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REVIEW

Optimal treatment in locally advanced cervical cancer

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ABSTRACT

Introduction: Locally advanced cervical cancer (LACC) (International Federation of Gynecology and Obstetrics (FIGO) 2009/2018 – stages IB2-IVA/IB3-IVA, respectively) is treated using a multimodal approach that includes chemoradiotherapy followed by brachytherapy.

Areas covered: This review provides an overview of the progress made over the past decade in the treatment of LACC. Prognostic factors, FIGO classification and the role of imaging staging will be discussed. Efficacy of external-beam radiotherapy, brachytherapy and chemotherapy will be detailed. Indications for para-aortic staging lymphadenectomy and adjuvant hysterectomy, as well as follow-up and special population, will be covered.

Expert opinion: The initial workup is one of the most crucial steps in the optimal care of patients, which should be realized by a multidisciplinary expert team. With the implementation of modern conformal radiotherapy techniques, the local control rate has been optimized. Nevertheless, 40% of patients experience recurrence with distant metastasis and a dismal prognosis. Currently, a clear benefit of neo- and adjuvant chemotherapy has not been established. The future likely involves (1) improved selection of patients for whom treatment intensification is justified, (2) a combination of new drugs with chemoradiation that are currently being tested in trials, and (3) the development of tailored treatment based on molecular characteristics.

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1. Introduction

According to GLOBOCAN 2018, cervical cancer (CC) is the fourth most common cancer in women worldwide after breast, colorectal and lung cancers and is the second most common in developing countries, where more than 85% of these cases occur. Worldwide, an estimated 569,847 new cases and 311,365 deaths are recorded, although incidence and mortality vary widely among countries [1,2].

Several risk factors are recognized, including sexually transmitted diseases (primarily human papillomavirus infection (HPV), other human immunodeficiencies and herpes simplex virus), reproductive and sexual factors (multiple sexual partners, early age at first sexual intercourse and at first delivery, and oral contraceptive pills), and behavioral factors (e.g. smoking) [3].

Persistent infection with HPV, a sexually transmitted deoxyribonucleic acid (DNA) virus, is detected in 99% of CC cases. Although the majority of HPV infections are transitory, HPV persists in 10% of cases, leading to the development of a pre- or invasive lesion 15 to 20 years after the initial infection. Primary prevention has been realized through HPV vaccination and screening via Papanicolaou (Pap) cytological test or HPV DNA testing [4–7].

Most frequently reported symptoms are vaginal bleeding, dyspareunia or pain due to local muscular or nervous infiltration. However, CC may be asymptomatic when it is detected at an early stage during screening.

Squamous cell carcinoma (SCC), adenocarcinoma (ADC), and adenosquamous carcinoma (ADSC) are the three most common histological subtypes, accounting for 70%, 25% and 5% of cases, respectively. In contrast to SCC, which has experienced a progressive decrease in incidence and mortality in recent decades, the incidence and mortality of ADC has increased during the same timeframe [8]. This evolution has been attributed to the Pap test and its ability to more efficiently detect squamous, rather than glandular, neoplasia [9].

Overall survival (OS) at 5 years is approximatively 92%, 65% and 17% for early-stage, locally advanced and metastatic disease, respectively. The prognosis of patients with recurrent disease remains very poor, except in cases of local recurrence accessible to curative treatment.

Treatment strategy is dictated by the International Federation of Gynecology and Obstetrics (FIGO) classification. The majority of trials referenced in this review are based on the 2009 version; however, the updated FIGO 2018 classification should now be used. Surgery is the principal treatment for early-stage disease (FIGO 2018 stages IA–IB2). For patients with locally advanced cervical cancer (LACC) (FIGO 2018 stages IB3–IVA), concomitant cisplatin-based chemoradiation (CCRT) followed by intrauterine brachytherapy (BT) is recommended by all international society guidelines [10].

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Article highlights

- Exhaustive, initial clinical, radiological, and even surgical workup is crucial
- Concomitant cisplatin-based conformal external-beam radiotherapy followed by image-guided adaptive brachytherapy is the current standard of care
- The exact benefit of neo- and adjuvant chemotherapy has not yet been established
- Various new therapeutic strategies are under evaluation in ongoing trials, such as antiangiogenesis agents and checkpoint immune receptor inhibitors

Although early-stage CC is often curable, 40 to 50% of patients are diagnosed at the locally advanced stage, which accounts for the principal cause of death. This review is dedicated to discussing the most recent and multidisciplinary approaches for LACC.

2. Prognostic factors

LACC includes a heterogeneous group of diseases. In the era of personalized medicine, improved understanding and identification of the site-specific risk of relapse could provide an opportunity to tailor treatment and select patients who may benefit from new therapeutic strategies.

Various prognostic factors have been previously studied, including clinical (age, tumor size, nodal metastasis), morphological (tumor histology, HPV status), biological (anemia, leukocytosis, lymphopenia, thrombocytosis at diagnosis) and radiological (initial [^{18}F]FDG-PET/CT avidity) variables [11–14]. Also, HPV genotypes convey different prognoses [15,16].

Moreover, molecular biomarkers, such as cyclooxygenase-2, p53 and vascular endothelial growth factor (VEGF), have been studied, but their prognostic utility remains unclear [17–19]. In 2017, the Cancer Genome Atlas Research Network identified new genomic and proteomic characteristics allowing subclassification of CC into the following categories: keratin-low squamous, keratin-high squamous, and adenocarcinoma-rich clusters. *ERBB3, CASP8, HLA-A, SHKBP1* and *TGFBR2* were identified as commonly mutated genes. They also reported amplification events in *BCAR4, CD274* and PDCD1LG2 genes, also known as PD-L1 and PD-L2, respectively. Endometrial-like CC, especially in HPV-negative tumors, was discovered and characterized by mutations in *KRAS, ARID1A* and *PTEN*. Furthermore, more than 70% of CCs exhibit genomic alterations in PI3K–MAPK or TGFβ signaling pathways [20]. In the near future, it is likely that potent biomarkers will contribute to the selection of patients who may benefit from treatment intensification or, conversely, from treatment de-escalation.

3. International federation of gynecology and obstetrics (FIGO) classification

In 2018, FIGO updated their clinical classification by incorporating the use of imaging modalities and/or pathological findings for determining the stage. Lateral extension measurement was removed from stage IA, and stage IB now includes three subgroups based on tumor size (in greatest dimension): stage IB1 (≤ 20 mm), stage IB2 (>20 mm to ≤ 40 mm) and stage IB3 (>40 mm). A major change also included incorporation of lymph node (LN) status. If nodal status is positive, the stage is designated IIIC; in cases of only pelvic LN involvement, the stage is IIIC1. If para-aortic (PAo) LNs are positive, the stage is assigned IIIC2. Notations 'r' (imaging) and 'p' (pathology) indicate the method used to derive the stage [21,22].

Four recent large-scale retrospective cohort studies were conducted to validate this new classification [23–26]. They demonstrated good discrimination between the three groups in stage IB. Nodal status clearly impacts survival, with the risk of death nearly 1.5- and 2-fold greater for pelvic and PAo LN involvement, respectively. However, this effect varies greatly based on local T stage, leading to survival heterogeneity in patients with stage III subgroups [23].

4. Imaging workup

4.1. Local diagnostic

Gynecologic examination with colposcopy-guided biopsy and pelvic magnetic resonance imaging (MRI) are mandatory for primary tumor 'T' staging [27]. Thomeer et al. [28] published a meta-analysis comparing the diagnostic performances of clinical examination and MRI in detecting parametrial invasion and advanced stage (FIGO stage ≥ IIB). For the evaluation of parametrial invasion/advanced disease, sensitivity was 40%/53% and 84%/79% with clinical examination and MRI, respectively, clearly in favor of MRI [28]. Knoth et al. [29] demonstrated 27% of discrepancies between MRI and clinical gynecologic examination. With MRI, upstaging is more frequent than downstaging. Tumor size and parametrial infiltration seemed to be more correctly assessed with MRI. Vaginal and pelvic side wall infiltrations were more precisely evaluated by gynecologic examination [29].

All these differences can have a major impact on the management of patients. Indeed, the accuracy of this staging is crucial in order to decide the best strategy for the patients: surgery or CCRT. A combination of informations gained from clinical examination (by experienced gynecologic oncologist) and MRI is probably the best approach.

Functional (dynamic contrast-enhanced or diffusion-weighted) MRI techniques can provide additional informations [30,31]. Transrectal or transvaginal ultrasound can also give detailed information when performed by ultrasound-trained gynecologists in experienced centers [10]. Cystoscopy or rectoscopy may be discussed to realize a biopsy if suspicious lesions in the bladder or rectum are detected on MRI.

4.2. Nodal diagnostic

Nodal staging is key as it influences both prognosis and treatment planning. The performance of Positron emission tomography/computed tomography using ^{18}F-2′-deoxy-2′ fluorodeoxyglucose ([^{18}F]FDG-PET/CT) and chest/abdomen contrast-enhanced computed tomography for LN detection is clearly superior to standard MRI and tomography [32].

PAo LN detection is a crucial point as it can result in upstaging and consecutive modification of treatment planning with extended-field radiotherapy (RT). The incidence of PAo LN involvement increases with tumor 'T' stage, ranging from 5% in patients with stage I disease to 23% in those with stage III. Nevertheless, the best strategy for detection of this PAo LN is a very controversial subject, regarding whether to implement a surgical versus radiological approach.

A meta-analysis based on 385 patients reported that pooled estimates for sensitivity and specificity of [^{18}F]FDG-PET/CT in detecting PAo LN metastasis were 0.71 (95% CI 0.54–0.83) and 0.97 (95% CI 0.93–0.98), respectively [33]. In addition, a 2013 Cochrane review found no evidence that surgical staging was beneficial [34].

Of note, Martinez et al. [35] and De Cuypere et al. [36] concluded that the risk of PAo LN metastasis in case of negative pelvic LN status on [^{18}F]FDG-PET/CT is very low, so PAo lymphadenectomy does not seem justified in this subgroup of patients. In contrast, for patients with preoperative pelvic LN uptake on [^{18}F]FDG-PET/CT, surgical staging led to treatment modification in more than 25% of cases and should therefore be performed [35,36].

Lymph node size can also modify the ability of [^{18}F]FDG-PET/CT to correctly identify metastatic LNs. Metastases measuring less than 5 mm have been identified in approximately half of patients with negative PAo LN on [^{18}F]FDG-PET/CT [37].

Only two randomized control trials (RCTs) have been performed to address the question of radiological-clinical or surgical PAo LN evaluation. The Lai et al. [38] study was prematurely closed and limited by many methodological biases. UTERUS-11 study, with a median follow-up of 90 months, compared the two methods of PAo LN staging in 225 patients FIGO 2009 IIB-IVA with laparoscopic approach in > 95% of cases in the surgical arm. In fact, OS and progression-free survival (PFS) were not statistically different, whereas cancer-specific survival (CSS) favored the surgical approach. Moreover, surgical staging was safe and neither delayed CCRT nor increased complications [39]. The results of the Lymphadenectomy in Locally Advanced Cervical Cancer (LiLACS) phase III trial are pending, but this study is not currently recruiting [40].

4.3. Distant metastases

Initial [^{18}F]FDG-PET/CT staging demonstrates 6 to 14% of cases with distant metastases with a high specificity (98%), positive predictive value (79%) and a sensitivity of 55% [41]. It is considered the best imaging modality for this evaluation.

4.4. Response assessment

[^{18}F]FDG-PET/CT can also be used in response assessment 3 months after completion of CCRT in combination with clinical exam and MRI. MRI interpretation can be difficult due to the presence of post-therapy inflammation or scarring, although the addition of functional MRI sequences can be useful. Several authors showed that metabolic response was predictive of long-term survival. Nevertheless, attention should be given to interpretation of the partial metabolic response due to its high false-positive rate. In conclusion, [^{18}F]FDG-PET/CT 3 months post-treatment has higher negative predictive than positive predictive values [42–44]. It appears that the most accurate post-treatment response assessment remains multimodal and associates a clinical evaluation with the pelvic MRI and the [^{18}F]FDG-PET/CT .

5. Treatment phases

Major advances have occurred in the treatment of LACC over the past two decades, including the emergence of the crucial role of imaging in RT planning with the implementation of conformal techniques, such as intensity-modulated radiation therapy (IMRT)/volumetric arc therapy (VMAT), image-guided radiation therapy (IGRT) and image-guided adaptive brachytherapy (IGABT), sparing the organs at risk (OAR) and concentrating the therapeutic dose to the primary disease. Furthermore, the addition of chemotherapy (CT) to RT has resulted in a significant improvement in local, regional and distant control rates.

5.1. Radiotherapy

5.1.1. External-beam radiotherapy (EBRT)

During the last few decades, significant evolutions in EBRT technology have occurred, moving from three-dimensional conformal radiation therapy (3D-CRT) to IMRT/VMAT and IGRT. With these improvements, survival has increased, and treatment-related morbidity has decreased [45]. IMRT allows more conformal shaping of RT dose to a specified target, with reduced high-dose exposure to surrounding OAR. A meta-analysis on 1008 patients with LACC found equivalent 3-year OS (Odds ratio (OR) 2.41, 95% CI 0.62–9.39, p = 0.21) and disease-free survival (DFS) (OR 2.41, 95% CI 0.62–9.39, p = 0.21) with IMRT and conventional RT but reduced acute toxicities [46]. On the other hand, Lin et al. [47] demonstrated that IMRT plus IGABT was associated with improved 5-year OS compared to patients treated with two-dimensional (2D)-RT and BT (61% versus 57%; p = 0.04). Furthermore, decreased grade 3–4 late bowel and bladder toxicities (18% vs 11%; p = 0.02) were observed [47].

A further benefit of IMRT is the opportunity to provide an additional 10–15 Gy dose to involved pelvic LNs using sequential or increasingly simultaneous integrated boost (SIB) techniques.

In a shorter treatment delivery time, VMAT allows reduction of the dose to the small bowel relative to IMRT, while doses to other OARs were comparable [48].

Furthermore, IGRT (by compensating for patient positioning errors and anatomical variations) is strongly recommended for reducing the dose to normal tissue and to ensure full dose coverage to the residual tumor upon completion of EBRT.

5.1.2. Brachytherapy (BT)

2D-based BT has been gradually replaced by IGABT based on 3D volumetric imaging. This adaptive target volume concept reflects tumor shrinkage at the end of CCRT, with a risk-adapted dose prescription to different clinical target volumes

[49]. Also, IGABT clearly improves local control rate (LCR) and decreases toxicities [50–52].

The EMBRACE I prospective study included 1416 patients and was based on pioneering technical and clinical experience of several European institutions. The RetroEMBRACE trial, based on 814 patients, reported that 3-year local and pelvic control rates reached 98–100% and 96% for FIGO stage IB1 and IB2 disease, respectively, and 93–96% and 89–91%, respectively, for stage IIB disease [52,53]. Stage III/IVA disease results were more variable, ranging from 73% to 86%. This improved local and pelvic control was associated with an OS benefit of approximately 10% compared to historical cohorts. Overall major morbidity (grades 3 to 5) was limited after IGABT (3 to 6% per organ) (10% and < 6% in grades III and IV late toxicities, respectively) [53–55]. EMBRACE II is an ongoing multicenter study initiated in April 2016 that is prospectively validating the findings of the both previous studies [56].

A Cochrane review confirmed that high-dose rate (HDR) and low-dose rate (LDR) irradiation are associated with similar survival and late toxicity. However, patients are increasingly treated by HDR irradiation because it allows outpatient BT application [57].

Overall treatment time (OTT) should be less than 50 to 55 days. Indeed, a significant detrimental effect was well-described with a consistent loss of local control probability of approximately 1% per day of treatment prolongation beyond thresholds between 7 and 8 weeks [58,59]. The use of IMRT or stereotaxic body radiation therapy (SBRT) as a substitute for BT is not recommended because population-based studies have shown worse CSS with IMRT/SBRT as opposed to BT [60,61].

5.2. Chemotherapy

5.2.1. Concomitant chemotherapy

Five phase III investigating CCRT using either cisplatin, 5-fluoro-uracil (5-FU), or hydroxyurea demonstrated a reduction in the risk of local and distant recurrences in patients with LACC and in patients with high-risk criteria after hysterectomy [62–66]. In 1999, the National Cancer Institute issued an alert recommending that 'concomitant (cisplatin-based) chemoradiotherapy should be considered instead of radiotherapy alone in women with cervical cancer'.

5.2.1.1. Results of meta-analyses. In 2008, a meta-analysis including 13 studies comparing CCRT to RT demonstrated an absolute benefit of 6% in 5-year OS (from 60 to 66%; Hazard ratio (HR) 0.81, 95% CI 0.71–0.9, p < 0.001) for the entire population but a decreased benefit with increasing stage. Acute toxicities were more frequent in the CCRT group, but few trials have evaluated late toxicity and quality of life (QoL) outcomes. However, interpretation of the real benefits were complicated by the use of different treatments in the control arms and by inconsistencies in patient outcomes [67]. In 2010, the Cochrane review reported that CCRT improved OS and PFS whether platinum or other chemosensitizing agents were used with absolute benefits of 10% (HR 0.83, p = 0.017) and 13% (HR 0.77, p = 0.009), respectively [68]. Datta et al. [69] performed another meta-analysis in 2017 based on 2445 patients with > 95% SCC histology receiving either CCRT or RT only without surgery. The results confirmed that CCRT significantly improves outcomes, with increased LCR and OS rates of 8.4% (p < 0.001) and 7.5% (p < 0.001), respectively. This analysis also described a 10.4% (p < 0.001) higher incidence in grade III/IV acute toxicities, with an equivalent occurrence of late toxicities. There were no differences in outcomes between weekly or 3-weekly cisplatin regimens [69].

Importantly, placement of CT has been poorly documented in the era of IGABT, as meta-analyses on the benefit of CT were conducted without image-guided or dose escalation techniques.

5.2.1.2. Impact of number of cycles of chemotherapy. In a retrospective trial including 189 patients (with stages III or IVA or with any stage who are also LN positive), Schmid et al. [70] showed a decreased in the distant metastasis-free survival (DMFS) with a decreased number of CT cycles (fewer than 5 cycles) [70]. The EMBRACE I trial confirmed these results [56]. Recently, Escande et al. [71] demonstrated that patients receiving 5 cycles of concomitant CT experienced better outcomes than those receiving only 4 cycles in terms of metastatic (3-year DMFS = 56.3% vs 81.9%; HR 0.35, 95% CI 0.21–0.57) and both local (3-year LC = 77.2% vs 93.9%; HR 0.31, 95% CI 0.14–0.68) and regional control (3-year LRC = 62.8% vs 84.6%; HR 0.43, 95% CI 0.24–0.76) [71].

5.2.1.3. Monotherapy versus combination chemotherapy. Petrelli et al. [72] conducted a meta-analysis on 1500 patients, revealing that CCRT with cisplatin-based doublets significantly improved OS (OR 0.65; 95% CI 0.51–0.81; p = 0.0002), PFS (OR 0.71; 95% CI 0.55–0.91; p = 0.006), and the rate of locoregional relapse (OR 0.64; 95% CI 0.47–0.89; p = 0.008) compared to CCRT with weekly cisplatin alone. However, higher toxicities were reported in the doublets group [72]. Another meta-analysis published by Ma et al. [73], on 1503 patients, showed that CCRT with platinum-based doublets significantly improved OS (HR 0.75; 95% CI 0.60–0.94; p = 0.01) and PFS (HR 0.78; 95% CI 0.65–0.94; p = 0.01) compared to CCRT with cisplatin monotherapy but was also accompanied by increased toxicities [73]. In conclusion, CCRT with a cisplatin-doublet seems to improve survival at the cost of inducing higher toxicity, which is probably why this concept is not adopted in daily practice.

5.2.1.4. Platinum versus non-platinum-based chemotherapy. In the Vale et al. [67] and Cochrane meta-analyses, a survival benefit was observed for both groups of trials using platinum and non-platinum-based CCRT [67,68]. Nevertheless, no trials allowing a direct comparison have been published.

5.2.1.5. Weekly versus tri-weekly cisplatin schedule. In 2020, a meta-analysis demonstrated that weekly cisplatin was associated with a higher incidence of local recurrence (OR 1.72; 95% CI 1.07–2.78; p = 0.03) and RT completion while lower risk of hematological toxicity. No significant differences were observed in terms of survival or acute adverse

effects [74]. The results of the phase III TACO trial are eagerly anticipated.

5.2.1.6. Place of carboplatin. No phase III randomized studies have compared carboplatin to cisplatin during CCRT. The use of carboplatin is supported by small phase I and II studies and pre-clinical evidence of synergism of this drug with RT [75]. A meta-analysis of 12 studies and 1698 patients suggested poorer complete response (OR 0.53; 95% CI 0.34–0.82) and a trend toward inferior survival (3-year OS = OR 0.70; 95% CI 0.46–1.05) with weekly carboplatin [76].

5.2.2. Adjuvant chemotherapy

The role of adjuvant CT after CCRT has been explored in several phase II studies, showing an increased response rate [77–79]. Nevertheless, 4 phase III RCTs reported conflicting evidence (Table 1). In 2003, 926 patients were randomized into four arms: conventional RT; conventional RT plus adjuvant CT; conventional RT plus CCRT and conventional RT plus CCRT and adjuvant CT. CT consisted of intravenous mitomycin C and oral 5-FU. The pattern of failure revealed a significant increase in locoregional recurrence in the non-CCRT arm. On the other hand, metastatic rates were not significantly different. Five-year DFS was 48.2%, 54.1%, 64.5% and 59.7% for arms 1, 2, 3 and 4, respectively [80].

Another randomized study on 515 patients compared CCRT with cisplatin and gemcitabine followed by two cycles of adjuvant cisplatin and gemcitabine, and conventional CCRT. They showed that PFS (HR 0.68, 95% CI 0.49–0.95, p = 0.023) and OS (HR 0.68; 95% CI 0.49–0.93, p = 0.022) at 3 years were both significantly improved in the gemcitabine arm. There was an increased benefit in patients with stages III–IVA. However, there was also an increased occurrence of grade 3–4 hematologic toxicities and diarrhea (86.5% vs 45.3%, p < 0.001) [81,82]. A Cochrane review based on these 2 trials concluded that there are insufficient data and a need for further RCTs to definitively test the utility of adjuvant CT in this context [83]. Tang et al. [84] evaluated the addition of one cycle of cisplatin and paclitaxel prior and two cycles after CCRT in patients with ADC histology. Patients who received adjuvant CT exhibited significantly longer DFS (60.4% vs 71.4%, p < 0.05), less local relapse (62.9% vs 74.7%; p < 0.005) and distant metastases (p < 0.005) [84]. Fourthly, the ACTLACC trial randomized 259 patients to receive CCRT with weekly cisplatin or adjuvant CT with paclitaxel plus carboplatin for 3 cycles followed by observation. There was no significant difference in PFS, OS or locoregional failure. However, systemic recurrences were significantly reduced in the adjuvant CT arm (8.4% vs 10.1%, p = 0.029), but only 75% of patients in the adjuvant CT arm completed the planned 3 cycles of CT with the trial being stopped early due to futility [85]. Despite the survival benefit reported in some of these trials, adjuvant CT is still not considered as a standard of care, mostly due to statistical flaws, excessive toxicity of some experimental treatments and inclusion of only patients with ADC histology in one study. The phase III OUTBACK trial achieved its full recruitment and the results are eagerly awaited.

5.2.3. Neo-adjuvant chemotherapy (NACT)

The data concerning NACT were based on limited RCTs, with very heterogeneous inclusion criteria. Indeed, the design of all trials was different with respect to NACT before surgery, RT or CCRT, including many types of comparative arms, such as

Table 1. Adjuvant chemotherapy trials.

	LORVIDHAYA ET AL. [80]	DUENAS-GONZALEZ ET AL. [81,82]	TANG ET AL. [84]	TANGJITGAMOL ET AL. [85]
Years of enrollment	1988–1994	2002–2004	1998–2007	2015–2017
Number of patients	926	515	880	259
Stage (FIGO)	IIB to IVA	IIB to IVA	IIB to IVA	IIB to IVA
Other criteria	Stage IIB: only central tumor > 3 cm and/or half of the parametrium involved	Patients with positive PAo LN (1> cm) from imaging must be negative in biopsy	Patients with positive PAo LN from imaging received extended-field RT	Patients with PAo enlargement from imaging are excluded
Histology	SCC-ADC	SCC-ADC-ADSC and poorly differentiated	ADC-ADSC	SCC-ADC-ADSC
CCRT phase	mitomycine C + oral 5-FU	CCRT arm = cisplatin ACT arm = cisplatin + gemcitabine	cisplatin	cisplatin
ACT phase	oral 5-FU (3 cycles)	cisplatin + gemcitabine (2 cycles)	cisplatin + paclitaxel (2 cycles) + 1 cycle before CCRT	carboplatin + paclitaxel (3 cycles)
Median follow-up	89 months	46.9 months	60 months	27.4 months
Survival outcomes	DFS at 5 years = better only in CCRT arm OS = NS	PFS and OS = in favor of ACT arm	DFS = in favor of ACT arm	3-year PFS = NS 3-year OS = NS
Local relapse	Significantly higher in non-CCRT arms	NS	in favor of ACT arm	NS
Distant relapse	NS	lower in ACT arm	in favor of ACT arm	lower in ACT arm
Toxicity	increased in CCRT arm	grade 3–4 more frequent in ACT arm	leukopenia and thrombocytopenia significantly higher in ACT arm	grade 3–4 neutropenia higher in ACT arm

ACT = adjuvant chemotherapy; ADSC = adenosquamous carcinoma; ADC = adenocarcinoma; CCRT = concomitant chemoradiotherapy; DFS = disease-free survival; FIGO = International Federation of Gynecology and Obstetrics; 5-FU = 5-fluoro-uracil; LN = lymph node; NACT = neo-adjuvant chemotherapy; NS = not significant; OS = overall survival; PAo = para-aortic; PFS = progression-free survival; RT = radiotherapy; SCC = squamous cell carcinoma

surgery, RT or CCRT [86]. Therefore, the major obstacle is the adage of comparing 'apples and oranges'.

5.2.3.1. NACT followed by surgery versus surgery (*Table 2*)

A 2012 Cochrane meta-analysis involving 1078 patients reported that patients treated with NACT followed by surgery showed significantly better PFS (HR 0.75, 95% CI 0.61–-0.93, p = 0.008) and OS (HR 0.77, 95% CI 0.62–0.96, p = 0.02) compared to those receiving surgery alone [87]. Another meta-analysis performed by Kim et al. [88] in 2013 reported that NACT followed by surgery reduced the need for adjuvant RT according to risk factors (lymphovascular space invasion, deep stromal invasion, parametrial invasion, LN metastasis, and positive resection margins). However, NACT did not significantly improve OS or PFS. In observational studies subanalysis, OS was poorer in NACT arm (HR 1.68, 95% CI 1.12–2.53) [88]. More recently, Zhao et al. [89], on 2158 patients, demonstrated no differences in terms of OS, PFS, local or distant recurrences. In contrast, a subgroup analysis of patients with stage IB2-IIB showed that NACT followed by surgery significantly improved OS (OR 1.44, 95% CI 1.01–2.05, p = 0.05), decreasing the local and distant (OR 0.43, 95% CI 0.25–0.73, p = 0.002) recurrence rates, LN metastasis rate, and levels of parametrial infiltration [89].

Nevertheless, due to the high rate of adjuvant RT after surgery alone in LACC, the standard used in these studies should no longer be surgery alone but rather, CCRT. Consequently, the control arm is obsolete, and the results of these meta-analyses are outdated.

5.2.3.2. NACT followed by surgery versus RT alone.

A meta-analysis by Tierney et al. [90] involving 872 patients with stage IB – IVA revealed a 35% decrease in the risk of death (HR 0.65, p = 0.0004) in patients who received NACT followed by surgery compared to those who received RT alone, with an absolute improvement of 14% (from 50 to 64%) in the 5-year OS rate [90]. Once more, RT without concomitant CT has become an obsolete standard, and the CT regimens used in these studies were not contemporary.

5.2.3.3. NACT followed by surgery versus CCRT (*Table 3*).

The results of two phase III RCTs are currently available to address this issue. Gupta et al. [91] studied 635 patients with stages IB2, IIA, and IIB and compared NACT (3 cycles of carboplatin+ paclitaxel) followed by surgery to platinum-based CCRT. The primary endpoint was DFS. The authors found that 5-year DFS was lower (69.3% vs 76.7%; HR 1.38, 95% CI 1.02–1.87, p = 0.038) in the NACT followed by surgery group with no significant differences in 5-year OS (75.4% vs 74.7%; HR 1.02, 95% CI 0.75–1.40, p = 0.87). Adverse events (AEs) at 90 days were higher in CCRT arm: rectal (5.7% vs 13.3%; p = 0.002); bladder (2.8% vs 7.3%; p = 0.017) and vaginal (19.9% vs 36.9%; p < 0.001) toxicities, respectively. AEs at 24 months were higher in CCRT arm but only for vaginal toxicity (12% vs 25.6%; p < 0.001).

Unfortunately, because of a slower-than-anticipated accrual over a 10-year period, the study was closed at 87% of the planned sample size [91]. Additionally, a trial led by the European Organization for Research and Treatment of Cancer (EORTC55994), including 626 patients with stages IB2-IIA2-IIB, was reported by Kenter et al. [92] during ASCO 2019 (not yet published). In intention-to-treat (ITT), an advantage of the CCRT arm in terms of PFS (56.7% vs 65.6%, p = 0.011) but not in OS (71.7% vs 75.6%, p = 0.253) was demonstrated but was not confirmed in patients who completed the total treatment. This trial reported a trend towards better results for CCRT in stage IIB (OS = 68% vs 76%; HR 1.32, 95% CI 0.93–1.88), BMI < 25 and age > 50 years, as well as a trend towards better results in NACT

Table 2. Neo-adjuvant chemotherapy followed by surgery versus surgery.

	RYDZEWSKA ET AL. [87]	KIM ET AL. [88]	ZHAO ET AL. [89]
Years of enrollment	1987–2005	1987–2010	1997–2016
Number of trials	6 RCTs	5 RCTs + 4 observational	13 studies
Number of patients	1078	1784	2158
Stage (FIGO)	IB to IIIB	IB1 to IIA	IB to IIB
Histology	SCC-ADC-ADSC	SCC-ADC-ADSC	SCC-ADC-ADSC
NACT phase	cisplatin-based CT + vincristine/ bleomycin/5-FU or mitomycin C	cisplatin or carboplatin – based CT + vincristine/bleomycin/ 5-FU/mitomycin C or paclitaxel	various regimens
Surgery	type III Piver radical HT -pelvic lymphaD (3 trials) -pelvic + PAo lymphaD (2 trials)	type II or IV HT -pelvic lymphaD (all trials) -PAo lymphaD (if need)	radical HT -lymphaD = NE
Survival outcomes	PFS and OS = in favor of NACT arm	PFS = NS OS = NS OS (observational trials) = poorer in NACT arm	PFS and OS = NS -sub-analysis (IB2-IIB) PFS = NS OS = better in NACT arm
Local Relapse	NS	NS	NS -sub-analysis (IB2-IIB) = decreased in NACT arm
Distant relapse	NS	decreased in NACT arm	NS -sub-analysis (IB2-IIB) = decreased in NACT arm

ADC = adenocarcinoma; ADSC = adenosquamous carcinoma; CT = chemotherapy; FIGO = International Federation of Gynecology and Obstetrics; 5-FU = 5-fluorouracil; HT = hysterectomy; lymphaD = lymphadenectomy; NACT = neo-adjuvant chemotherapy; NE = not evaluated; NS = not significant; OS = overall survival; PAo = para-aortic; PFS = progression-free survival; RCTs = randomized controlled trials; SCC = squamous cell carcinoma

Table 3. Neo-adjuvant chemotherapy followed by surgery versus concomitant chemoradiation.

	GUPTA ET AL. [91]	KENTER ET AL. [92]
Years of enrollment	2003–2015	2002–2014
Number of patients	635	626
Stage (FIGO 1994)	IB2-IIA or IIB	IB2-IIA2-IIB
Histology	SCC	SCC-ADC-ADSC
First endpoint	DFS	OS at 5 years
Median follow-up	58.5 months	96 months
NACT phase	carboplatin + paclitaxel (3 cycles)	-cisplatin monotherapy (dose at least 225 mg/m^2) (46%) -doublet (+ paclitaxel) (20%) -triplet (+ paclitaxel + ifosfamide) (19%) -other (15%)
CCRT phase	-EBRT 40 Gy (20 x 2 Gy) + ICBT (LDR 2 × 30 Gy or HDR 5 × 7 Gy) -CT = cisplatin weekly	-EBRT 45–50 Gy (pelvis) with external boost or BT -CT = cisplatin weekly
Adjuvant treatment after protocol completion	*in NACT arm, -21.5% crossover to CCRT (pre-surgery and intraoperative unresectable disease) -13.3% = adjuvant CCRT -9.8% = adjuvant RT alone	*in NACT arm, -24% = no surgery (34% CT toxicity; 24% progressive; 16% insufficient response; 14% patient refused) -14% = adjuvant RT *in CCRT arm, -6% = no CCRT (55% patient refused; 25% protocol violation, …) -4% = surgery
Survival outcomes	5 year PFS = in favor of CCRT 5 year OS = NS	OS (ITT and completed treatment) = NS PFS (ITT) = in favor of NACT arm PFS (completed treatment) = NS
Survival sub-analysis	*stages IB2 or IIA: DFS = NS	*stage IB2: OS = trend in favor of NACT arm *stage IIB: OS = trend in favor of CCRT arm
Toxicity	-grade 3–4 thrombocytopenia = higher in NACT arm -grade 3–4 bladder and GI = NS -AEs at 90 days, higher in CCRT arm (rectal, bladder and vaginal) -AEs at 24 months, higher in CCRT arm (only vaginal)	-treatment period grade 3–4: higher in NACT arm (GI and hematologic) -follow-up period grade 3–4: higher in CCRT arm (GI and GU)

ADC = adenocarcinoma; ADSC = adenosquamous carcinoma; AEs = adverse events; BT = brachytherapy; CCRT = concomitant chemoradiotherapy; CT = chemotherapy; DFS = disease-free survival; EBRT = external-beam radiotherapy; FIGO = International Federation of Gynecology and Obstetrics; GI = gastro-intestinal; GU = genito-urinary; HDR = high-dose rate; IC = intra-cavitary; ITT = intention-to-treat; LDR = low-dose rate; NACT = neo-adjuvant chemotherapy; NS = not significant; OS = overall survival; PFS = progression-free survival; RT = radiotherapy; SCC = squamous cell carcinoma

for combination CT. Concerning toxicity, treatment period grade 3–4 (gastro-intestinal and hematologic) was higher in the NACT arm (40.8% vs 22.6%), but follow-up period toxicity (gastro-intestinal and genito-urinary) was higher in the CCRT arm (15% vs 20.7%).

In the NACT group, 24% of patients received no surgery due to CT toxicity (34%), progression (24%) or insufficient response (16%). In the CCRT arm, only 6% of patients received no CCRT due to refusal (55%). In terms of response in the NACT group, 23% complete response, 15% 'optimal' response and 52% suboptimal response was observed [92]. Both trials had a similar study design and globally equal results. However, several points were different, such as primary outcome (OS or DFS), stages (inclusion of IIA1 or not) and histology (only SCC or mixed). Regarding treatment-related complications, short-term hematologic complications were significantly more frequent in the NACT followed by surgery group than in the CCRT group. In contrast, long-term complications, such as small bowel and vaginal toxicities, were more frequent in the CCRT group. Together, these findings suggest that the standard of care for patients with LACC should remain definitive CCRT.

5.2.3.4. NACT followed by CCRT versus CCRT. In 2016, a review on 323 patients was conducted to evaluate NACT followed by CCRT. Due to limited data, the authors were unable to investigate the benefit of OS or PFS; however, they could determine the grade 3–4 toxicity rate (25%) and the response rate (70%). The most frequent grade 3–4 toxicity was neutropenia, followed by anemia, and then diarrhea [93]. The phase III INTERLACE trial is ongoing.

5.3. New agents

Even with current optimal treatment, recurrence rates remain high among patients with LACC, with only 65-70% of patients remaining disease-free long term. These unsatisfactory results have encouraged physicians to explore other novel strategies combined with the standard treatment [94]. Inhibition of angiogenesis by bevacizumab, a humanized anti-VEGF monoclonal antibody, has been found to have major activity in the metastatic CC setting [95]. In a phase II study, patients with stage IB to IIIB were treated with weekly cisplatin during CCRT followed by BT. Patients also received 3 cycles of bevacizumab during CCRT. The regimen was well tolerated, with grades 3 and 4 toxicity of 26.5% and 10.2%, respectively. OS, DFS, and local relapse-free rate at 3 years were 81.3%, 68.7%, and 23.2%, respectively [96].

Another approach involves using immune checkpoint receptors inhibitors, such as anti-programmed cell death/cell death ligand (PD-1/PD-L1) and anti-cytotoxic T lymphocyte-associated antigen 4 (CTLA-4). Currently, data are increasingly available regarding utilization of these molecules in the metastatic setting [97]. CCRT in combination with checkpoint

inhibitors may induce an increased immunogenic environment by initiating DNA breaks, cell death, and antigen presentation, leading to enhancing anti-tumor activity. Moreover, CC itself is a highly immunogenic disease due to chronic HPV infection. Indeed, in the presence of chronic HPV infection, a natural immune response develops with activation of the adaptive immune system. Of note, PD-L1 expression increases with higher grades cervical intra-epithelial neoplasia, and 88% LACC cases exhibit ≥ 1% positive PD-L1 [98]. Several trials with CTLA-4 (ipilimumab), PD-1 (pembrolizumab, nivolumab) or PD-L1 (durvalumab and atezolizumab) checkpoint inhibitors are ongoing in the LACC setting [97,99].

Therapeutic live vaccines targeting HPV have also been developed using bacterial vectors from a variety of bacterial species [97,100]. Adoptive cell therapy with tumor-infiltrating lymphocytes, activated and expanded *ex vivo* is another potential strategy [101,102].

Finally, triapine, a ribonucleotide reductase inhibitor, showed preliminary interesting results in a phase II trial, in combination with CCRT. A phase III trial is currently ongoing [103].

5.4. Special populations

5.4.1. Adenocarcinoma

Most of our knowledge on the treatment of CC comes from studies in which the majority of patients had SCC. Moreover, no RCTs are specifically dedicated to this histological subtype.

Compared to SCC, ADC appears to be associated with a worse prognosis, a greater distant metastases rate, a higher resistance to RT and less chemosensitivity [104–107]. However, there is no definitive information regarding the prognostic significance of ADC among patients with LACC treated with definitive RT or CCRT.

Despite the suggested differences, according to the international guidelines, current management of the ADC histological subtype is similar to that of SCC in LACC.

6. Adjuvant hysterectomy (HT)

The evidence that systematic HT following CCRT improves survival in women with LACC is lacking. Moreover, due to RT-induced inflammation and vascular fibrosis, surgery has an increased risk of significant per- and post-operative complications, such as entero-vesical and vesico-vaginal fistulas. Residual disease (RD) after primary CCRT is directly associated with local recurrence, and optimal treatment of this situation remains unclear [51].

One of the primary limitations to adjuvant HT is that imaging modalities cannot accurately predict RD. Classically, tumor response is assessed by clinical examination, pelvic MRI and [^{18}F]FDG-PET/CT 3 months after completion of treatment. Valduvieco et al. reported a 60% correlation between MRI and clinical findings at 3 months with a further increase of up to 80% at 6 months [108]. Vincens et al. [109] reported a false-positive rate of 50% between MRI and pathological findings. It seems that diffusion-weighted sequences could be useful [109]. Indeed, interpretation of pelvic MRI can be difficult due to the presence of radiation-induced inflammation or scarring. [^{18}F]FDG-PET/CT can be helpful, but attention should be given to its interpretation due to its higher negative predictive than positive predictive values [42–44]. Very few and old data have been published concerning the results of surgery after CCRT. Moreover, these publications are mixtures of different situations in terms of disease stage, dose and techniques of EBRT and CT schedules. Furthermore, variability was observed with respect to the type of surgical method and realization of lymphadenectomy or not. Consequently, there is major difficulty in interpreting these results. But, all these studies confirmed a higher rate of postoperative complications with similar outcomes [55,110–115].

However, it is important to underline the 'recommendations' of National Comprehensive Cancer Network (NCCN) guidelines. For stage IB3 or IIA2 tumors, their panel of experts had a major disagreement about recommending adjuvant HT (category 3) after primary CCRT [116]. Also, a Cochrane review analyzed whether the addition of HT to standard non-surgical treatments had a clear benefit for patients with LACC, in terms of local control and/or OS. The findings were considered insufficient to demonstrate a survival benefit associated with adjuvant HT [117]. The morbidity is higher after HT, but this could be decreased using a laparoscopic technique [64,118]. Although routine HT remains not recommended, this approach could potentially be considered in patients in whom the primary extent of disease or the anatomy of the uterus precludes an adequate coverage by BT [116].

7. Follow-up

Surveillance will ideally benefit patients with local relapse, offering potentially curative treatment. More than 75% of recurrences occur within the first 2–3 years after the initial treatment, suggesting a role for intensive surveillance during this period. Follow-up schedules may be individualized, taking into account prognostic factors, treatment modality and side effects. No prospective studies with direct comparisons of follow-up regimens have been published. The primary objective of surveillance is to provide a clinical and cost-effective approach for detecting recurrence and affecting survival outcomes. International guidelines recommend follow-up evaluation every 3–4 months for the first 2 years and every 6 months for the next 3 years. Patients should return to annual population-based general physical and pelvic examinations after 5 years [119]. Follow-up visits should include a complete physical examination, with a pelvic–rectal exam and a detailed patient history. In women treated with primary RT, the incidence of an abnormal Pap test ranges from 6% to 34%, with atypical squamous cells of undetermined significance accounting for most of the abnormalities. Indeed, the value of Pap cytology in the detection of recurrence is very limited; moreover, the results may represent artifacts in irradiated patients [120]. In patients with clinical suspicion of recurrence, [^{18}F]FDG-PET/CT detected disease with both high sensitivity (86%) and specificity (87%). It only has a role in cases of suspected recurrence where MRI or CT imaging is equivocal. There is no definitive evidence supporting the routine use of

[^{18}F]FDG-PET/CT in patient follow-up. Biopsy should always be obtained in case of doubt [10,121].

8. Sexual function after treatment

LACC is frequently diagnosed in women at a median age of 50. Thus, late sequelae related to treatment must be taken into consideration with a particular interest for their sexual function. Sexual morbidity is a complex issue, commonly due to physical and/or psychological impacts related to various tumor and treatment factors. Several retrospective studies concluded that sexual dysfunction is particularly common after RT for CC, although women treated with radical HT can also notice an alteration of their sexual function [122–124]. The impact of RT is mainly attributed to pelvic fibrosis, vaginal stenosis and decreased vaginal lubrication, resulting in dyspareunia and sexual worries [125]. Based on the EMBRACE study, Kirchheiner et al. [126] described that 41.5% of patients reported no, 12.3% occasional and 46.3% frequent sexual activity after treatment. Before treatment, vaginal dryness, shortening, tightening and pain during intercourse were only reported by 7.1%, 2.9%, 4.8% and 10.5% of patients, respectively. During follow-up (median 36 months), these side effects increased to 38.4%, 36.4%, 34.2% and 33.5%, respectively [126]. In younger women treated with RT, induction of premature menopause is systematic after EBRT. Indeed, RT directly damages the endocrine function of the ovaries. However, a systematic review in gynecological cancers (including 93% of CC) found that ovarian transposition can preserve the ovarian function in 94% of women having BT and 65% of women undergoing both BT and EBRT [127]. It is also of utmost importance to develop efforts to prevent vaginal morbidity and prospectively propose individualized sexual rehabilitation options after treatment such as menopause hormone remplacement therapy [128], vaginal dilatation, pelvic physiotherapy, …

9. Conclusions

Major progresses have been made in treating patients with LACC (FIGO 2018 stages IB3-IVA) during the past decades.

The updated 2018 FIGO classification uses imaging and pathological findings to designate the final stage of the disease. This new version has improved capacity to discriminate between the three subgroups of stage IB. Furthermore, inclusion of LN status is a major change that more accurately reflects the prognosis. Nevertheless, survival remains heterogeneous among patients within stage III subgroups.

Imaging has assumed an increasingly important place in the initial workup and the post-treatment evaluation but also in RT planning. In the latter, imaging has allowed implementations of more conformal radiation techniques, such as IMRT/VMAT, IGRT and IGABT. These new approaches in combination with concomitant CT clearly increase local control rates while also influencing OS and decreasing toxicities.

Cisplatin-based CCRT demonstrates survival benefit compared to RT alone. Currently, the standard of care is concomitant cisplatin-based chemoradiation followed by IGABT with an OTT less than 55 days. Cisplatin at 40 mg/m2 per week is administered on the first or second day of each week of EBRT for 5 cycles. EBRT is typically administered at 1.8 Gy/day five days per week for 25 days, delivering a total dose of 45 Gy to the entire pelvis. The primary tumor is subsequently boosted, using image-guided BT, with an additional 30 to 40 Gy for a total dose of 85 Gy. Bulky nodes are boosted with an additional 10 to 15 Gy focused on adenopathy. In cases of positive PAo LN (evaluated by metabolic imaging and/or surgery), the RT field is extended to cover this region up to the level of the 10th dorsal vertebrae. In cases of initial parametrial invasion or major residual disease at the end of EBRT, interstitial BT techniques should be used to increase the dose delivered to the high-risk clinical target volume; this latter technique should be limited to institutions with experience and expertise. Carboplatin (area under the curve two) may represent an alternative in patients considered unfit for cisplatin (Figure 1).

The precise role of neo- and adjuvant CT is still debated due to conflicting data. The results of major trials, such as INTERLACE and OUTBACK, are eagerly awaited.

Despite these significant advances, OS at 5 years remains around 65-70%, and the disease will recur in approximatively 40% of patients. The prognosis is therefore still suboptimal, and new strategies trials are ongoing.

These trials are testing new drugs in combination with cisplatin-based CCRT continued in maintenance, such as anti-angiogenesis agents, checkpoint immune receptors and RNR inhibitors. Adoptive T-cell therapy has also shown promising results in the metastatic setting and could be implemented in the context of LACC disease.

To perform a systematic hysterectomy after CCRT followed by IGBAT is not recommended due to having no proven benefits on survival and an accompanying high rate of morbidities, particularly in the form of urinary fistulae. On the other hand, place of surgery in case of residual disease or local relapse is a debate not fully resolved. Individual decisions should be made for each patient in this situation. Concerning residual disease, the major problem remains how to identify patients who would most benefit from surgery.

The evidence concerning follow-up is currently lacking. At minimum, physical examination and clinical history should be performed by specialists with frequencies adapted to the risk of recurrence. Systematic cytological Pap test and imaging are not recommended.

10. Expert opinion

The optimal care of patients suffering from LACC begins with an exhaustive initial diagnostic workup performed by a multidisciplinary expert team. Indeed, this step determines and individualizes the entire treatment plan, which includes a thorough clinical and radiological examination. For selected patients, a surgical approach to obtain a definitive PAo LN status may be indicated. However, the best strategy for the detection of PAo LN status remains a controversial topic. The subgroup that tends to derive the most benefit of surgical approach is that of patients with positive pelvic nodes and negative PAo nodes on pre-therapeutic [^{18}F]FDG-PET/CT. However, only

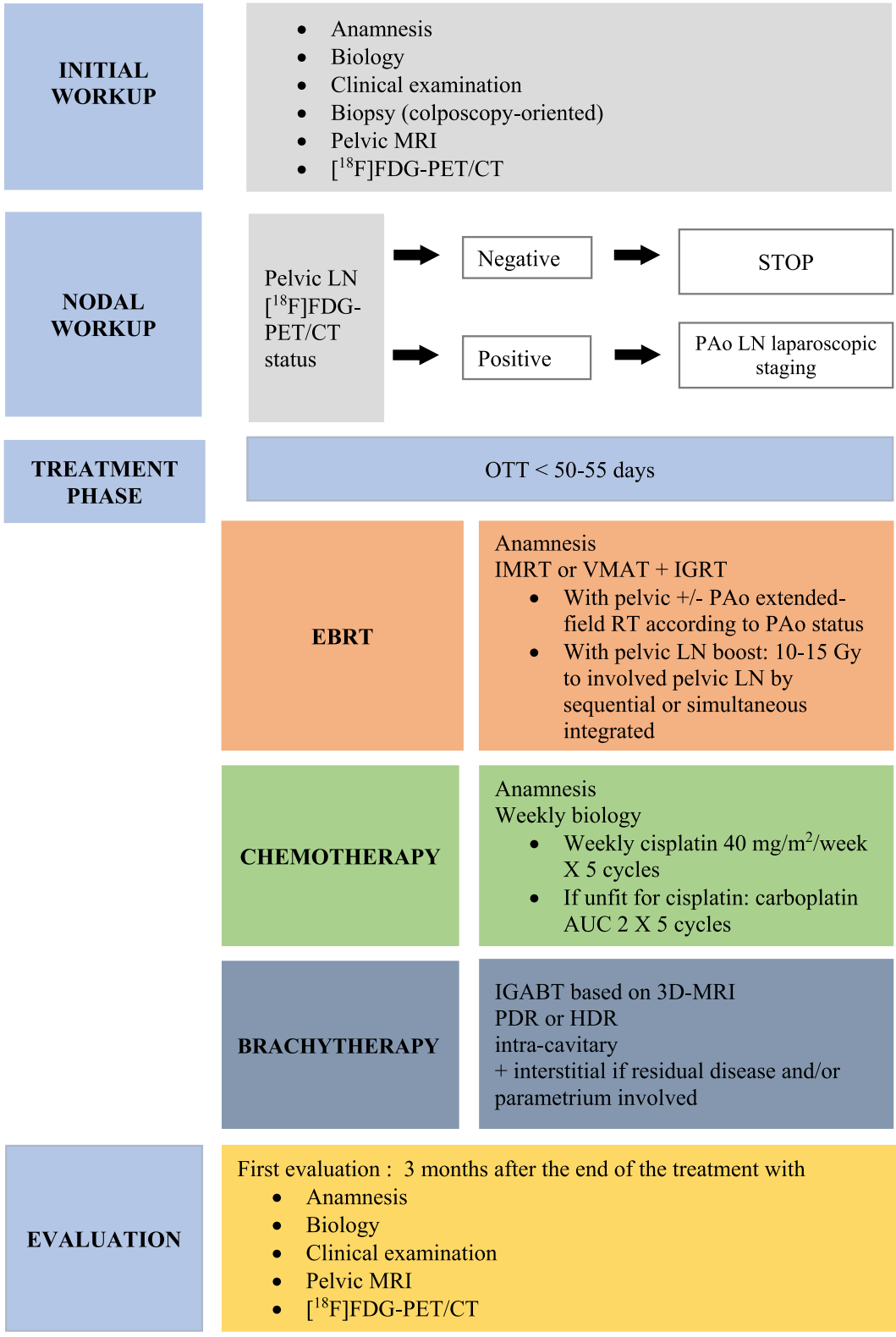

Figure 1. Optimal treatment for LACC: step by step. AUC = area under the curve; EBRT = external-beam radiotherapy; [^{18}F]FDG-PET/CT = ^{18}F-2′-deoxy-2′ fluorodeoxyglucose; HDR = high-dose rate; IGABT = image-guided adaptive brachytherapy; IGRT = image-guided radiotherapy; IMRT = intensity-modulated radiation therapy; LN = lymph node; MRI = magnetic resonance imagery; OTT = overall treatment time; PAo = para-aortic; PDR = pulsed-dose rate; RT = radiotherapy; 3D = three-dimensional; VMAT = volumetric arc therapy.

the results of a well-designed RCT will end this debate by clarifying the hypothetical survival benefit of such surgical staging.

Beyond this multidisciplinary initial workup, profiling the patient and tumor risks of relapse based on biomarkers is essential. Some have been proposed (tumor size, nodal

status, histology, metabolic avidity, etc.) but are not satisfactory. Molecular biomarkers are probably the key and could be used as predictive factors to help us select better patients for intensification of systematic therapy. Moreover, all of these molecular alterations are of potential clinical relevance, as a number of these proteins may represent targets for new drugs in the metastatic setting and could subsequently be tested in the initial treatment of LACC disease.

As far as definitive treatment is concerned, conformal RT techniques in combination with concomitant chemotherapy clearly improve local control rates and overall survival, while decreasing toxicities. It is likely that a 'plateau' curve has been reached concerning local control rate, except perhaps for very bulky tumors. In contrast, uncontrolled distant metastatic spread is still responsible for the majority of failures among patients with LACC. How can we better select patients with aggressive disease and tailor their treatment? The molecular characteristics described above must be explored for their capacity to discriminate between low- and high-risk patients. Furthermore, adenocarcinoma represents 20% of cases with a constantly rising incidence. Currently, LACC is treated independently of the histological subtype, with data supporting reduced chemosensitivity for ADC, likely explained on a molecular basis.

Various therapeutic strategies, some still under investigation, have been proposed to improve the outcome of patients suffering from LACC: adding novel targeted agents with CT, using other CT schedules either alone or in combination with platinum, modifying the dose or CT regimen, neoadjuvant CT followed by surgery or CCRT, adjuvant CT, and, more recently, use of immunotherapeutic approaches. Nonetheless, no therapeutic strategy has demonstrated a clear impact on patient outcome, although the key to improving the control of subclinical micrometastases likely relies on systemic adjuvant therapy. The results of the well-designed OUTBACK and INTERLACE trials are eagerly anticipated. Post treatment systematic hysterectomy has also been unable to demonstrate an improved outcome but is linked to significant morbidity and should no longer be proposed (except in very specific situation).

Last but not least among the remaining challenges is to control treatment-related morbidity and to ensure QoL for patients. Patients treated with RT can develop vaginal stenosis and dryness and should receive education by expert team regarding sexual and vaginal issues. Furthermore, CC survivors are at risk for second cancers. Data suggest that patients receiving RT for pelvic cancers are at risk for radiation-induced secondary neoplasms, especially at irradiated sites near the cervix (colon, rectum/anus, and bladder); careful surveillance is recommended in these patients.

At the time of this review and after having witnessed major multidisciplinary efforts made to improve the outcome of patient suffering from LACC, it appears essential to recall that 85% of these neoplasms occur in developing countries where access to appropriate therapy is absent or suboptimal. Furthermore, national health systems should concentrate on optimizing their prevention program, which constitutes the most cost effective approach to reduce the incidence and mortality of cervical cancer.

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