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Total Mesometrial Resection With (Neo)Adjuvant Chemotherapy in Locally Advanced Cervical Cancer: A Tumor Response Score

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Abstract. *Background/Aim: There is a lack of data concerning the surgical treatment of locally advanced squamous cell carcinoma of the uterine cervix (LACC) with neoadjuvant and adjuvant chemotherapy (NACT, ACT) as well as total mesometrial resection (TMMR). The aim of the study was to present a novel approach for treating LACC using a tumor response score for NACT. Patients and Methods: A total of 12 patients with LACC were treated with NACT [cisplatin, ifosfamide, paclitaxel (TIP)], TMMR and ACT containing TIP. To measure the response during NACT, we scored i) the maximum tumor diameter (maxTD) in gynecological examination, ii) the MRI for radiologic maxTD, iii) the tumor volume and iv) the squamous cell carcinoma antigen before and after two applications of TIP. Results: TIP reduced all score-parameters in 10 of 12 patients ($p<0.005$). We found a possible reduction of lymph node metastasis in 72.7%. The proposed score detected sufficient and insufficient tumor response. Conclusion: TIP followed by TMMR with ACT could be a possibility for patients denying radiochemotherapy. The tumor response score can detect patients with inadequate benefit from NACT.*

Cervical cancer poses a serious hazard for women's health worldwide (1). From a global perspective it shows the fourth highest incidence as well as mortality of all female malignant diseases (2). Every year 500,000 women are diagnosed with cervical cancer and 300,000 die from its consequences (3). Depending on factors such as age, socioeconomic status, ethnicity and available medical infrastructure, the incidence of locally advanced cervical cancer can range up to 50% (4, 5), although nation-wide established screening programs can decrease the incidence of cervical cancer (6). However, in countries with a well-organized healthcare system cases of locally advanced cervical cancer can be also found, including young patients (7-9). In Germany, the most common therapy options are radical hysterectomy or chemoradiation/ radiochemotherapy (RCHT), with surgery historically being the main therapeutic approach. RCTH is mainly recommended for locally advanced cervical cancer (6, 10). Until TNM-stadium II, radical hysterectomy and RCHT are rated equal, although a combination of surgery and radiation should be avoided (11). Nevertheless, the guidelines emphasize on the various possibilities for therapy, especially in cases of locally advanced cervical cancer. An excerpt of the German guidelines, showcasing possible therapy strategies, is depicted in Figure 1 (6). Focusing on this patient group, a therapy's (long-term) morbidity has to be thoroughly taken into account as well as the patient's age and quality of life, in addition to the oncological outcome.

In our experience, single patients with locally advanced cervical carcinoma explicitly ask for therapy options other than chemoradiation. Patients' reasons for this can be simple fear of radiation in general or of concrete, especially long-term radiation-associated side-effects, such as vaginal, bladder or rectal toxicity (12-18). Moreover, pelvic radiation can induce further pelvic adhesions or inflammation, potentially leading to enteropathy, bleeding, obstruction, fistula or cystitis and can possibly decrease the chance of offering a surgical approach in case of a recurrence (19-34). In order to offer selected patients a surgical therapy-option, the possibility of the Extended Mesometrial Resection (EMMR), Total Mesometrial Resection (TMMR) and Laterally Extended Endopelvic Resection (LEER) can be discussed, depending on the individual case (35-39). The

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Key Words: Locally advanced cervical cancer, LACC, total mesometrial resection, TMMR, neoadjuvant chemotherapy, adjuvant chemotherapy, cisplatin, ifosfamide, paclitaxel, TIP, tumor response.

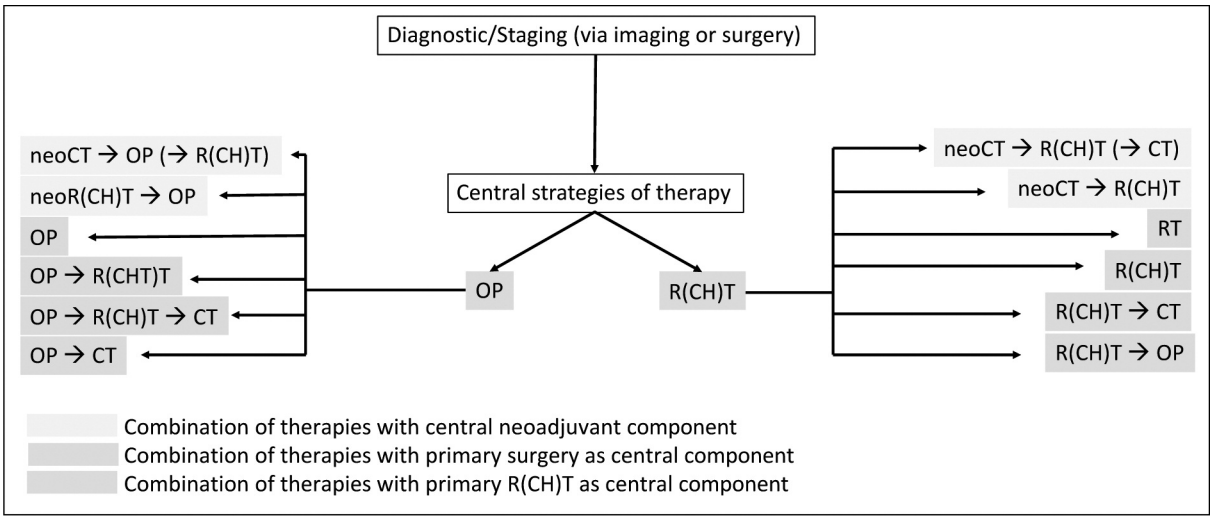

Figure 1. *Translated excerpt from the German guidelines for treatment of cervical cancer, page 89 (6). RT: Radiation therapy; CT: chemotherapy, R(CH)T: radio(chemo)therapy; OP: surgery; neoCT: neoadjuvant chemotherapy; neoR(CH)T: neoadjuvant radio(chemo)therapy; →: followed by.*

German guideline explicitly mentions the stated surgical therapies as valid treatment option. In this context the guideline states, that there is no sufficient data for therapy-recommendations in case of lymphatic metastasis after NACT (40).

There is data discussing the possibility of combining conventional radical hysterectomy with neoadjuvant chemotherapy (NACT) or adjuvant chemotherapy (ACT). When viewing the literature, it becomes apparent, that numerous different chemotherapeutic agents, some as mono-, others as combinational therapies, are examined in varying intervals of application (1, 41-53). Although representing an individual healing attempt for each patient, the option of applying neoadjuvant chemotherapy is also mentioned in the current German guidelines. According to our knowledge, data about TMMR together with NACT and ACT using cisplatin, ifosfamide and paclitaxel as treatment options for locally advanced cervical cancer is lacking. In this retrospective study we report on a series of patients with locally advanced cervical cancer asking for an individual healing attempt, focusing on the described combination of chemotherapy and radical surgery as TMMR. In this context, we also present a possible tool for examining the tumor response during NACT, thus establishing a standardized procedure for such special cases.

Patients and Methods

At the Department of Gynecology of the University Clinic Würzburg 12 patients were treated with locally advanced squamous cell carcinoma of the uterine cervix, whose data was examined retrospectively as single center study from 2014 to 2021.

The patients' age at diagnosis ranged from 33 to 50 years with a median age of 42 years. The general clinical data is illustrated in Table I. In this work we followed the TNM-classification of the German S3-guideline, version 2014 (54). The presented cases were treated as individual therapeutic approaches and all patients were thoroughly educated about the contents of the German guidelines, explicitly suggesting chemoradiation and offering a consultation at the department of Radiation therapy prior to any intervention.

In order to obtain an overview of existing data about the subject of chemotherapy plus radical surgery, a review of literature was conducted in the medical database PubMed. Publications from 2015 or later were included, if they consisted of meta-analysis, reviews or systematic reviews. Key words used were "cervical cancer", "surgery" and "chemotherapy". Initially, all manuscripts were sighted based on the title and abstract. If the content was related, the manuscripts were reviewed and the data was extracted. Thus, 10 meta-analysis or (systematic) reviews were found, highlighting the sparse amount of data concerning this subject.

The majority of our patients received the following procedure: staging consisting of computer tomography (CT) of chest and abdomen, including the pelvis, magnetic resonance imaging (MRI) of the pelvis, cystoscopy and rectoscopy together with a gynecological examination while being anesthetized. With all diagnostic data being available, the patient's case was presented and discussed the clinic's interdisciplinary tumor board. A consultation at the department of Radiation therapy was recommended to every patient and all were extensively informed about this procedure being an individual healing attempt. Informed written consent was obtained in all cases. NACT consisted of cisplatin (75 mg/m^2), ifosfamide (5 g/m^2) and paclitaxel (175 mg/m^2), basing on the findings from Buda *et al*. (1). This form of NACT shall be called "TIP-regime" (referring to taxol, ifosfamide and platin) in the following. Cisplatin was applied over a duration of 60 minutes, paclitaxel over 180 minutes and ifosfamide over 24 h *via* an intravenous port catheter system. This procedure was repeated if possible three times with three weeks between each application. For reducing side-effects, the patients received aprepitant, dexamethason,

Table I. *General clinical data of each patient containing year of diagnosis, suspicious lymph nodes in imaging, positive lymph nodes in pathology, invasion of lymphatic vessels and blood vessels, Grading, number of applications of neoadjuvant chemotherapy (NACT) and adjuvant chemotherapy (ACT), secondary diagnoses, potential radiochemotherapy (RCHT) received.*

Patient number	Year of diagnosis	Clinical T-stadium	Suspicious lymph nodes in imaging (cNü+)	Number of positive lymph nodes (pN+)	Invasion of lymphatic vessels (L1)	Invasion of blood vessels (V1)	Grading (G)	Number of applications of NACT (TIP-scheme)	Number of applications of ACT	Secondary diagnoses (known before diagnosis of cervical cancer)	RCHT received
1	2014	Ib2	cN+	0/46	-	-	3	3	0	-	
2	2014	IIa	cN+	4/67	L1	-	3	4	1	Arterial hypertension	RCHT received
3	2017	Ib2	cN+	0/63	-	-	3	2	3 applications Carboplatin/ Paclitaxel, due to connatal acustic deficiency	Connatal acustic deficiency (60% loss of hearing)	
4	2018	Ib2	cN+	0/29	-	-	3	2	2 applications Carboplatin/ Paclitaxel	Arterial hypertension, chronic asthma	
5	2019	IIb	cN+	1/56	L1	-	2	3	3	-	
6	2019	Ib2	cN+	0/47	-	-	2	3	3	-	
7	2019	Ib2	cN+	6/82	L1	V1	3	3	0	-	RCHT received
8	2020	Ib2	cN0	-	-	-	1	2	0	Granulomatous polyangiitis	RCHT received
9	2020	IIb	cN+	0/14	L1	-	3	3	0	Eczema, schizophrenia, hypothyreosis, hypercholesterolemia	
10	2020	Ib2	cN+	0/46	-	-	3	3	1	Leg vein thrombosis	
11	2020	IVb	cN+	0/58	-	-	3	4	2	Anal prolaps	
12	2020	Ib2	cN+	0/58	-	-	3	4	Pending	-	

mesna, ranitidin, clemastin, mannitol, potassium chloride, magnesium sulfate, ondansetron pegfilgastrim, ciprofloxacin and intravenous fluid. Psychological and ecotrophological support was also offered. After two cycles of the TIP-regime, a response control was initiated by gynecological examination, squamous cell carcinoma antigen (SCC) and pelvic MRI. After the patients had received the third TIP-regime, an extended radical hysterectomy was performed as TMMR. In individual cases, also a 4th application of NACT was given, if adequate tumor response could be seen with yet considerable tumor mass remaining and sufficient tolerance towards the chemotherapy's side-effects. Four weeks after surgery, the patients were seen by the surgeon for a postoperative examination and explanation of the further procedures. In the following, 3 additional applications of the TIP-regime were given as adjuvant chemotherapy. After accomplishing the adjuvant chemotherapy, the aftercare was initiated, which was performed every three months. After 6 months, a MRI of the pelvis was added. All clinical response controls and all surgeries were performed by the same physician. As individual cases are presented retrospectively, standardized procedures are partly lacking.

From the years 2014 until 2019 the radiological response controls varied with CT, MRI or Positron emission tomography computed tomography (PET-CT) being used. All imaging was examined once again by one radiologist consultant for this work, in order to reduce inter-observer-variability. The value of pelvic MRI for evaluating locally advanced cervical cancer and its response to therapy has been shown (1, 55-62). Over the course of time, the described standard operating procedure was developed, which is depicted as a flow-chart in Figure 2.

As each therapy was seen as individual therapeutic approach, we used certain parameters to measure the response during NACT in a standardized manner:

1. The gynecological examination, always performed by the same physician, measuring the maximum tumor diameter (referred to as palpation maxTD, in cm),
2. the MRI of the pelvis for measuring the maximum tumor diameter (radiologic maxTD, in mm),
3. the tumor volume (TV, in mm^3) and
4. the tumor marker squamous cell carcinoma antigen in ng/ml, as all tumors were squamous cell carcinomas.

The radiologic maxTD was measured according to the Response Evaluation Criteria in Solid Tumors (RECIST) using the maximum

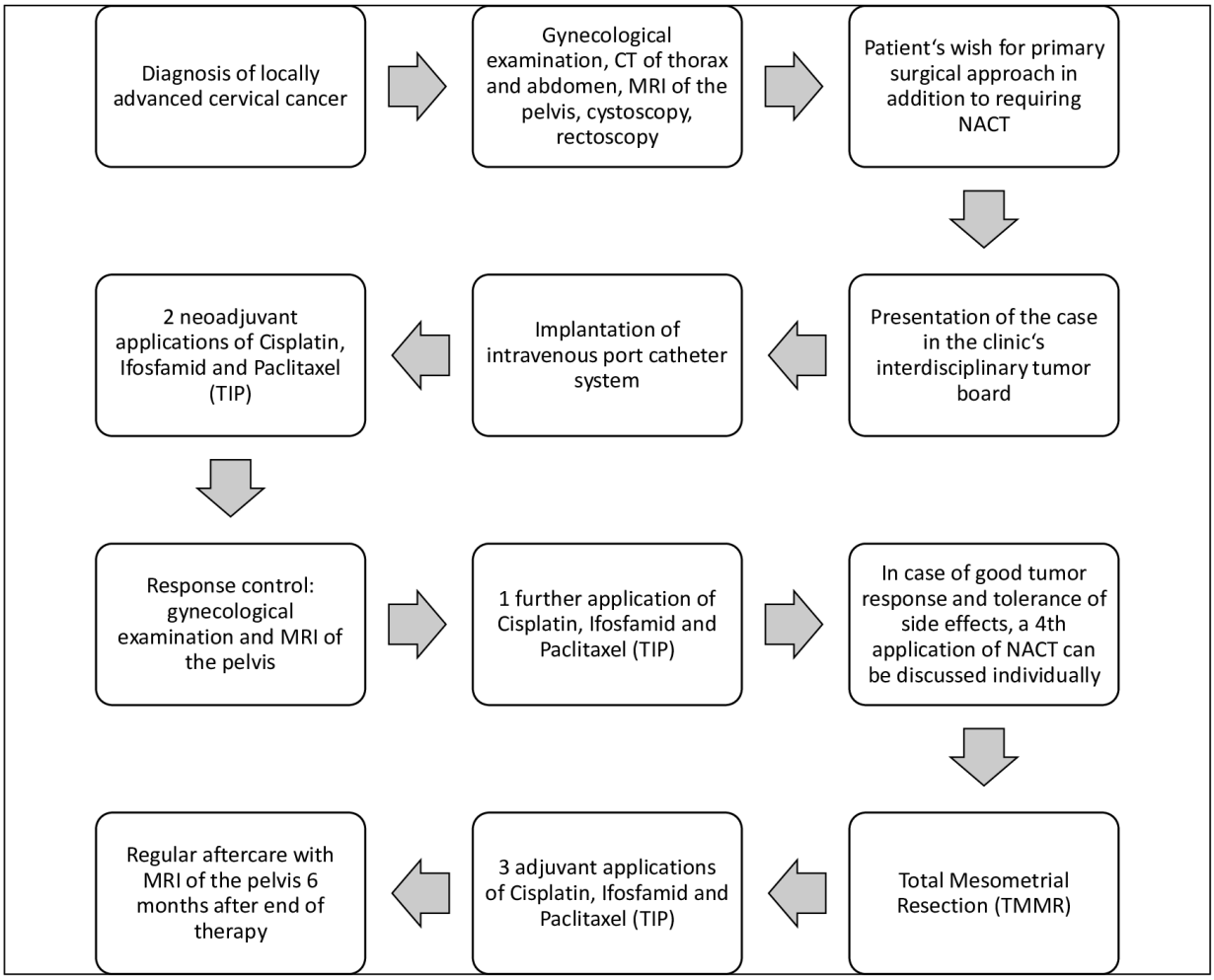

Figure 2. *Simplified flow-chart of standard operating procedures for organizing neoadjuvant chemotherapy (NACT) followed by total mesometrial resection (TMMR) and adjuvant chemotherapy (ACT).*

axial diameter in paraxial planes. Further, we assessed the axial-orthogonal diameter and the cranio-caudal diameter from the saggital plane (63, 64). The TV was evaluated following the PRICE-2-study (64), using the following formula:

$TV=D_{AP} \times D_{CC} \times D_{LL} \times \pi/6$
(D_{AP}=anterior-posterior diameter, D_{CC}=cranio-caudal diameter, D_{LL}=lato-lateral diameter, π=Pi).

These examinations should be conducted prior to NACT and after two applications. If sufficient tumor response was seen, we continued with chemotherapy, followed by TMMR. In order to establish standardized procedures for these individual cases, we created a score to evaluate the tumor response during NACT. Components of this score are the decrease of palpation maxTD as well as radiologic maxTD, TV and SCC, all of which in percent. Points are given for each of the stated parameters, according to its reduction after at least 2 applications of NACT. If the reduction is less than 30%, 0 points are given. 30% or more equal 1 point. More than 50% lead to 2 points and a reduction of 80% or more leads to 3 points. This is repeated for all named parameters. The single points are then summed up. More than 6 points indicate an adequate tumor response. Hence, NACT can be continued. 6 points or less trigger a discussion, whether or not the NACT is to be continued. In this case, the gynecological examination with palpation maxTD outweighs radiologic maxTD, TV and SCC. The scoring system is illustrated in Figure 3.

The side-effects of NACT, surgery and ACT according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 were extracted from the clinical documentation-system, consisting of written and electronic documents. They are depicted in Table II.

Statistical analysis was performed by using the one-sample-*t*-test, one-sample-Wilcoxon Test, Wilcoxon signed rank test and Friedman's analysis of variance on SPSS for Mac, version 25 (IBM, Armonk, NY, USA). The Wilcoxon signed rank test was used to examine whether the reduction in the palpation maxTD after two

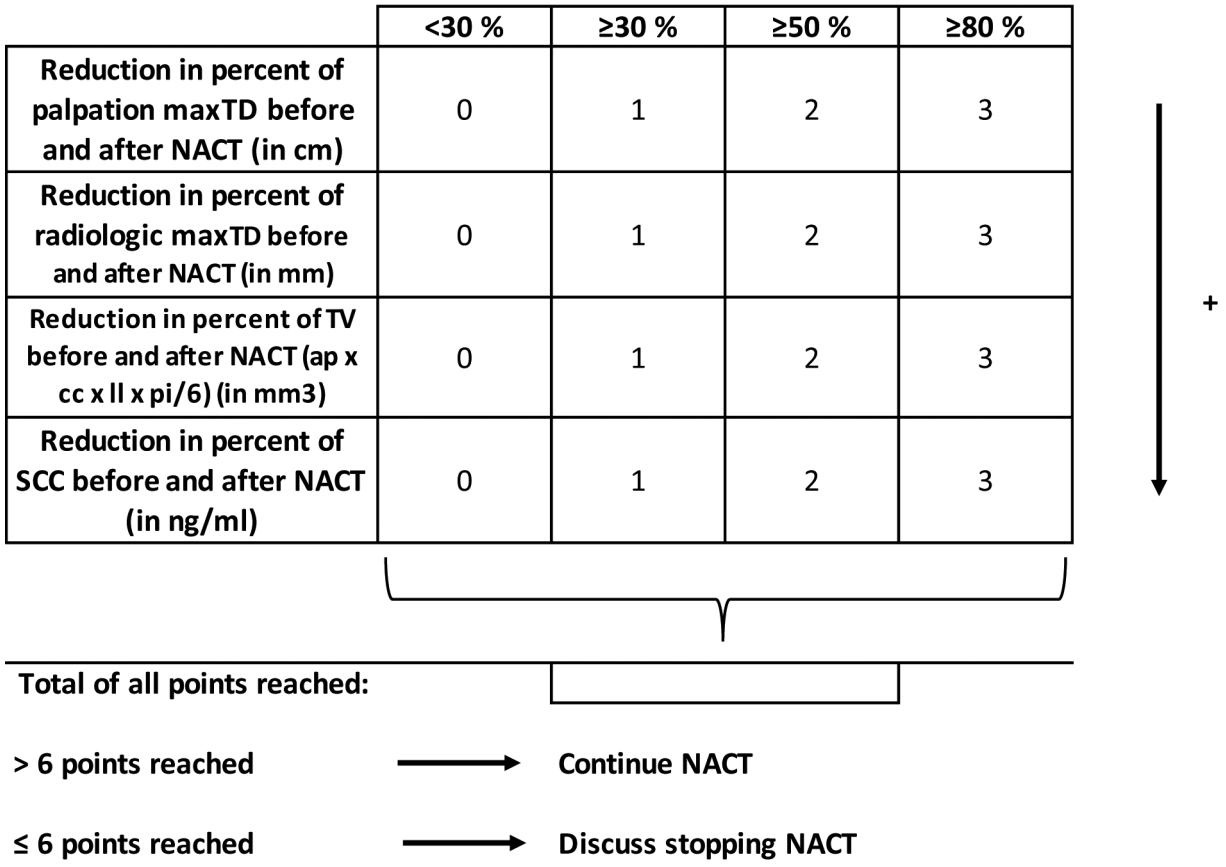

Figure 3. *Tumor response score. According to the reduction in percent of palpation maximum tumor diameter (maxTD), radiologic maxTD, tumor volume (TV) and squamous cell carcinoma antigen (SCC), points are given. If the total of all points exceeds 6 points, the NACT can be continued.*

applications of NACT was statistically significant. The one-sample-*t*-test was used to examine whether the reduction of radiologic maxTD in percent was statistically significant. With the one-sample-Wilcoxon test we examined whether the reduction in TV showed statistical significance. Lastly, the Friedman's analysis of variance, adjusted by Bonferroni correction, was applied in order to examine whether the reduction of SCC in percent was statistically significant.

Results

The gynecological examination showed a reduction in the palpation maxTD after two applications of NACT. Except for patients 8 and 9, all patients showed a reduction in palpation maxTD of at least 50% (50%-90%), with an average reduction of 60.1%. The median palpation maxTD before and after NACT is depicted in Figure 4a. Individual data is summarized in Table III. The reduction showed statistical significance (N=12, $p<0.005$).

According to the results of the gynecological examination, a decrease of radiologic maxTD and TV during NACT could be examined. This can be seen in Figure 4b and Figure 4c. Both palpation as well as radiologic maxTD and TV depict a reduction of the tumor during NACT, illustrating sufficient tumor response in most cases and illustrating that palpation maxTD and radiologic maxTD appear to be relatively similar. The reduction of radiologic maxTD in percentage ranged from 100% to 21% and showed statistical significance (N=11, $p<0.0001$). This is illustrated in Table IV. The reduction of TV, which can be seen in Table V, ranged from 100% to 51% and was also statistically significant (N=11, $p<0.005$). Within two patients (patient 3 and 11) a radiologic complete response could be measured. When comparing the percentage of reduction between palpation and radiologic maxTD and TV, it becomes evident that TV shows a higher percentage of tumor reduction than the palpation and radiologic maxTD.

With 6 patients (patient number 6-12) we used the tumor marker SCC for further visualizing the therapeutic response during NACT and in order to have an additional tool for the future period of aftercare. Blood samples for SCC were obtained before NACT, after two TIP-regimes and after surgery. Figure 4d depicts the decrease of SCC during NACT and after surgery, visualizing tumor response during chemotherapy. This is additionally shown for each patient in

Table II. *Number of patients suffering from side-effects during neoadjuvant chemotherapy (NACT), surgery and radiochemotherapy (RCHT).*

NACT	Number of patients suffering from:	Degree of side effects following CTCAE (Common Terminology Criteria for Adverse Events) 5.0		
		1°	2°	3°
	Abdominal pain	2		
	Anemia	2	5	2
	Arthralgia	1		
	Blurred vision	1		
	Constipation	1		
	Depression	2		
	Dizziness	2		
	Dry eyes	1		
	Elevated creatinine	1		
	Fatigue	1		
	Febrile neutropenia			2
	Gastritis Type C	1		
	Headache	1		
	Hypokalemia	1		
	Mucositis	1	1	
	Nausea	4	3	
	Polyneuropathia	2		
	Syncope			3
	Vascular access complication			3
	Vomiting		2	
Surgery	Number of patients suffering from:	Degree of side effects following CTCAE (Common Terminology Criteria for Adverse Events) 5.0		
		°1	°2	°3
	Adhesive ileus			1
	Anemia		1	
	Lymphocele	1		
	Thromboembolic event			1
	Urinary retention		1	
RCHT	Number of patients suffering from:	Degree of side effects following CTCAE (Common Terminology Criteria for Adverse Events) 5.0		
		°1	°2	°3
	Anemia	1	1	
	Diarrhea	3		
	Nausea	1		
	Proctitis	1		
	Vascular access complication		1	

Table VI. The reduction in percent of SCC ranged from 36% in patient 8 to 96% in patient 5 after two applications of NACT. The reduction of SCC after all applications of NACT and surgery showed statistical significance (N=7, $p<0.002$). The reduction of SCC after two applications of NACT was not statistically significant (N=7, $p<0.25$).

The described tumor response score, being used in a retrospective manner in this work, showed adequate scores except for two patients. Patient number 8 experienced an interruption of NACT and initiation of RCHT due to the lacking tumor response after two applications of TIP. Patient number 9 showed, as described above, adequately increased mobility of the tumor in gynecological examination, consequently allowing primary surgery although the overall response was inadequate. This was done in order to follow the patient's explicit wish for primary surgery.

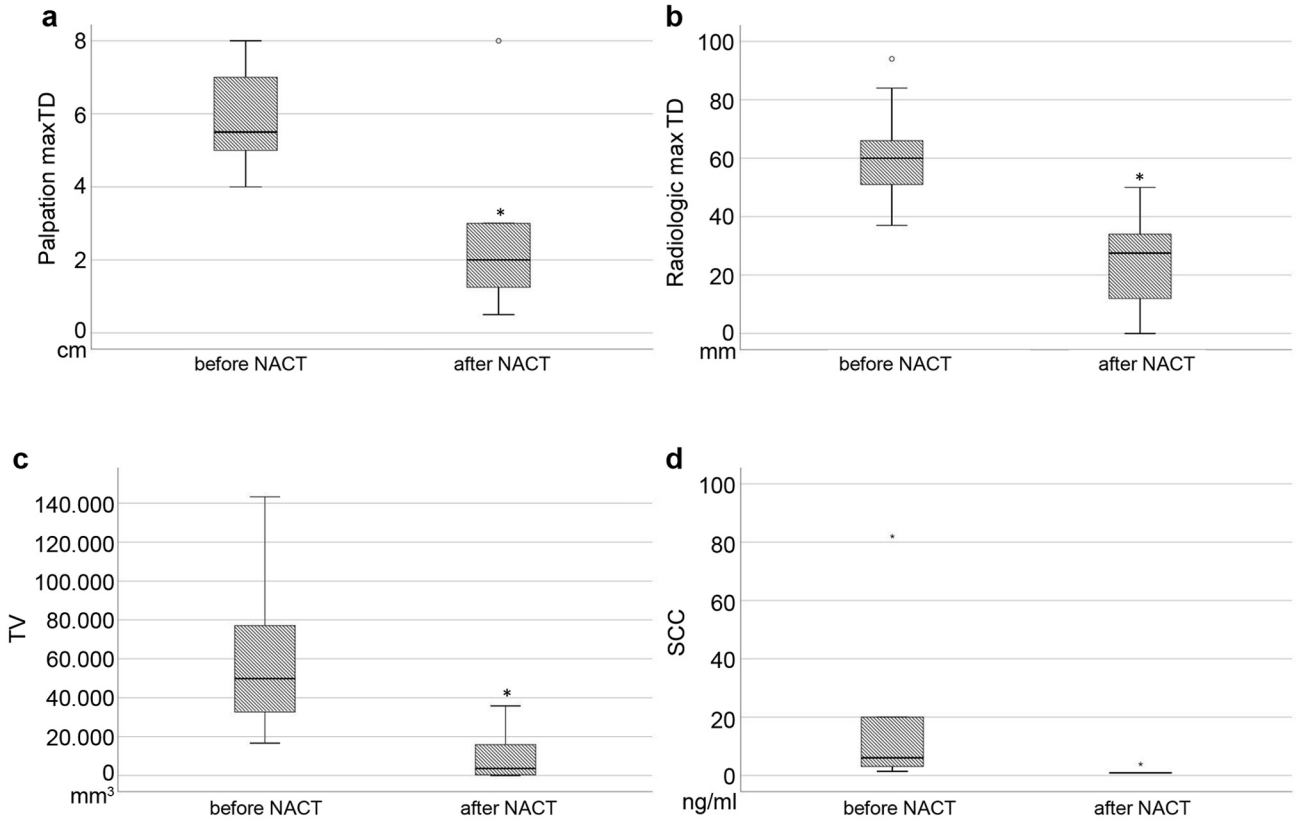

Figure 4. *Maximum tumor diameter, measured by palpation (palpation maxTD) (a) and by MRI (radiologic maxTD) (b), tumor volume (TV) (c) and tumor marker squamous cell carcinoma antigen (SCC) (d) before and after neoadjuvant chemotherapy (NACT). *marks statistically significant reductions of palpation and radiologic maxTD and TV after NACT.*

Table VII showcases the lymphonodal status of each patient. All patients except for patient 8 (91.7%), presented lymph nodes, which were radiologically suspicious for metastasis. All of these patients showed a reduction of their suspicious lymph nodes after at least 2 applications of NACT, measured *via* CT or MRI. Patient number 2 and patient number 4 underwent lymph node sampling *via* laparoscopy, revealing positive lymph nodes in patient 2. These findings were confirmed within the resected lymph nodes in wake of the following TMMR. Patient 11 presented a bulky paraaortic lymph node, which could be biopsied *via* CT and which showed metastasis. Yet in the final pathological result after TMMR, all resected lymph nodes were free of malignant cells. With 11 patients, an average of 51 lymph nodes, ranging from 14 to 82 lymph nodes, was resected (pelvic/paraaortic lymph node dissection), revealing lymph node metastasis in 3 patients (25.0%). All of these patients had shown suspicious lymph nodes in the prior imaging. Assuming that all suspicious lymph nodes in CT or MRI were affected by lymph node metastasis, this would be a reduction of 72.7%.

The same surgeon performed all gynecological examinations and all surgeries and every time adequate resection (R0) was achieved. The final pathological findings referring to Grading (G), invasion of blood (V) or lymphatic vessels (L) can be seen in Table I. From 12 patients, patient number 8 showed an insufficient tumor response after two applications of NACT, as stated above. Consequently, the NACT was not continued and radiation therapy was initiated. Because of this, there are no histological findings for this patient.

Following the described standard operating procedure, all patients should receive 3 applications of ACT. This could often not be realized: With patient number 1, no ACT was recommended, as there was no more active tissue to be seen in the PET-CT. Patient 2 denied any further ACT after her 1st application. Consequently, RCHT was offered, because of positive lymph nodes, which she also interrupted after 5 applications. She then wished no further therapy. Patient number 3 received all three adjuvant TIP-regimes, but with no ifosfamide, because of her connatal acoustic deficiency. Having experienced side-effects during NACT, patient number 4 only accepted 2 applications of ACT without

Table III. *Response control via palpation maxTD during NACT. The reduction in percent showed statistical significance, using the Wilcoxon Signed Rank Test (N=12, p<0.005).*

Patient number	Number of applications of NACT	Palpation maxTD before NACT (in cm)	Palpation maxTD after NACT (in cm)	Reduction in percent of palpation maxTD
1	3	6	3	50
2	4	5	1	80
3	2	5	1.5	70
4	2	8	3	62.5
5	2	6	2	66.7
6	2	8	3	62.5
7	3	5	2	60
8	2	8	8	0
9	2	4	3	25
10	2	4	1	75
11	2	5	0.5	90
12	4	6	1.2	80

ifosfamide. Patient number 7 accepted the recommended adjuvant RCHT, as she had presented several positive lymph nodes in the final pathological results. Patient number 9 explicitly only wished for NACT followed by TMMR. She denied any further therapy. After repeated pancytopenia, patient number 10 only received 1 adjuvant TIP-regime. Patient number 11 accepted 2 and patient number 12 accepted 3 applications of ACT.

Until now, all patients are alive and only patient number 7 experienced a recurrence of cervical cancer as bone metastasis of the superior pubic ramus. She had received NACT, TMMR, ACT as well as subsequent RCHT because of positive lymph nodes. The bone metastasis was detected as suspect lesion *via* pelvic MRI during aftercare and was secured with CT-guided biopsy. A therapy with carboplatin, paclitaxel, bevacizumab and bisphosphonates has been initiated.

Table II illustrates the side-effects the patients suffered from chemotherapy, surgery and RCHT. Concerning chemotherapy, 8 of 12 patients experienced hematopoetic side-effects consisting of anemia, thrombocytopenia and/or febrile neutropenia of at least grade 2 according to CTCAE version 5.0. This led to the necessity of transfusing erythrocyte- or thrombocyte-concentrates. In addition, 5 patients suffered from flush and dyspnea during application of paclitaxel, which is not depicted in the CTCAE. In 4 cases, the number of applications of chemotherapy, the chemotherapeutic drugs or the dose of chemotherapy had to be adapted, because to the side-effects. After surgery, one patient suffered from adhesive grade 3 ileus several years after surgery. Moreover, one case of grade 1 lymphocele, one grade 3 thromboembolic event and one case of grade 2 urinary retention were found. RCHT led to one case of grade 1 anemia and grade 3 diarrhea, three cases of grade 1 nausea, one case of grade 1 proctitis and one case of grade 2 vascular access complication (port system dislocation). Moreover, patients number 2 and 7 received additional RCHT after TMMR and ACT. This was discussed as individual solution for both patients, basing on the final pathological results after TMMR.

Discussion

We investigated patients with locally advanced cervical cancer seeking for alternative therapeutic options other than primary chemoradiation. If demanded by a patient, the surgical concept of TMMR, combined with neoadjuvant and adjuvant chemotherapy, can be a possibility, in order to offer single patients with locally advanced cervical cancer an individual solution. Herein we report that NACT with TIP-regime can be highly effective in downstaging locally advanced cervical carcinoma by significantly reducing palpation and radiologic maxTD, TV and SCC. Additionally, we saw a possible reduction of lymph node metastasis in up to 72.7% of cases.

Similar to our findings, the Studio Neo-Adjuvante Portio (Snap01)- and Snap02-study, report higher response rates in the TIP-arm than in the ifsofamide-cisplatin- (IP)-arm with a higher number of side-effects. Nausea and hematopoietic side-effects were the most common. Lissoni *et al*. reported grade 3-4 anemia in 18.3%, thrombocytopenia in 14.0% and neutropenia in 59.1% of cases. Buda *et al*. reported grade 3-4 anemia in 32.8%, thrombocytopenia in 23.3% and neutropenia in 76.4% of cases. Grade 2-3 nausea and vomiting occurred in 62.4% (1, 60). In both studies, the IP-arm showed less therapeutic response but also less side-effects. Other than Snap01 and -02, we used granulocyte stimulating factor from the beginning after every chemotherapy and not only in case of repeated neutropenia.

Table IV. *Response control via radiologic maxTD during NACT. Bold fields show lacking imaging in certain cases. The reduction in percent showed statistical significance. (One-sample-t-test, N=11, p<0.0001).*

Patient number	Number of applications of TIP-scheme before next imaging	Modality	Radiologic max. Tumordiameter ($_{max}$TD) before NACT (in mm)			Modality	Radiologic max. Tumordiameter after NACT (in mm)			Percentage reduction $_{max}$TD axial
			Axial - max	Axial-orthog	cc (from sag)		Axial - max	Axial-orthog	cc (from sag)	
1	3	MRI	66	46	39	Missing				
		PET-CT	66	43	35	PET-CT	Not measurable			
2	4	MRI	49	31	94	Missing				
		PET-CT	51	33	84	PET-CT	27	19	15 (cor)	47
3	2	MRI	51	36	38	MRI	0	0	0	100
4	2	ext. MRI	68	61	66	Missing				
		Missing				CT	42	37	42	39
5	2	MRI	54	33	38	MRI	14	13	18	74
6	2	MRI	65	54	48	MRI	28	12	18	57
7	3	MRI	63	39	49	MRI	28	24	19	55
8	2	ext. MRI	64	50	46	MRI	50	38	36	22
9	2	ext. MRI	43	33	44	MRI	34	27	33	21
10	2	MRI	33	26	37	MRI	12	7	7	64
11	2	MRI	45	25	42	MRI	0	0	0	100
12	2	MRI	54	43	26	MRI	9	7	8	83

A promising possibility of effective NACT before radical surgery is proposed by Salihi *et al*.; 36 patients with stage I to II cervical cancer were treated with 9 weeks' NACT dose-dense paclitaxel-carboplatin (median weekly dose Paclitaxel 60 mg/m^2, Carboplatin area under the curve 2.7). After NACT, tumor response was measured *via* MRI: 11 of 36 patients showed complete and 21 patients showed partial response. Thirty patients were eligible for surgery after NACT. Pathology revealed pathologic complete response (disappearance of disease) in 10 patients and partial response 1 (residual disease with less than 3 mm stromal invasion including in situ carcinoma) in 5 patients. This shows comparable response rates to TIP. Furthermore, hematologic side-effects were lower with no febrile neutropenia (61).

Data can be found about the combination of regular radical hysterectomy with NACT or ACT. According to our knowledge, data explicitly examining TMMR together with NACT and ACT with TIP-regime is lacking. The aim of NACT can be to achieve a sufficient downstaging, in order to enable or improve an adequately radical operability. When viewing the existing literature, it becomes apparent, that there have been several studies examining NACT prior to regular radical hysterectomy with various different chemotherapeutic agents. Some chemotherapies are used as mono-, others as combinational therapy. Some of these are cisplatin, nedaplatin, paclitaxel, topotecan, ifosfamide, epirubicin, bleomycin, vincristine, mitomycin-C, 5-fluoruracil and irinotecan. The intervals of application vary (1, 10, 41-53, 60). In addition, the way the NACT was applied also varied between intravenous and intraarterial injection (53, 65-69).

There are studies showing the benefit of NACT followed by radical surgery *versus* radical surgery alone (70-76). Achieving an optimal pathological response (*e.g.* no more tumor in the uterine cervix with negative lymph nodes or less than 3 mm stromal invasion of rest-tumor) during such NACT is an independent prognostic factor for the patients' overall- and disease-free survival (OS) (1, 10, 60, 77, 78). Furthermore, there are data indicating, that early clinical response is associated with overall-, disease-free and long-term survival (79, 80). Buda *et al*. and Lissoni *et al*. could show in the Snap01- and Snap02-study that NACT according to the TIP-regime followed by radical surgery could generate optimal pathological response more often than NACT containing ifosfamide and cisplatin (IP) in patients with locally advanced cervical cancer (48.3% *versus* 23.0% in Snap01 and 42.9% *versus* 25.3% in Snap02) (1, 60). As in our patient group, the majority of cervical cancers presented the clinical stage of cTIb2 and a Grade of 2 or 3. The average tumor diameter, as well as the patients' average age were comparable. Other than our work, with 91.7% suspicious lymph nodes in the primary imaging, only 35.4% of the patients in the TIP-group of the Snap01-study and 29.7% in the Snap02-study presented radiological lymph node involvement. Buda *et al*. and Lissoni *et al*. used only clinical examination and MRI, to measure the tumor

Table V. *Response control via imaging measuring TV during NACT. Bold fields show lacking imaging in certain cases. The reduction of TV in percent was statistically significant (one-sample-Wilcoxon Test, N=12, p<0.005).*

Patient number	Number of applications of TIP-scheme before next imaging	Tumor volume before NACT (ap × cc × ll × pi/6) (in mm^3)		Tumor volume after NACT (ap × cc × ll x× pi/6) (in mm^3)		Percentage reduction of TV
		Modality		Modality		
1	3	MRI		Missing		
		PET-CT	Not measurable	PET-CT	Not measurable	
2	4	MRI		Missing		
		PET-CT	74,022.21	PET-CT	4,029.09	95
3	2	MRI	36,530.44	MRI	0	100
4	2	ext. MRI		Missing		
		Missing	143,344.6	CT	34,174.24	76
5	2	MRI	35,456.01	MRI	1,715.31	95
6	2	MRI	88,215.92	MRI	3,166.73	96
7	3	MRI	63,037.63	MRI	6,685.31	89
8	2	ext. MRI	77,073.74	MRI	35,814.16	54
9	2	ext. MRI	32,691.41	MRI	15,861.9	51
10	2	MRI	16,622.17	MRI	307.88	98
11	2	MRI	24,740.04	MRI	0	100
12	3	MRI	31,610.71	MRI	263.89	99

diameter, before and after 3 applications of TIP-regime, in order to asses tumor response. Furthermore, the clinical response was determined following the WHO criteria:

- Complete response (CR): disappearance of disease
- Partial response (PR): 50% or more decrease in total tumor size
- Partial response 1 (PR1): residual disease with less than 3 mm stromal invasion including in situ carcinoma
- Partial response 2 (PR2): persistent residual disease with more than 3 mm stromal invasion on surgical specimen
- No change (NC): less than 50% decrease as well as less than 25% increase of tumor size,
- Progressive disease (PD): more than 25% increase of tumor size (1, 81).

Except for our study, there has been no study with main focus on and no special tool for thoroughly measuring the tumor response during NACT. In the TIP-group of the Snap01-study 98% of patients and 95% in the Snap2-study underwent surgery after at least one application of TIP-regime. No surgery or merely simple hysterectomy was performed in single cases due to minimal clinical response, stable disease or overt clinical progression. A total of 20.2% of patients in the TIP-group of the Snap01-study showed pathological CR, meaning complete disappearance of the tumor in the cervix with negative lymph nodes. In the Snap02-study this was 22.9%. Partial response 1 (residual disease with less than 3 mm stromal invasion including in situ carcinoma) was achieved by TIP-regime in 28.1% in Snap01 and in 20.0% in Snap02. Both CR and PR1 were called optimal pathologic response. In our work there was no case of pathologic CR in 11 patients, with patient number 8, who only received RCHT, not being counted. Yet partial response 1 was seen in 4 of those 10 patients, who had received surgery at the time this work was written. Consequently, we reached optimal pathologic response in 36.4% of cases.

Although it represents an individual healing attempt for every patient, the current German guideline mentions the possibility of using neoadjuvant chemotherapy. Herein NACT is mentioned as a possible option, which can be discussed, if preoperative diagnostic shows risk factors, which increase the risk of adjuvant radiation therapy, such as bulky disease (greater 4 cm), suspicion of lymphatic metastasis, as well as pathologic risk factors including Grading (G3), vascular invasion (V1) and invasion of lymphatic vessels (L1) (6). The scientific interest for this subject is underlined by the current study organized by the Nord-Ostdeutsche Gesellschaft für Gynäkologische Onkologie (NOGGO e.V.) called NACROPAD-study: in this prospective, multicenter study, NACT consisting of 6 applications of the TIP-regime followed by regular radical hysterectomy is compared to primary radiochemotherapy for cervical cancer stadium Ib2 to IIb. Following our experience, 6 applications of TIP-regime could lead to a high number of drop-outs, because of side-effects of the chemotherapy. Alternatively, a sandwich-procedure, with three applications of TIP-regime as NACT, followed by surgery and three further applications of TIP-regime as ACT could be seen as an alternative procedure. This is due to the assumption, that the side-effects of the

Table VI. *Response control via tumor marker SCC during NACT. Bold fields show lacking results in certain cases. The reduction of SCC after NACT and surgery showed statistical significance (N=7, p<0.002). The reduction of SCC after NACT was not statistically significant (N= 7, p<0.25). This was tested with Friedman's Analysis of Variance, adjusted by Bonferroni correction.*

Patient number	Number of applications of NACT	SCC before NACT (in ng/ml)	SCC after NACT (in ng/ml)	Reduction of tumor marker SCC after NACT in percent	SCC after surgery (in ng/ml)
1	3	Missing	Missing	-	Missing
2	4	Missing	Missing	-	Missing
3	2	Missing	Missing	-	Missing
4	2	Missing	Missing	-	Missing
5	2	20	0.8	96	0.6
6	2	9	0.8	91	0.6
7	3	89	3.9	95	1.3
8	2	82	21	36	-
9	2	3.1	0.9	71	0.1
10	2	3.1	0.9	71	0.4
11	2	Missing	0.9	-	0.9
12	2	1.7	0.9	53	0.9

Table VII. *Tumor response concerning the nodal status before neoadjuvant chemotherapy (NACT), after 2× NACT and after surgery.*

Patient number	cN+ in imaging prior to NACT	Response seen in suspicious lymph nodes after NACT	Lymph nodes in CT-navigated biopsy positive (pN+)	Laparoscopy for lymph node sampling performed	Lymph nodes in laparoscopy positive (pN+)	Number of positive lymph nodes in TMMR
Patient 1	cN+	1	-	0	-	0/46
Patient 2	cN+	1	-	1	1	4/67
Patient 3	cN+	1	-	0	-	0/63
Patient 4	cN+	1	-	1	0	0/29
Patient 5	cN+	1	-	0	-	1/56
Patient 6	cN+	1	-	0	-	0/47
Patient 7	cN+	1	-	0	-	6/82
Patient 8	cN0	Already prior to NACT cN0	-	0	-	-
Patient 9	cN+	1	-	0	-	0/14
Patient 10	cN+	1	-	0	-	0/46
Patient 11	cN+	1	1	0	-	0/58
Patient 12	cN+	1	-	0	-	0/58

1: Yes; 0: no; -: no laparoscopy performed.

chemotherapy could be coped better if spread during a longer period of time with a "break" before and after surgery.

When viewing the existing data for locally advanced cervical carcinoma, treated by adjuvant chemotherapy after NACT followed by radical surgery, it becomes evident that sufficient studies are lacking. In two reviews Asano *et al*. and Falcetta *et al*. could find promising results for platinum-based adjuvant chemotherapy after surgery, but only in early-stage cervical cancer (82, 83). Landoni *et al*. present results indicating a beneficial impact of adjuvant chemotherapy on patients with locally advanced cervical cancer, who had received NACT and surgery in a retrospective study with 333 patients (84). Luvero *et al*. present a single-center 10-year follow-up, suggesting that ACT alone after NACT and radical surgery could be an alternative postoperative therapy for locally advanced cervical cancer (85). Feng *et al*. could also present a promising study with 261 patients, who had received NACT and radical surgery and were then treated with three *versus* six applications of ACT. The prognosis of optimal responders during NACT, who were treated with postoperative ACT, was significantly better than those without ACT. ACT was found to be an independent

prognostic factor for disease-free survival. Six applications of ACT showed no significant benefit compared to three applications (86). The findings of Sun *et al*. indicate that especially those patients with extra-cervical residual disease after surgery can benefit from adjuvant chemotherapy. Other than the findings of Feng *et al*., the results from Sun *et al*. suggest that optimal responders during NACT may not require ACT (87). Gadducci *et al*. also advise to take the histological finding, such as the perineural invasion, into account when discussing adjuvant therapy (88).

Except for two patients, the pelvic MRI showed a sufficient response concerning maxTD and TV according to the RECIST-criteria. Patient number 8 and patient number 9 experienced a decrease of maxTD less than 30% and a decrease of TV of 22% and 21%. Both scored less than 6 points on the described tumor response score: patient number 8 scored 3 and patient number 9 scored 4 points. With patient number 8, the gynecological examination showed insufficient response, as well as the SCC only dropping 36%. Hence, the NACT was not continued and chemoradiation was induced. Yet with patient 9, the SCC-reduction was 71% and the gynecological examination revealed a tumor response to a degree, which showed higher mobility and allowed the surgeon to perform a TMMR instead of the initially planned LEER, reducing the extent and consequently the morbidity of the operation, following the patient's explicit wish for surgery. Thus, the third application of TIP-regime was conducted with patient 9 and TMMR was performed afterwards with R0 resection. This indicates, that the presented score could detect the tumor response adequately for all patients and that it can be a helpful tool for standardizing the process of evaluating tumor response during NACT. The gynecological examination can outweigh the other parameters of the tumor response score and each case of locally advanced cervical carcinoma is to be assessed individually. Nevertheless, also the SCC possesses a stated value concerning the visualization of tumor response during therapy and prediction of recurrence. Different authors could show correlations between SCC levels and parameters such as tumor stage, tumor volume, parametrial involvement, lymph node status, the risk of lymph node metastasis, response to chemotherapy and prognosis (89-98). Consequently, SCC should be regularly documented, beginning before the start of treatment. Furthermore, this emphasizes the importance of a multimodular approach for evaluating the tumor response during therapy. The presented score ought to be further examined and tested, given the small number of patients in this retrospective work. In addition to the parameters of the described tumor response score, the lymphatic response should to be taken into account. All of the patients, who initially showed suspicious lymph nodes, they all experienced a visible lymphatic tumor response. Moreover, only 3 of these 11 patients with initially suspicious lymph nodes showed lymph node metastasis in the final pathological results. These findings suggest the radiological tumor response, not only of the tumor itself, but also of the pelvic and paraaortic lymph nodes, to be of value for measuring the tumor overall response during NACT. Its value for predicting progression free and overall survival has already been shown (85, 99). Moreover, there is data suggesting that NACT can reduce lymph node metastasis, especially in locally advanced cervical cancer (76, 100). Yet this data is inconsistent, as there are also studies stating, that the influence of NACT on lymph node metastasis is neglectable (101, 102).

The strategy of NACT and TMMR, followed by ACT without radiation, can offer the following two major advantages for selected patients, if they explicitly deny chemoradiation or if there are contraindications for radiation. Firstly, the patients do not suffer from radiation-associated side-effects, offering them a potentially better quality of life. With the effect of the NACT we could reduce the resection of the vaginal cuff to an extent, which allowed intercourse after surgery while still achieving R0-resection. Secondly, the possibility of radiation in case of recurrence of cervical cancer is not affected and poses a more promising approach than vice versa. Nevertheless, two of 12 patients (patient 2 and patient 7) received RCHT although they had undergone NACT with adequate tumor response and TMMR. This was because of positive lymph nodes in the final pathological results and led to a higher therapy-associated morbidity. This underpins the necessity of adequate patient education and further research in adequate tumor response control parameters. Adding to this, patients have to be informed thoroughly, that the described therapy of NACT, TMMR and ACT is to be seen as an individual approach and the considerable toxicity of the TIP-regime, the risk of lacking therapeutic response and the risk of chemoradiation despite the described therapy, have to be mentioned sufficiently. The recommendations according to the current guidelines have to be discussed with each patient. We experience that especially young patients with locally advanced cervical cancer continue to actively ask for primary surgery and have the best requirements for coping with the side-effects of chemotherapy and surgery. Following our knowledge so far, we recommend the initiation of a standardized operating procedure for such cases. Thus, the described concept of NACT, tumor response score, TMMR and ACT could be a promising possibility to suffice the needs of selected patients, swiftly detect possibly insufficient tumor response and offering them an alternative therapeutic approach. Moreover, the selection of patients for NACT could benefit from prognostic markers for predicting the chance of adequate response to chemotherapy (103-109).

Conclusion

The therapy of LACC remains challenging, with single patients denying primary RCHT. Our described operating

procedure consists of NACT with a tumor response score and is followed by TMMR and ACT. This could be an interesting therapy option for selected patients asking for primary surgical treatment.

Conflicts of Interest

The Authors declare that they have no competing interests.

Authors' Contributions

All Authors are responsible for a significant part of the manuscript. Each author's main focus was: M. Kiesel: Project development, Data collection and analysis, Manuscript writing. S. Sauer: Assessment and management of radiologic data and literature, measurement of radiologic max TD and TV. S. Löb: Data management. S.-L. Herbert: Creation of illustrations. A. Wöckel: Meta-analysis. C. Wulff: Project supervision.

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