IB2 _____ IIA _____ IIB _____ IIIA/IIIB _____ IVA/IVB _____</p> <p>Have the answers to this question been taken from a register <input type="checkbox"/> or are they estimated? <input type="checkbox"/></p>	<p>9. What is your usual procedure for positive <i>pelvic</i> lymph nodes in cases of operable local tumours (please check only one box)?</p> <p><input type="checkbox"/> Discontinue the radical HE, paraaortal lymphonodectomy and primary radiochemotherapy (RCTX) <input type="checkbox"/> Continue the radical HE, paraaortal lymphonodectomy and adjuvant RCTX <input type="checkbox"/> Continue the radical HE, paraaortal lymphonodectomy and adjuvant chemotherapy</p>																
Staging	Stage-specific questions																
<p>4. Which imaging/staging examinations do you usually perform from stage IB1 (please check – multiple answers are possible)?</p> <p><input type="checkbox"/> Bimanual exam <input type="checkbox"/> Cystoscopy <input type="checkbox"/> Rectoscopy <input type="checkbox"/> CT <input type="checkbox"/> MRI <input type="checkbox"/> PET-CT <input type="checkbox"/> Surgical staging</p>	<p>10. What is your usual procedure for positive <i>paraortic</i> lymph nodes in cases of operable local tumours (please check only one box)?</p> <p><input type="checkbox"/> Discontinue the radical HE and primary radiochemotherapy, including the paraaortic region (extended field) <input type="checkbox"/> Discontinue the radical HE and palliative chemotherapy <input type="checkbox"/> Continue the radical HE and adjuvant radiochemotherapy <input type="checkbox"/> Continue the radical HE and adjuvant chemotherapy</p>																
<p>5. If you regularly perform surgical staging which operative approach do you use in the majority of cases (please name only one procedure)?</p> <p><input type="checkbox"/> Open transperitoneal <input type="checkbox"/> Open retroperitoneal <input type="checkbox"/> Laparoscopic transperitoneal <input type="checkbox"/> Laparoscopic extraperitoneal <input type="checkbox"/> Robot-assisted transperitoneal <input type="checkbox"/> Robot-assisted retroperitoneal</p>	<p>11. In stage IA1 L0 do you perform a sentinel lymphonodectomy in addition to re-conisation/simple hysterectomy?</p> <p><input type="checkbox"/> Yes <input type="checkbox"/> No</p>																
<p>6. Do you perform sentinel lymph node procedures in women with cervical cancer (please give only one answer)?</p> <p><input type="checkbox"/> In all stages routinely <input type="checkbox"/> Only for tumours <2 cm, but then for all patients <input type="checkbox"/> Only within studies <input type="checkbox"/> Only if requested by the patient</p>																	

Fig. 1 Questionnaire. (continued next page)

12. For a patient with cervical cancer in stage IB1 < 2 cm who still wants to have a child, do you (please check only one box)...

- ...always perform a radical HE because you do not approve of trachelectomy.
- ...refer the patient to a centre experienced in trachelectomy.
- ...always perform a radical trachelectomy.
If yes: As a radical vaginal trachelectomy
 As a radical abdominal trachelectomy
 As a robot-assisted radical trachelectomy

13. When do you, as surgeon, recommend adjuvant radio-chemotherapy after radical hysterectomy in stages IB1/IB2 (multiple answers possible):

	Yes	No
For positive nodes; R1/R2 resection and/or tumour invasion of the parametrium	<input type="checkbox"/>	<input type="checkbox"/>

If N0, R0 and stage pT1b1 or pT1b2, do you recommend adjuvant RCT in the presence of the following risk factors (please check as appropriate):

Only grade 3 (G3)	<input type="checkbox"/>	<input type="checkbox"/>
Only tumour size > 4 cm	<input type="checkbox"/>	<input type="checkbox"/>
Only age < 40 years	<input type="checkbox"/>	<input type="checkbox"/>
Only by invasion of the lymphovascular space (L1)	<input type="checkbox"/>	<input type="checkbox"/>
Only adenocarcinoma as histological type	<input type="checkbox"/>	<input type="checkbox"/>

For 2 risk factors:

Combination G3 + age < 40	<input type="checkbox"/>	<input type="checkbox"/>
Combination G3 + tumour > 4 cm	<input type="checkbox"/>	<input type="checkbox"/>
Combination G3 + L1	<input type="checkbox"/>	<input type="checkbox"/>
Combination G3 and adenocarcinoma	<input type="checkbox"/>	<input type="checkbox"/>
Combination tumour > 4 cm and age < 40	<input type="checkbox"/>	<input type="checkbox"/>
Combination tumour > 4 cm and L1	<input type="checkbox"/>	<input type="checkbox"/>
Combination tumour > 4 cm and adenocarcinoma	<input type="checkbox"/>	<input type="checkbox"/>
Combination age < 40 and L1	<input type="checkbox"/>	<input type="checkbox"/>
Combination age < 40 and adenocarcinoma	<input type="checkbox"/>	<input type="checkbox"/>
Combination L1 and adenocarcinoma	<input type="checkbox"/>	<input type="checkbox"/>

For 3 risk factors:

Combination G3 + tumour > 4 cm + age < 40	<input type="checkbox"/>	<input type="checkbox"/>
Combination G3 + tumour > 4 cm + L1	<input type="checkbox"/>	<input type="checkbox"/>
Combination G3 + tumour > 4 cm + adenocarcinoma	<input type="checkbox"/>	<input type="checkbox"/>
Combination G3 + age < 40 + L1	<input type="checkbox"/>	<input type="checkbox"/>
Combination G3 + age < 40 + adenocarcinoma	<input type="checkbox"/>	<input type="checkbox"/>
Combination G3 + L1 + adenocarcinoma	<input type="checkbox"/>	<input type="checkbox"/>
Combination tumour > 4 cm + age < 40 + L1	<input type="checkbox"/>	<input type="checkbox"/>
Combination tumour > 4 cm + age < 40 + adenocarcinoma	<input type="checkbox"/>	<input type="checkbox"/>
Combination tumour > 4 cm + L1 + adenocarcinoma	<input type="checkbox"/>	<input type="checkbox"/>
Combination age < 40 + L1 + adenocarcinoma	<input type="checkbox"/>	<input type="checkbox"/>

For 4 risk factors:

Combination G3 + tumour > 4 cm + age < 40 + L1	<input type="checkbox"/>	<input type="checkbox"/>
Combination G3 + tumour > 4 cm + age < 40 + adenocarcinoma	<input type="checkbox"/>	<input type="checkbox"/>
Combination G3 + tumour > 4 cm + L1 + adenocarcinoma	<input type="checkbox"/>	<input type="checkbox"/>
Combination tumour > 4 cm + age < 40 + L1 + adenocarcinoma	<input type="checkbox"/>	<input type="checkbox"/>
Combination G3 + age < 40 + adenocarcinoma + L1	<input type="checkbox"/>	<input type="checkbox"/>

14. Do you as a general rule initiate a neoadjuvant therapy in stage IB2 or IIB prior to a planned radical hysterectomy (please check only one box)?

- Yes, a neoadjuvant chemotherapy
- Yes, a neoadjuvant radiochemotherapy
- No
- I always refer these stages to primary radiochemotherapy.

15. What is your therapy for the majority of patients in FIGO stage IIB (please check only one box)?

- Primary radiochemotherapy
 - Surgical staging and subsequent primary radiochemotherapy
 - Radical hysterectomy and adjuvant radiochemotherapy
 - Others (please specify)
-
-

16. Which type of staging do you perform in FIGO stages IIIA/IIIB?

- Clinical staging before radiochemotherapy
- Surgical staging before radiochemotherapy

17. What is your therapy in stage IVA (multiple answers possible)?

- Always primary radiochemotherapy
- Always primary exenteration
- Primary exenteration only for urogenital or intestinogenital fistula
- Individual decision

Postoperative decisions/follow-up

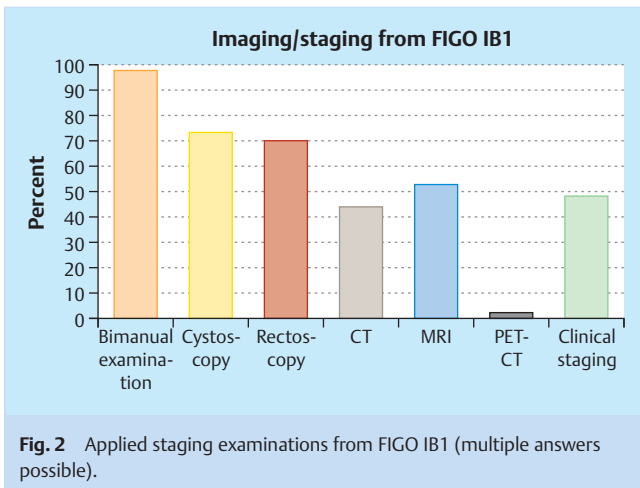
18. What examinations do you perform on patients after primary radiochemotherapy (without prior radical hysterectomy) in the follow-up period (multiple answers possible)?

- Clinical examination
- Renal ultrasonography
- Vaginal ultrasonography
- Determination of tumour markers
- Pelvic MRI
- PET-CT
- Cervix abrasion
- PAP smear

19. In your opinion when is an operation indicated after primary radiochemotherapy (without radical hysterectomy) (please check only one box)?

- There is no indication because there is no advantage in survival.
- Secondary hysterectomy is always performed.
- A secondary hysterectomy is performed only on suspicion of a persisting tumour (e.g. in the abrasion).
- On suspicion of a local recurrence a secondary exenteration is always performed.

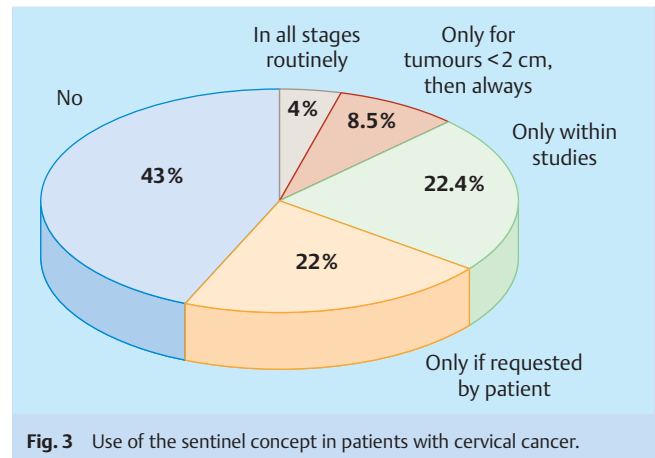
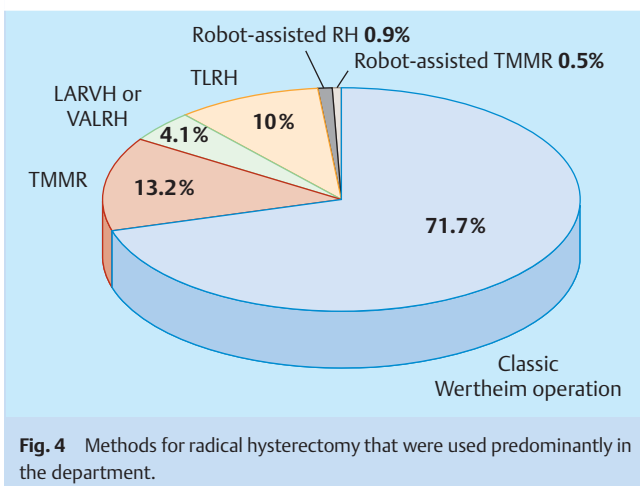
Fig. 1 Questionnaire. (continued)



lows to the groups 1, 2 and 3, respectively, 14 (61%), 6 (26%) and 3 (13%). Three university hospitals did not give an answer to the number of treated patients per year. For medical centres and regional/general hospitals the assignments were as follows: 1 = 94%, 2 = 6%, 3 = 0% and, respectively, 1 = 95.5%, 2 = 4.5% and 3 = 00%. Altogether 91% of all patients with cervical cancer were treated in a hospital that handles less than 26 such patients per year.

Staging

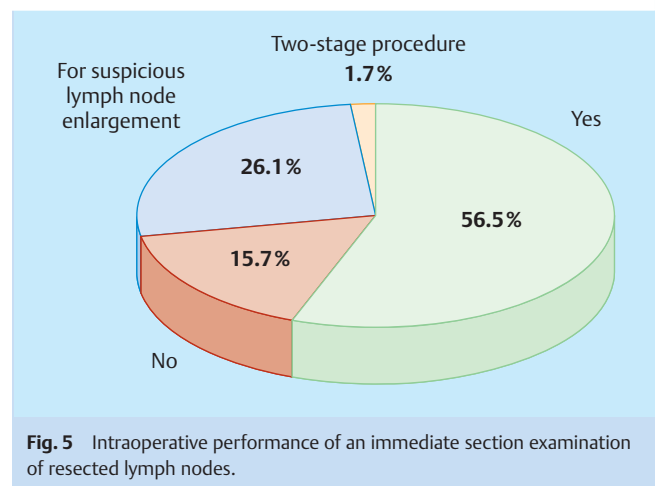
In practically all hospitals, staging from stage IB1 was done according to FIGO by bimanual examination (98%). Cystoscopy and rectoscopy were done in 73% and, respectively, 70% of the gynaecological departments. 44% of the hospitals used CT routinely, 52% used MRI, whereas in only 2% PET-CT was used for staging (Fig. 2). Surgical staging was preferred in 48% of the responding hospitals. Here the following approaches for surgical staging were used: open transperitoneal in 41%, open retroperitoneal in 9%, laparoscopic transperitoneal in 47%, laparoscopic extraperitoneal in 1% and robot-assisted transperitoneal in 2%. The sentinel concept was not utilised in 43%; 9% of the hospitals performed sentinel lymphonodectomy in all patients with tumours ≤ 2 cm, 22% only within studies and 22% only if requested by the patient. In 9 gynaecological departments (4%) the sentinel concept is applied to all tumour stages (Fig. 3). Almost all hospitals



(96%) reject the sentinel concept as an addition to conisation/simple hysterectomy for patients with a cervical cancer stage pT1a1.

Therapy

In the great majority of the gynaecological hospitals in Germany the classic open Wertheim operation is used (71.5%). Other procedures for RH with markedly lower usage are represented by laparoscopic-assisted vaginal or vaginal-assisted laparoscopic RH in 4%, total laparoscopic RH in 10%, TMMR in 13%, robot-assisted RH in 1% and robot-assisted TMMR in 0.5%. In 32% of the hospitals several procedures were regularly applied (Fig. 4). An intraoperative immediate section of all resected lymph nodes is offered in 57% of the hospitals, in 26% only for suspiciously enlarged lymph nodes. In 2% of the hospitals – in the sense of a two-stage procedure – a lymphonodectomy is performed first followed by RH only after confirmation of tumour-free lymph nodes (Fig. 5). In the cases with the identification of positive pelvic lymph nodes in patients with a local operable tumour the RH is discontinued in 16% of the hospitals and, after performance of a paraaortic lymphonodectomy, a primary radiochemotherapy is initiated. 74% of the physicians continue the RH (including a paraaortic lymphonodectomy) and recommend adjuvant RCTX or adjuvant chemotherapy (10%) (Fig. 6). Upon identification of positive



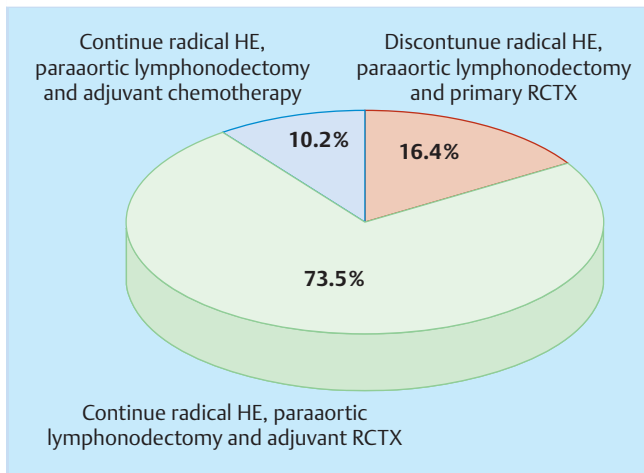


Fig. 6 Procedure in cases with positive pelvic lymph nodes on immediate section.

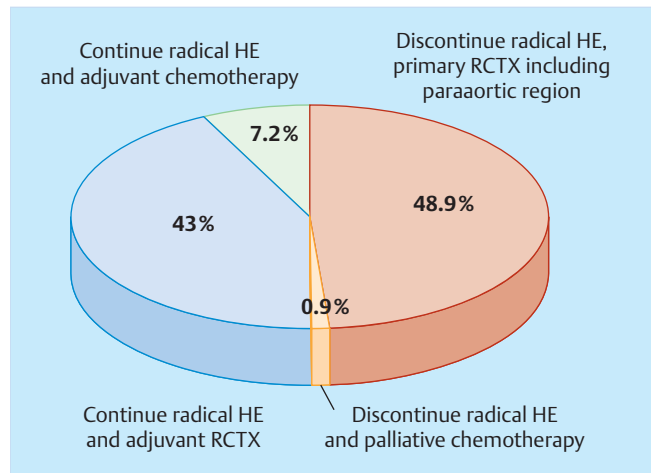


Fig. 7 Procedure in cases with positive paraaortic lymph nodes on immediate section.

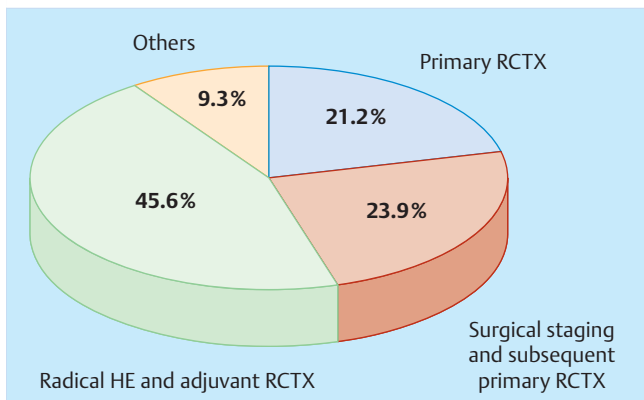


Fig. 8 Preferred therapy for FIGO stage IIB.

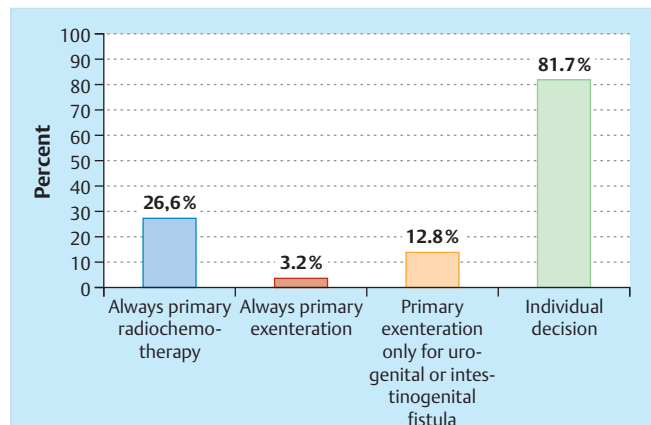


Fig. 9 Primary therapy in stage IVA (multiple answers possible).

paraaortic lymph nodes of a locally operable cervical carcinoma, the operation is terminated in 50% of the patients. In 43% the RH is continued in this clinical situation and an adjuvant RCTX is subsequently carried out, in 7% adjuvant chemotherapy (Fig. 7). Young patients with a still unfulfilled desire to have children and a cervical cancer of less than 2 cm in size are referred in 80% to a centre with expertise in radical trachelectomy. 17% of the hospitals perform uterus-sparing operations in house, usually as a radical vaginal trachelectomy (14%). Three percent of the gynaecological departments reject a trachelectomy and always prefer a RH for this constellation.

In FIGO stage IB2 neoadjuvant chemotherapy is applied in 6% of the clinics prior to the planned RH and in 10% a neoadjuvant RCTX, whereas in 75% the RH is performed as primary procedure. 9% of the hospitals refer patients in this stage to a primary RCTX. Also in FIGO stage IIB a primary RH followed by adjuvant RCTX is preferred by the majority of German hospitals (46%), primary RCTX without and with laparoscopic staging in 21% and 24%, respectively. More extensive therapeutic options are employed in 9% of the hospitals (Fig. 8). For patients in stage IIIA/IIIB most physicians consider a clinical staging to be sufficient prior to a primary RCTX (69%), merely 31% vote for a surgical staging be-

fore commencing therapy. In stage IVA of cervical cancer individual decisions are preferred in most hospitals (Fig. 9).

The indications for adjuvant RCTX after RH form a very heterogeneous pattern. Whereas all hospitals (100%) favour an adjuvant therapy in cases with positive lymph nodes, invasion of the

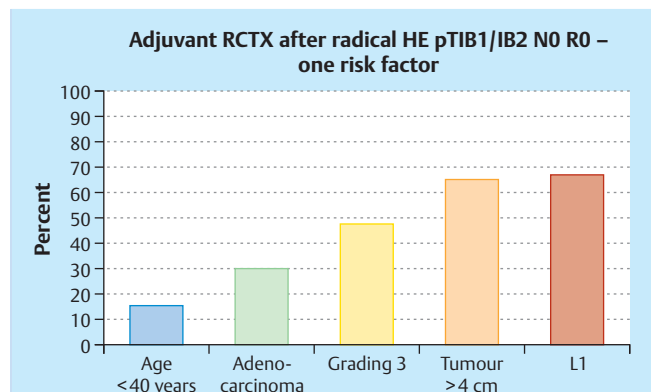
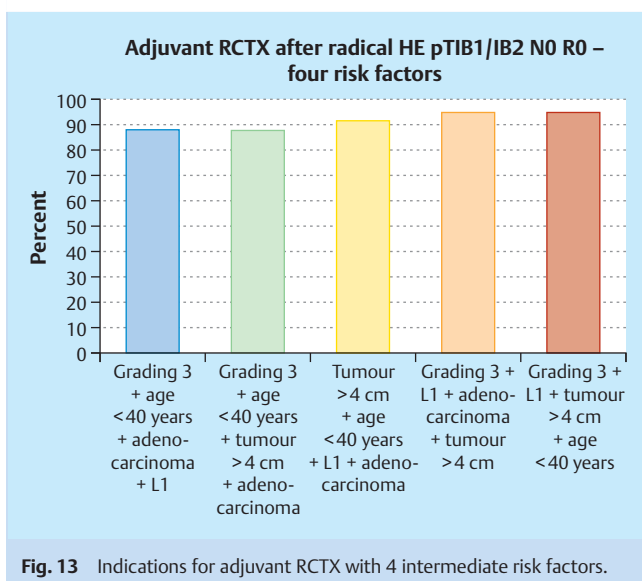
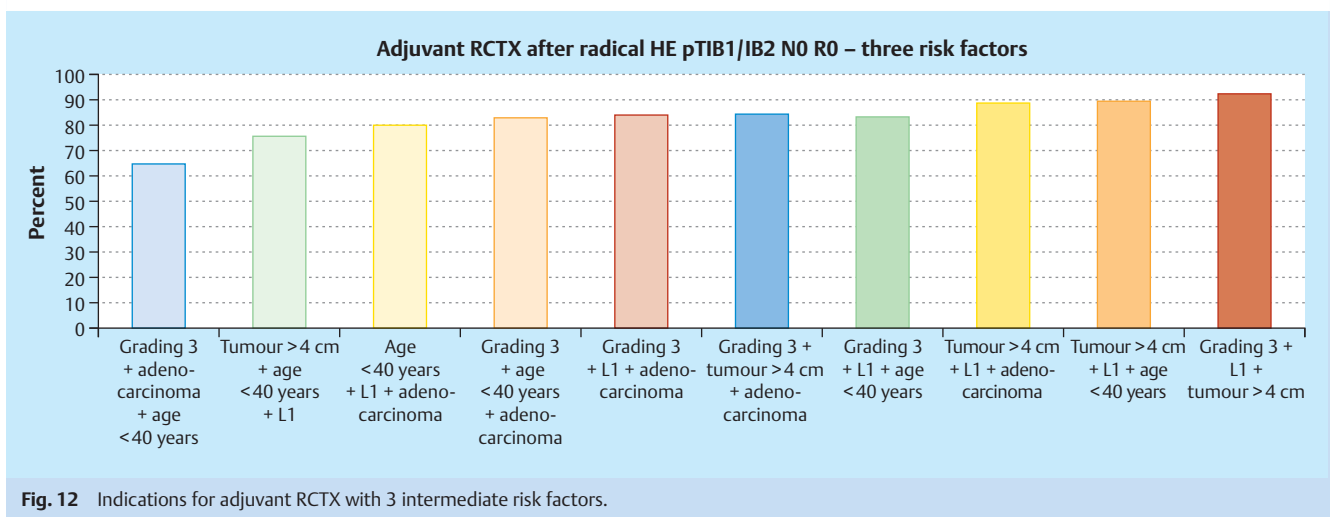
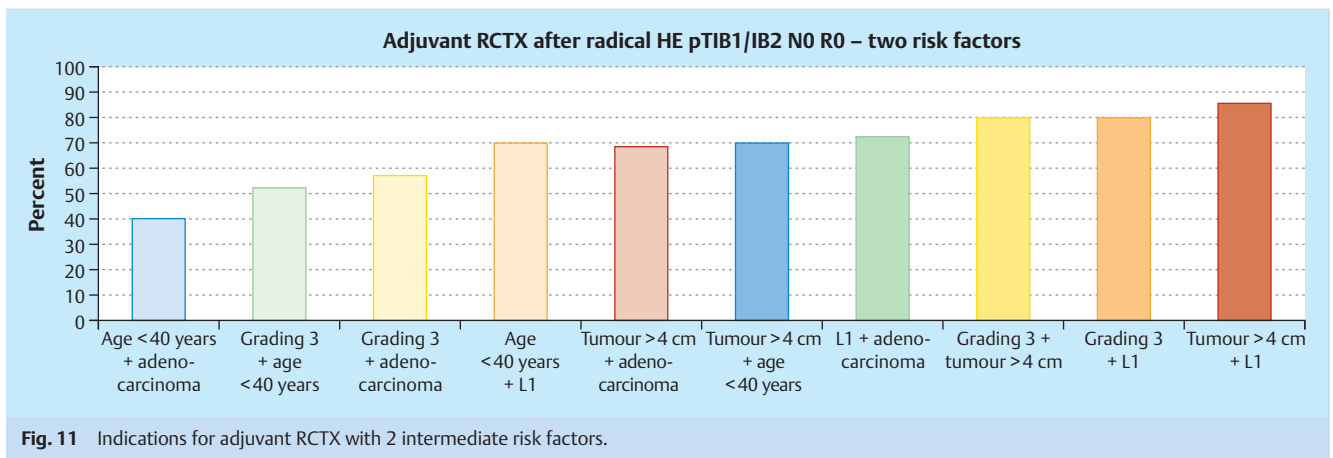


Fig. 10 Indications for adjuvant RCTX with one intermediate risk factor.



parametrium and an R1/R2 resection, the presence of the risk factors stage 3, tumour size >4 cm, age <40 years, adenocarcinoma as histological type and invasion of the lymphovascular space (L1) alone or in combination is considered in widely differing ways (Fig. 10 to 13). In the case of one of the above-mentioned risk factors 15–68% of the hospitals recommend an adjuvant RCTX, in the case of 2 factors 42–88%, for 3 factors 68–97% and for 4 factors 90–97%.

Follow-up

In the course of follow-up after primary radiochemotherapy in practically all hospitals a gynaecological examination (99%) and vaginal ultrasonography (99%) are performed. In 90% of the hospitals in addition ultrasonography of the kidneys is performed, a PAP smear in 75%, a cervical abrasion in 28%, a pelvic MRI in 41%, a tumour marker determination in 28% and/or a PET-CT in 4% (Fig. 14). On identification of a local persisting tumour/intra-uterine recurrence after primary radiochemotherapy only 28% of the hospitals consider a secondary hysterectomy as not being indicated, since it is not associated with a benefit in terms of survival. In contrast 7% of the hospitals always perform a secondary hysterectomy, 57% do so only when tumour persistence is detected. Eight percent consider a primary exenteration to be indicated in this clinical situation (Fig. 15).

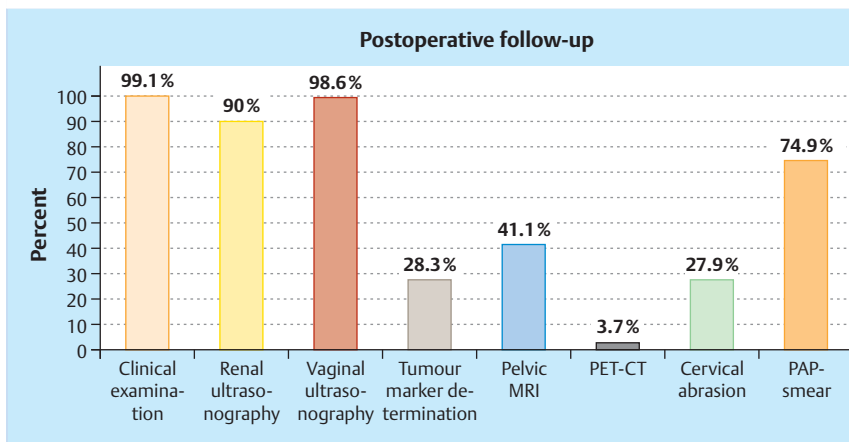


Fig. 14 Examinations performed in the course of follow-up (multiple answers possible).

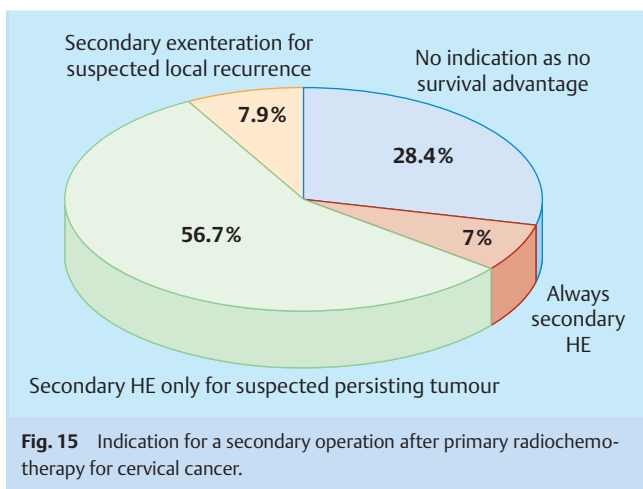


Fig. 15 Indication for a secondary operation after primary radiochemotherapy for cervical cancer.

Discussion

To what extent national guidelines are applied in the therapy for cervical cancer can only be determined on the basis of characteristic reimbursement data or with the help of questionnaires [47, 48]. Whereas the former is only meaningful when a separate character can be coded for every possible treatment modality, the latter is dependent on a high participation. The response rate of 34% achieved with the present questionnaire is adequate and also allows representative conclusions on the composition of the hospitals. The fact that within just a few years 28% of all hospitals have attained certification as oncological centres is indicative of an increased awareness of quality in the treatment of patients with gynaecological cancers. In spite of the gratifying decline in the incidence of these cancers, the number of patients with cervical cancer treated per hospital must be considered very critically. The numbers correspond to those gathered by Ackermann et al. in 2005 [98]. Only 19 hospitals of those that replied to our questionnaire treat more than 25 patients per year when thereby all stages IA1 to IVA are collected together. If this is extrapolated to all hospitals in Germany, at most 1000 patients are treated in hospitals with extensive expertise and only very few in high-volume hospitals. The great majority of women are treated in hospitals with low case numbers which, in turn, will lead to increasing problems in further training and the establishment of modern therapeutic concepts. The centralisation of therapy for patients with invasive cervical cancer should be a target for the future.

In 2006 the FIGO committee again decided to leave the staging of cervical cancer as a purely clinical process [49]. All German hospitals confer but only in 70% are the cystoscopic and rectoscopic examinations required by FIGO actually carried out. The routine use of CT and MRI in 44% and 52% reflect the widely differing data with regard to the sensitivity and specificity of these two imaging procedures found in the literature [50–54]. PET-CT, the costs of which are not reimbursed in Germany, is of no significance as a staging method in correspondence with its low sensitivity according to Ramirez et al. and LeBlanc et al. [7, 8, 10, 55]. 48% of the hospitals consider surgical staging to be a valid alternative to imaging and to clinical staging, although as yet no randomised clinical trial has been able to confirm the oncological advantages seen in retro- and prospective studies [56, 57]. The successfully recruiting prospective randomised Uterus-11 study of AGO on the value of surgical staging in patients with cervical cancers of stages IIB–IVA should provide pathbreaking answers to this matter. Why 41% of the hospitals would still choose an open transperitoneal approach for surgical staging is not clear, since it is just the formation of postoperative adhesions before an RCTX that is the main argument against surgical staging.

The significance of the sentinel concept in cervical cancer is evaluated very differently nationwide in Germany. The results of the Uterus-3 trial of AGO published by Altgassen et al. still represent the largest investigation of this topic worldwide. These results are suggestive that SLN can achieve a sufficiently high detection and sensitivity in patients with a tumour size < 2 cm [14, 58]. Merely 9% of all hospitals in Germany employ the sentinel concept routinely for carcinomas < 2 cm. 44% of the hospitals would apply the concept if requested by the patient or in clinical trials. The international trend to define patient collectives who would benefit from less radical surgery with equal oncological efficacy is only implemented in a few hospitals [59]. In addition, the advantages associated with the SLN technique such as the discovery of rare lymph drainage pathways [60] or the detection of micrometastasis [61] are not exploited. Lymph node metastasis in stage IA1 is rare [15, 62]. This supports the opinion of the majority of hospitals in Germany not to use SLN in this stage. It is, however, possible that by this means one could identify with minimal morbidity just those few patients with early lymph node metastasis, whose prognosis is otherwise rather poor [63–65].

The uterus-sparing operation in cases of early invasive cervical cancer is accepted in 97% of the gynaecological departments on account of its excellent oncological and reproductive results [66–68]. In Germany this is almost exclusively performed as rad-

ical vaginal trachelectomy in contrast to other countries where abdominal radical trachelectomy also has a high relevance [47]. Various procedures are in use in Germany for radical hysterectomy, in some cases even in one hospital. A positive development is that innovative procedures with excellent oncological outcome, such as TMMR by the Leipzig group [29] or VALRH by the Berlin group [25] are proportionally well represented. Thus we can hope that in the years to come the monocentric data will be confirmed by multicentric results. Less easily understandable are the answers of German hospitals in 74% and 43%, respectively, to continue with RH in the presence of positive pelvic or paraaortic lymph nodes. This could be based on the fact that 43% of the hospitals do not perform intraoperative immediate sections or on economic reasons, especially as practically all hospitals recommend an adjuvant RCTX in the presence of positive lymph nodes. The recommendation of GOG 109 study for an adjuvant therapy in cases of N1, parametrial infiltration and an R1/R2 resection are almost unanimously implemented in German hospitals [40,69]. The comments of the gynaecological departments about an adjuvant therapy after RH in the presence of only one or several intermediate risk factors clearly reflect the, also internationally, much too high rate of trimodal therapy, the oncological utility of which has not yet been clarified for many combinations of these risk factors [41,42]. Marnitz et al. have impressively demonstrated that the rate of adjuvant RCTX can be minimised to 10% with the help of laparoscopic staging and with knowledge of the histological results of preoperative biopsies/conisation; in this way the significantly elevated morbidity of RH and RCTX can be avoided [39]. For this complex of topics, in particular, a revised German guideline with clear unambiguous statements is needed.

The optimal therapy for patients in FIGO stages IB2 and IIB has been a subject of controversial discussion for many years, but is still not clear as is reflected in the results of this and earlier questionnaires [98]. The spectrum of nationally as well as internationally applied therapies encompasses primary radical hysterectomy ± adjuvant radiochemotherapy, neoadjuvant (radio)chemotherapy followed by radical hysterectomy, primary radiochemotherapy (RCTX) or TMMR. In the not yet closed prospective randomised international EORTC study 55994, neoadjuvant chemotherapy followed by radical hysterectomy is being compared with primary RCTX in the tumour stages IB2–IIB. A randomised study to compare the primary operation followed by adjuvant RCTX with primary RCTX for these tumour stages has not yet been undertaken. In non-randomised studies that have compared various therapeutic procedures, both significant and non-significant differences have been presented [70–77].

Whereas in the last century, an operation for patients with cervical cancers up to stage IIB was in most cases the therapy of choice, in the present century primary radiochemotherapy has become established worldwide for patients in FIGO stage IIB on the basis of the results of 5 prospective randomised studies. The significant improvement in survival (referred to OS) in favour of combined radiochemotherapy as compared to radiation alone has been proven in several metaanalyses. For patients in stage IIB the improvement in survival amounts to 7% [33], or in a large retrospective analysis by Beck et al. on the basis of data for 5476 patients even to 13% [34]. The result of the questionnaire with regard to therapy in stage IIB with a rate of 46% for RH as primary therapy is thus surprising.

For patients with a cervical cancer in stage IVA individual therapeutic decisions should be made because there are no randomised comparisons between primary exenteration and primary

RCTX, this opinion is shared by 82% of the German hospitals. The question why only 13% of the hospitals prefer a primary exenteration in cases of pre-existing fistula formation must be evaluated critically with regard to the available surgical expertise in Germany [78–80].

The follow-up of patients after primary therapy for cervical cancer, especially primary RCTX, is regulated with regard to time intervals but not with regard to extent. Also in Germany the clinical examination with vaginal ultrasonography is used routinely even when its utility with regard to detection of local recurrence/progression is limited. Thus, according to Duyn et al. only 32% of the recurrences are detected in the follow-up [81], or according to Ansink et al. merely 26% [82]. Imaging procedures such as CT or MRI or PAP smears are, however, not superior to the clinical examination [83]. The utility of MRI in the follow-up is also disputed, as described by Balleyguier et al. [84], accordingly the moderate use in 41% of the hospitals is justified. PET-CT is associated with a high rate of false negative and false positive findings in the diagnosis of recurrences as has been demonstrated by Chung et al. in 276 patients [85], whereas in other studies it has revealed a good correlation between complete metabolic response and survival [86]. Further studies on the value of PET-CT in the follow-up are needed. The determination of the tumour markers SCC and CEA is undertaken in 28% of the German hospitals [46,87], even when the available data suggest that the determination of these markers is not reliable [46,87].

Routinely taken cytological samples – as is done in 75% of the gynaecological departments – should no longer be considered as the sole follow-up examination on account of the low detection rate for recurrences of between 0 and 17% [88–91,97]. According to Nijhuis et al. the combination of examinations under anaesthesia with biopsy sampling/cervical abrasion can detect or exclude a local persisting tumour after primary RCTX with a high probability [91]. This method should thus be employed more often than its current implementation in merely 28% of the hospitals. The wide spectrum of answers with regard to secondary operation in patients after primary RCTX for cervical cancer reflects the lack of evidence on this topic. While Motton et al. did not observe any increased rate of complications, Classe et al. and Colombo et al. recorded complications in 26–48% of their secondary operations. To what extent a simple hysterectomy is oncologically more meaningful than a radical hysterectomy or an exenteration also remains to be clarified. None of the studies could show any advantages with regard to overall survival, merely local control or, respectively, PFS were improved [91–97]. A randomised study of surgical strategies for persisting tumours is ethically not possible.

Of course, the results presented here have their limitations. The design and length of the questionnaire did not allow the inclusion of all interesting questions and all possible answers. Also the fact that only a good third of the hospitals responded means that the results are still representative, although a higher participation would have been highly desirable.

Conclusion



The results of this questionnaire on the therapy for cervical cancer in Germany in 2012 reveal on the one hand that innovative concepts (laparoscopic procedures for RH, TMMR, surgical staging) have found acceptance in German hospitals while, on the other hand, long established treatment concepts (RH in case of

positive pelvic and/or paraaortic lymph nodes, therapy in FIGO stage IIB, recommendation for adjuvant therapy) are being retained. Randomised prospective studies should be put into practice. The lack of evidence for many questions leaves room for a broad spectrum of opinions and treatment pathways. The future new version of the S3 guidelines on the diagnostics and therapy for patients with cervical cancer should thus include unambiguous statements for many of these aspects.

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Conflicts of Interest

None.

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