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Adenocarcinoma of the uterine cervix: Pathologic features, treatment options, clinical outcome and prognostic variables

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ABSTRACT

Adenocarcinoma accounts for 10–25% of all cervical cancers, and its relative and absolute rate has raised over the past decades. Most, but not all the authors, reported that adenocarcinoma has a greater propensity to lymph node, ovarian and distant metastases and a worse prognosis compared with squamous cell carcinoma. However, whether histologic type is an independent prognostic factor is still a debated issue. Moreover, adenocarcinoma is a very heterogenous disease, including different histological subtypes. Whereas radical hysterectomy and definitive radiotherapy achieve the same clinical outcome in early stage squamous cell carcinoma, surgery seems to obtain better survival compared with definitive radiotherapy in early stage adenocarcinoma. Chemoradiation is the standard treatment for locally advanced cervical cancer regardless of histologic type, although several retrospective studies showed that patients with adenocarcinoma were more likely to die than those with squamous cell carcinoma both before and after concurrent chemoradiation era. The prognostic relevance of biological variables, such as cyclin-dependent kinase inhibitors, p53, cyclooxygenase-2 [COX-2], cell surface tyrosine-kinases and programmed death-ligand [PD-L1], is still under investigation. Palliative chemotherapy is the only treatment option for persistent or recurrent cervical adenocarcinoma not amenable with surgery and radiotherapy. The use of immune checkpoint inhibitors as well as a therapeutic strategy targeting cell surface tyrosine kinases should be adequately explored in this clinical setting.

1. Introduction

Carcinoma of the uterine cervix represents a leading cause of female cancer mortality, causing 265,653 deaths per year worldwide (Williams et al., 2015). Squamous cell carcinoma is the most common histological type, whereas adenocarcinoma accounts for 10–25% of all cervical cancer cases (Williams et al., 2015; Shoji et al., 2013). Whereas squamous cell carcinoma incidence has declined in developed countries, both the relative and absolute rates of adenocarcinoma have raised over the past decades (Vizcaino et al., 1998; Schorge et al., 2004; Wang et al., 2004; Bray et al., 2005). A study conducted in 13 European countries revealed significant increases in cervical adenocarcinoma rates of at least 2% per year in Finland, United Kingdom, Slovakia, and Slovenia, and positive, even not significant, trends in most other countries (Bray et al., 2005). Clinically, adenocarcinoma of the uterine cervix can be asymptomatic or can present with abnormal bleeding or vaginal discharge similarly to the more common squamous cell carcinoma (Bray et al., 2005; Giordano et al., 2012; Cracchiolo et al., 2016). The typical evolution of this malignancy is the extension into vagina and pelvic structures as well as the diffusion into regional lymph nodes, whereas the distant spread in the abdomen, liver, lungs and bones is a less frequent event (Bray et al., 2005; Cracchiolo et al., 2016; Corrado et al., 2010; Matsuyama et al., 1989). However, most authors reported that adenocarcinoma has a greater propensity to lymph node, ovarian and distant metastases compared with squamous cell carcinoma (Drescher et al., 1989; Eifel et al., 1990, 1995; Irie et al., 2000; Shimada et al., 2006; Landoni et al., 2007; Jiao et al., 2016; Lee et al., 2011; Irie et al. (2000)) detected nodal metastases in 31.6% of 57 patients with adenocarcinoma *versus* 14.8% of 198 patients with squamous cell carcinoma of the uterine cervix in stage Ib-II treated with radical hysterectomy. A retrospective review of medical records and autopsy findings of 42 women dying of cervical cancer observed that patients with adenocarcinoma had a higher incidence of para-aortic node metastases (61.9% *versus* 30.0%, $p < 0.05$), uterine corpus involvement (100% *versus* 60.0%, $p < 0.05$), adrenal gland metastases (33.3% *versus* 0%, $p < 0.005$), ascites (42.8% *versus* 9.5%, $p < 0.05$) and hydrothorax (42.8% *versus* 14.3% $p < 0.05$) (Eifel et al., 1990) than those with squamous cell carcinoma (Drescher et al., 1989). A Japanese review of surgically-treated 3471 women with stage Ib - IIb cervical cancer found ovarian metastases in 5.3% and 0.8%, respectively, of adenocarcinomas

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and squamous cell carcinomas (Shimada et al., 2006). An Italian retrospective study, including 1695 patients with stage Ia2- IIa cervical cancer who underwent radical hysterectomy, showed that ovarian metastases were present in 2.4% adenocarcinomas *versus* 0.5% of squamous cell carcinomas, and that histological type was the strongest independent risk factor for ovarian involvement (p = 0.001) (Landoni et al., 2007). The meta-analysis of 5 studies on surgically-treated patients with early stage cervical cancer detected a 5.27-fold higher incidence of ovarian matastases (95% confidence interval [CI], 2.14–13.54) in adenocarcinomas than in squamous cell carcinomas (Jiao et al., 2016). Eifel et al. (1995), who reviewed a large series of stage Ib cervical cancers treated with radiotherapy, reported distant recurrences in 37% of the 229 adenocarcinomas *versus* 21% of 1538 squamous cell carcinomas (p < 0.01). In a Korean study including a large series of stage Ib-IIa cervical cancers treated with radical hysterectomy with or without adjuvant therapy, tumor recurred in 36 (5.7%) of the 636 patients with squamous cell carcinoma *versus* 20 (14.4%) of the 139 patients with adenocarcinoma of the uterine cervix (p < 0.001) (Lee et al., 2011). It is noteworthy that relapse rate in hematogenous/distant areas was higher in adenocarcinomas (9 of 20, 45.0%) than in squamous cell carcinomas (8 of 36, 22.2%, p = 0.07). However, other studies found no significant differences in node and ovarian metastases and as well as in parametrial, uterine or vaginal extension, lymphovascular-space involvement [LVSI] and depth of invasion between early- stage adenocarcinoma and early -stage squamous cell carcinoma of the uterine cervix (Nakanishi et al., 2000; Ruengkhachorn et al., 2016; Look et al., 1996). Diagnostic imaging techniques, such as computed tomography [CT], magnetic resonance [MR], and eventually positron emission tomography [PET]/CT, should be used for an adequate staging at presentation, especially in patients with apparently locally advanced disease (National Cancer Comprehensive Network, 2019).

Several studies on surgically- treated patients with stage Ia-IIa cervical cancer failed to detect different oncologic outcomes between adenocarcinoma and squamous cell carcinoma (Ruengkhachorn et al., 2016; Look et al., 1996; Harrison et al., 1993; Shingleton et al., 1995; Spoozak et al., 2012; Winer et al., 2015). Conversely, other investigations on patients with early stage disease who underwent primary radical hysterectomy with or without adjuvant radiotherapy or concurrent chemoradiation, reported a poorer disease-free survival [DFS] and overall survival [OS] for adenocarcinoma compared with squamous cell carcinoma (Irie et al., 2000; Nakanishi et al., 2000; Noh et al., 2014; Landoni et al., 1997; Hopkins and Morley, 1991; Park et al., 2010). Several studies on early or locally advanced cervical cancer treated with definitive radiotherapy or concurrent chemoradiation reported worse results in non squamous cell than in squamous cell carcinomas (Noh et al., 2014; Kleine et al., 1989; Oka et al., 1996; Chen et al., 1999; Katanyoo et al., 2012; Lee et al., 2015; Chen et al., 2014; Zhou et al., 2017a), and some authors found that non squamous cell carcinomas exhibited a lower response rate to neoadjuvant chemotherapy [NACT] compared with squamous cell carcinomas (Chen et al., 2008; Namkoong et al., 1995; Hwang et al., 2001). However, others authors did not confirm these observations (Cai et al., 2006; Kim et al., 2010; Xiong et al., 2011; Hu et al., 2019; Grigsby et al., 1988). Therefore whether histologic type is an independent prognostic factor is still a debated issue (Gien et al., 2010). Furthermore, it must take into consideration that adenocarcinoma is a very heterogenous disease, with a wide histopathologic spectrum.

2. Pathologic features

Adenocarcinoma of the uterine cervix can be classified in several histological subtypes (Wilbur et al., 2014).

2.1. Usual-type endocervical carcinoma

Usual-type endocervical carcinoma, which is related to human papilloma virus [HPV] infection, shows strong immunostaining for p16 and carcinoembryonic antigen [CEA], but not for p53 (Park et al., 2011). Han et al. (2010) compared the abilities of three-marker (estrogen receptor [ER]/ Vimentin/CEA), four-marker (ER/vimentin/CEA/progesterone receptor [PR]) and five-marker (ER/Vimentin/CEA/PR/p16) panels in discriminating between endocervical adenocarcinoma and endometrial carcinoma on paraffin-embedded, formalin-fixed tissues from 35 hysterectomy specimens. ER, PR and vimentin were more likely expressed in endometrial carcinoma, whereas CEA and p16 were frequently expressed in endocervical adenocarcinoma. The three-marker (ER/Vimentin/CEA) panel exhibited the most favorable performance in the differential diagnosis, whereas the assessment of PR and p16 did not give any additional meaningful information.

2.2. Mucinous carcinoma

Gastric-type adenocarcinoma and adenoma malignum are HPV-unrelated tumors (Park et al., 2011; Houghton et al., 2010; Kusanagi et al., 2010; Karamurzin et al., 2015; Kojima et al., 2007; Mikami et al., 2004; Kawakami et al., 2010; McCluggage, 2013; Nakamura et al., 2018; Carleton et al., 2016; Park et al., 2018a). The former variant is a mucinous carcinoma with positive immunostaining for CEA and gastric markers such HIK1083 and MUC6 (Park et al., 2011; Kojima et al., 2007; Mikami et al., 2004; Kawakami et al., 2010; McCluggage, 2013), and sometimes with HER2 amplification (Nakamura et al., 2018; Carleton et al., 2016). Tumor cells show clear or pale eosinophilic, abundant cytoplasm and distinct cell borders. Gastric-type mucinous adenocarcinomas are associated with a higher stage at presentation and higher rates of deep cervical invasion, vaginal involvement, parametrial invasion, and positive LVSI compared with usual type endocervical carcinomas (Park et al., 2018a, b). Adenoma malignum, also termed minimal deviation adenocarcinoma, is a well differentiated variant of gastric-type carcinoma, that shares the same immune profile and that is often detected in patients with Peutz-Jeghers syndrome (Wilbur et al., 2014; Park et al., 2011; Clements et al., 2009; Ishida et al., 2016). Primary signet-ring cell adenocarcinoma is extremely rare, and the diagnosis of this malignancy should be made after exclusion of metastatic disease to the cervix from a primary tumor arising in other sites, such as stomach, breast or colon (Giordano et al., 2012; Cracchiolo et al., 2016; Haswani et al., 1998; Moritani et al., 2004; Suarez-Penaranda et al., 2007; Insabato et al., 2007; Balci et al., 2010). Esophago-gastroduodenoscopy, colonoscopy and breast MR must be negative and the primary cervical origin should be supported by the presence of HPV-DNA detected by molecular analysis and by positive immunostaining for p16 (Cracchiolo et al., 2016; Haswani et al., 1998; Balci et al., 2010; McCluggage et al., 2008). The cytologic diagnosis of this histological subtype is difficult, since the presence of signet- ring cells on smear may also be due to a metastatic carcinoma to the cervix or to a gastrointestinal carcinoma with ascites without cervical involvement (Matsuura et al., 1997; Selvaggi et al., 1993).

2.3. Villoglandular papillary carcinoma

Villoglandular papillary adenocarcinoma, which accounts for 3.7–4.8% of all cervical adenocarcinomas, is characterized by young age at presentation (median, 33–36 years), superficial stromal invasion and frequent association with other tumor patterns (Young and Scully, 1989; Kaku et al., 1997; Collinet et al., 1999; Heatley, 2007; Zhou et al., 2016). The term “villoglandular papillary” should be used only when the villoglandular component is the exclusive or almost exclusive pattern (Young and Scully, 1989). The villoglandular structures are composed of stratified glandular cells, with mild to moderate nuclear atypia and mitotic figures (Khunamornpong et al., 2002; Zhao et al., 2016).

Each papilla has a central pedicle ranging in size and shape from short and thick to long and thin. HPV infection has a pathogenetic role, whereas it is controversial whether this histological subtype can be related to oral contraceptive use (Young and Scully, 1989; Zhou et al., 2016; Yamazawa et al., 2000; Jones et al., 2000; An et al., 2005; Giordano et al., 2007; Jones et al., 1993; Hagiwara et al., 2013).

2.4. Serous carcinoma

Serous adenocarcinoma of the cervix is a very rare HPV- related tumor, which histologically resembles the serous tumor developing more commonly in the ovary, fallopian tube and endometrium (Zhou et al., 1998; Togami et al., 2015). The diagnosis should be made after exclusion of cervical involvement from a tumor from other sites, especially from endometrium (Young and Clement, 2002). It is usually in advanced stage at presentation. Positive immunostaining for p16, CA125, CEA, p53 and WT1 has been detected in 100%, 92%, 58%, 50% and 0% of tissues samples from 12 patients with this malignancy (Togami et al., 2015). Up to 2014 only 47 cases of serous adenocarcinoma of the cervix have been described in the literature (Ueda et al., 2012; Khan et al., 2014).

2.5. Endometrioid carcinoma

Endometrioid carcinoma accounts for approximately 20% of all cervical adenocarcinomas (Alfsen et al., 2000). HPV16 is the predominant HPV type in this histological subtype (An et al., 2005). When endometrioid carcinoma involves both uterine cervix and body, it is rational to conclude that the tumor has arisen in the endometrium and subsequently had spread to the cervix (Obata et al., 2016). Minimal-deviation endometrioid adenocarcinoma of the uterine cervix is a very rare tumor, characterized by the presence of abnormal ciliation of the tumor cells at ultrastructural analysis (Gould et al., 2017). Park et al. (2009) detected an endometrioid adenocarcinoma arising from endometriosis of the uterine cervix in a 48 –year old Korean woman.

2.6. Clear cell carcinoma

Clear cell carcinoma, which accounts for 4–15.2% of cervical adenocarcinomas, is characterized by hobnail cells with abundant clear cytoplasm (Reich et al., 2000; Garg and Arora, 2012; Hasegawa et al., 2014; Jiang et al., 2014). This tumor is unrelated to high-risk HPV infection (Goto et al., 2005; Kocken et al., 2011; Ueno et al., 2013). It has been sometimes diagnosed in women with a history of exposure to diethylstilbestrol [DES] in utero (Troisi et al., 2007). Hiromura et al. (2000) described a case of clear cell carcinoma associated with cervical endometriosis, suggesting that the pathogenesis of this cervical malignancy might be similar to that of ovarian clear cell carcinoma. Although the median age at presentation ranges from 38 to 53 years, this tumor has been also observed in adolescents and children without prior DES exposure (Jiang et al., 2014; Thomas et al., 2008a). In a Dutch series including 41 not- DES exposed patients, clear cell carcinoma of the uterine cervix had a bimodal age distribution, with one peak at 26 years and a second peak at 71 years (Hanselaar et al., 1997). Hepatocyte nuclear factor 1-beta [HNF1-β] has been detected in 78% of 9 clear cell carcinomas, 40% of 26 usual-type endocervical adenocarcinomas, and 27% of 11 gastric-type adenocarcinomas of the uterine cervix, indicating a lack of specificity of this marker for clear cell carcinoma (Park et al., 2011).

2.7. Mesonephric carcinoma

Mesonephric adenocarcinoma is an extremely rare tumor arising from mesonephric ductus remnants or mesonephric hyperplasia areas, with approximately 30 cases described in the literature (Park et al., 2011; Clement et al., 1995; Silver et al., 2001; Fukunaga et al., 2008; Tekin et al., 2015; Yeo et al., 2016; Ditto et al., 2016). The age of patients ranges from 35 to 72 years, with a mean of 52 years. Histologically, the tumor is characterized by atypical, round to polygonal cells arranged in a ductal, tubular, papillary, solid, retiform or sex-cord-like pattern (Clement et al., 1995). It shows positive Immunostaining for epithelial markers, such as AE1/3, CK1, CAM 5.2, CK7, and epithelial membrane antigen [EMA], and negative immunostaining for CK20, CEA, ER and PR (Park et al., 2011; Silver et al., 2001; Fukunaga et al., 2008).

3. Treatment strategy

According to the NCCN guidelines, the primary treatment of early stage cervical cancer is either surgery or radiotherapy (National Cancer Comprehensive Network, 2019). Fertility-sparing approaches can be taken into consideration in highly selected cases. Conisation is an option for patients with stage Ia1 disease and negative LVSI, whereas laparoscopic pelvic lymphadenectomy and radical trachelectomy can be proposed to patients with stage Ia1 disease and positive LVSI or with stage Ia2 or stage Ib1 disease with tumor size $\leq$ 2 cm. Conservative surgery is not appropriate for tumors with potentially aggressive behavior, such as small cell neuroendocrine tumors, gastric-type cervical carcinoma and adenoma malignum. Tailored radical hysterectomy with bilateral pelvic lymphadenectomy is the preferred treatment for stage Ia1 with positive LVSI, stage Ia2, stage Ib1 and stage IIa1 cervical cancer. Pelvic external beam radiotherapy plus brachytherapy is an alternative option for patients not fit for surgery or who refuse surgery. Concurrent cisplatin based- chemoradiation plus brachytherapy is the standard treatment for stages Ib2-IIa2- IIb-III-IVa cervical cancer. Platinum-based NACT followed by radical hysterectomy has obtained good results in stage Ib2-IIb cervical cancer, and the recently closed European Organization for Research and Treatment of Cancer [EORTC] randomized trial has compared NACT plus radical surgery *versus* concurrent chemoradiation plus brachytherapy in this clinical setting (EORTC protocol 55,994) (Shoji et al., 2013; Hu et al., 2012; Sananes et al., 1998; Benedetti-Panici et al., 2002; Buda et al., 2005; Lissoni et al., 2009; Benedetti-Panici et al., 1996; Zanetta et al., 1997; Iwasaka et al., 1998; Tabata et al., 2004; Gadducci et al., 2013; Shimada et al., 2016; Gadducci et al., 2018). Two additional studies comparing concurrent chemoradiation *versus* NACT followed by surgery are still ongoing (NCT00193739, and NCT01000415).

The current guidelines for cervical cancer recommend the same treatment strategy for squamous cell carcinoma and adenocarcinoma. However, data from literature comparing treatment efficacy in these different histological types are not yet exhaustive.

3.1. Primary surgery

Table 1 shows the clinical outcome of patients with cervical adenocarcinoma treated with primary surgery. Several studies in microinvasive disease reported no difference in clinical outcome between adenocarcinoma and squamous cell carcinoma of the uterine cervix (Ruengkhachorn et al., 2016; Spoozak et al., 2012; Winer et al., 2015). The analysis of the 3987 patients with stage Ia1-Ia2 cervical cancer enrolled in the Surveillance, Epidemiology, and End Results [SEER] database from 1988 to 2005 showed no difference in cancer-specific survival [CSS] based on histology (Spoozak et al., 2012). In another SEER study including 1567 patients with cervical microinvasive adenocarcinoma, 5-year OS rates for stage Ia1 and stage Ia2 disease were 96.6% and 100% respectively following local excision, 98.4% and 96.9% following simple hysterectomy, and 96.5% and 99.4% following radical hysterectomy (Bean et al., 2017). Ruengkhachorn et al. (2016), who assessed a series of 151 patients with stage Ia cervical cancer treated with primary surgery, found that relapse rates were not significantly different between adenocarcinoma and squamous cell carcinoma. Two retrospective studies on surgically- treated patients with

Table 1
Clinical outcome of patients with cervical adenocarcinoma treated with primary surgery.

Author	Stage	Histological Type	
Spoozak et al. (2012)			HR for CSS
	Ia1	AC(n.554) *vs* SCC (n.1,610)	0.79 95%CI = 0.21-2.94 p = ns
	Ia2	AC (n.434) *vs* SCC (n.1,389)	0.51 95%CI = 0.18-1.47 p = ns
Ruengkhachorn et al. (2016)			Recurrence rate
	Ia	AC (n.35) *vs* SCC (n.116)	5.7% *vs* 2.6% p = ns
Winer et al. (2015)	Ia1-Ib2 (n.278)[a]	Mexican cohort AC(n.101) *vs* SCC(n. 76)	5-year OS = 98.2% *vs* 95.2%,p = ns
		Detroit cohort AC (n.29) *vs* SCC (n.72)	5-year OS = 91% *vs* 92 %,p = ns
Harrison et al. (1993)	Ib-Iia[d] (n.231)	AC(n.25) *vs* AD(n.57) *vs* SCC(n.220)	No difference in OS
Noh et al. (2014)	Ib-IIa (n.1323)[b]	AC *vs* AS *vs* SCC	5-year OS = 66.5% vs 79.6% vs 83.7% p < 0.0001
Landoni et al. (1997)	Ib-IIa[c] (n.337)	AC (n.50) *vs* SCC(n.287)	HR of death for AC = 2.68 (95% CI = 1.9-3.8) in multivariate analysis
Shimada et al. (2013)	Ib-Iib[f] (n.820)		5-years OS
	Ib1	AC(n.184)vs SCC(n.258)	92.0% vs 94.7% p = ns
	Ib2	AC(n.39)vs SCC(n.67)	75.5% vs 74.2% p = ns
	IIa	AC(n.11)vs SCC(n.83)	54.5% vs 87.4% p < 0.05
	IIb1	AC(n.46)vs SCC(n.132)	63.3% vs 78.8% p < 0.05
Sedlis et al. (1999); Rotman et al. (2006)	Ib		Recurrence
	N-		RT observation
	Risk factor for T[e] (n.277)	AC/AD	3/34(8.8%) 11/24(44.0%)
		SCC	21/103(20.4%) 32/115(27.8%)
			RT patients were 44% less likely to recur(HR = 0.56;90% CI = 0.37-0.86;p = 0.012)

Legend: HR = hazard ratio; CSS, cancer specific survival; AC, adenocarcinoma; SCC, squamous cell carcinoma; CI, confidence interval ; ns, not significant; OS, overall survival; AD, adenosquamous carcinoma; RT, radiotherapy.

[a] 222 were in stage IB1.
[b] Surgery + RT(n.831)or CCRT(n.492)(adjuvant treatment).
[c] Randomised to either surgery (n.170) or definitive RT(n.167).
[d] Surgery.
[e] Surgery -→random to adjuvant RT or observation.
[f] 446 pts received postoperative adjuvant treatment.

early stage cervical cancer showed equivalent OS in these two histologic types (Harrison et al., 1993; Winer et al., 2015). In a Japanese study on early stage patients who underwent radical hysterectomy, 5-year OS was poorer in adenocarcinoma than in squamous cell carcinoma (p = 0.0034) (Irie et al., 2000). It is noteworthy that OS did not differ between two groups in stage Ib disease, whereas it was significantly worse for adenocarcinoma in stage II disease.

Noh et al. (2014) noted that adenocarcinoma histology was the only independent poor prognostic variable for OS (HR = 1.729, 95%CI = 1.085–2.617, p = 0.0195) in a large series of early stage patients who underwent radical hysterectomy followed by adjuvant radiotherapy or concurrent chemoradiation. An Italian trial randomly allocated women with stage Ib - IIa cervical cancer to receive radical hysterectomy or definitive radiotherapy (Landoni et al., 1997). Adjuvant radiotherapy was administered after surgery to patients who had at least one of the following pathological risk factors: surgical stage greater than pT2a, < 3 mm of uninvolved cervical stroma, cut-through, and lymph-node metastases. The 5-year DFS and OS did not differ significantly between the two arms in the whole series, but adenocarcinoma histology was an independent poor prognostic variable for OS. Patients with adenocarcinoma assigned to surgery arm had a better 5-year DFS and OS than those allocated to radiotherapy arm (66% *versus* 47%, p = 0·02, and, respectively, 70% *versus* 59%, p = 0·05). Similarly Okame et al. (2016) who analyzed women with cervical stage Ib2-IIb mucinous adenocarcinoma, found better 3–year loco-regional control rates and better 5-year OS in the 19 patients who underwent radical hysterectomy compared with the 13 treated with definitive radiotherapy (79.0% *versus* 46.2%, p = 0.03, respectively, 70.7% *versus* 38.5%, p = 0.09). In a Japanese retrospective investigation on 820 surgically treated patients with stage Ib-IIb disease, adenocarcinoma was associated with a significantly worse OS in stage II disease, whereas histological type did not affect the clinical outcome in stage I disease (Shimada et al., 2013). The analysis of 2773 stage Ib-IIa cervical adenocarcinoma patients treated with primary surgery (n.1816), surgery + radiotherapy (n.795) and primary radiotherapy (n.162) revealed that women who underwent primary surgery had better CSS and OS, especially when tumor size was ≤ 4 cm (Zhou et al., 2017b).

The Gynecologic Oncology Group [GOG] 92 trial randomized surgically treated, stage Ib cervical cancer patients with negative lymph nodes and at least two adverse prognostic pathologic features (deep stromal invasion, positive LVSI, tumor size > 4 cm) to receive either adjuvant pelvic external beam radiotherapy or no further treatment (Sedlis et al., 1999; Rotman et al., 2006). Adjuvant radiotherapy obtained a significant reduction of recurrence rates (HR = 0.54,90% CI = 0.35 - 0.81, p = 0.007) and progression or death rates (HR = 0.58, 90% CI = 0.40 -0.85, p = 0.009), and this protective effect appeared to be greater for non- squamous cell than for squamous cell carcinomas.

3.2. Neoadjuvant chemotherapy followed by surgery

Few retrospective studies have specifically assessed the efficacy of cisplatin–based NACT followed by radical hysterectomy in locally advanced adenocarcinoma of the uterine cervix (Shoji et al., 2013; Hu et al., 2012; Benedetti-Panici et al., 1996; Zanetta et al., 1997; Iwasaka et al., 1998; Tabata et al., 2004; Shimada et al., 2016; Gadducci et al., 2018) (Table 2). The clinical overall response rate to NACT ranged from 67.0% to 81.7%. In the investigation of Benedetti-Panici et al. (1996),

Table 2
Clinical outcome of patients with cervical adenocarcinoma treated with neoadjuvant chemotherapy followed by radical surgery.

Authors	Patients	Stage	NACT regimen	Clinical outcome
Benedetti-Panici et al. (1996)	42	Ib_2-IIIb	Different regimens	5-year OS Responders (n.33) 84% (p < 0.0001) Non-responders (n.9) 0%
Zanetta et al. (1997)	21	Ib_2-IIb	CDDP 50 mg/m^2 weekly EPIDX 70 mg/m^2 weeks 1, 4, 7	48- month OS ~ 55%
Iwasaka et al. (1998)	16	Ib-IV	CDDP 50 mg/m^2 d1 + MIT-C 10 mg/m^2 d 1 + VP-16 100 mg/m^2 d1, 3, 5 every 4 weeks	Mean OS Responders (n.8) 45.7 months Non-responders (n.8) 28.3 months (p = ns)
Tabata et al. (2004)	14	Ib_1-IIb	CDDP 15 mg/m^2 d 1-5 + MIT-C 15 mg/m^2 d1 + VP-16 70 mg/m^2 d 1-3, + EPIDX 30 mg/m^2 d 1 every 4 weeks	The 8 pts with no or microscopic RD* had longer OS than the 6 pts with macroscopic RD (p = 0.012) * on surgical sample
Shimada et al. (2016)	52	Ib_2-IIb	DOC 60 mg/m^2 + CBDCA AUC5 every 3 weeks	2 –year OS Stage Ib2 (n.14) 81.8% Stage IIa2 (n.7) 85.7% Stage IIb (n.31) 92.6% p = ns
Gadducci et al. (2018)	82	Ib_2-IIb	Different platinum-based regimen	5-year OS Optimal responders or suboptimal responders with intracervical RD (n.46): 92% Cervical RD (n.46) 92 Suboptimal responders with extracervical RD or no responders (n.36) 4%; p = 0.012

Legend: NACT, neoadjuvant chemotherapy; OS, overall survival ; CDDP, cisplatin; EPIDX, epidoxorubicin; MIT-C, mitomycin-D; VP-16, etoposide; RD, residual disease; DOC, docetaxel; CBDCA, carboplatin; AUC, area under curve.

the clinical response to chemotherapy was the only independent prognostic factor for OS (p = 0.006). In another Italian study (Zanetta et al., 1997), the histologic examination of surgical specimens detected persistent microscopic and macroscopic disease in 4 (22.3%) and 14, respectively, of the 18 patients who underwent radical hysterectomy. Isakawa et al. (Iwasaka et al., 1998) noted that responders to NACT survived longer compared with non-responders, although the difference was not statistically significant. Moderate or marked pathological changes were detected in 3 (25%) of the 12 patients with stage I-II disease who underwent radical hysterectomy after NACT. Tabata et al. (2004) detected no residual disease and microscopic residual disease < 5 mm on surgical samples in 6 and 2, respectively, of 14 patients, with an optimal pathological response rate of 57%. An Italian retrospective investigation reported an optimal pathological response (no residual disease or residual disease < 3 mm), a suboptimal pathological response with intra-cervical residual disease and a sub-optimal pathological response with extra-cervical residual disease or no response in 10 (12.2%), 36 (43.9%) and 36 (43.9%), respectively of the 82 patients treated with different NACT regimens (Gadducci et al., 2018). A recent meta-analysis (He et al., 2014) failed to detect significant differences in response rates between squamous cell and non squamous cell carcinomas, but it evidenced better DFS and OS for patients with squamous cell carcinoma, especially for those with FIGO stages > IIb. However, we must consider that adenocarcinoma has a wide histopathologic spectrum and nowadays there no meaningful clinical data on the sensitivity to chemotherapy of each single subtype. A retrospective study on a small number of patients appeared to suggest that gastric-type mucinous adenocarcinoma is more chemoresistant than usual-type endocervical carcinoma (Kojima et al., 2018). Ditto et al. (2016) reported the first case of a bulky, stage IIb mesonephric adenocarcinoma of the uterine cervix treated with 3 cycles of cisplatin + doxorubicin + paclitaxel followed by radical hysterectomy. The pathological examination of the surgical specimen revealed vaginal stroma infiltration and positive LVSI, whereas all the 57 removed nodes were negative. The patient, who underwent adjuvant pelvic external beam radiotherapy, was disease-free after a follow-up of 6 months.

3.3. Definitive radiotherapy or concurrent chemoradiation

The analysis of the radiotherapy-treated patients included in the SEER database between 1988 and 2013 revealed that squamous cell carcinoma had significantly better CSS and OS compared with adenocarcinoma and adenosquamous carcinoma, whereas no significant CSS and OS differences emerged between adenocarcinoma and adenosquamous carcinoma (Zhou et al., 2017a) (Table 3). The retrospective assessment of patients treated with definitive radiotherapy at the Radiation Oncology Center in Washington showed a worse DFS for adenocarcinoma compared with squamous cell carcinoma in stage III, and a similar DFS for the two histological types in stages Ib-IIb (Grigsby et al., 1988). A Taiwan study on patients with stage IIb-IV disease found a significantly better DFS and a trend to a better OS for squamous cell carcinoma compared with adenocarcinoma or adenosquamous carcinoma treated with definitive radiotherapy or concurrent chemoradiation (Chen et al., 2014). The retrospective analysis of the patients with locally advanced cervical cancer enrolled in four GOG trials revealed that adenocarcinoma and adeno-squamous carcinoma had a worse OS than squamous cell carcinoma when treated with radiotherapy alone, but a similar OS when treated with cisplatin-based chemoradiation (Whitney et al., 1999; Rose et al., 1999; Keys et al., 1999; Lanciano et al., 2005; Thomas et al., 2008b; Rose et al., 2014).

Lee et al. (2015) analyzed 64,531 women with squamous cell carcinoma and 7265 with adenocarcinoma of the uterine cervix included in the Korea National Cancer Incidence Database, and compared the clinical outcome according to histologic types in patients treated before (1993–1997), during (1998–2002), and after (2003–2012) the introduction of concurrent chemoradiation. Staging was based on the SEER summary staging (localized, regional, distant) and FIGO staging. Patients with regional disease had FIGO stage IIa-IIIb and / or pelvic nodal involvement. Five year -OS increased from 64.5%(1993–1997) to 75.1% (2008–2012) (p < 0.001) for regional squamous cell carcinoma and from 53.7% to 62.8% (p = 0.027) for regional adenocarcinoma. Anyway, patients with adenocarcinoma were more likely to die than those with squamous cell carcinoma both before and after concurrent chemoradiation era (HR = 1.49, 95% CI = 1.37–1.62; and HR = 1.40;

Table 3
Clinical outcome of patients with cervical adenocarcinoma treated with definitive radiotherapy or concurrent chemoradiation.

Authors	Patients	Stage	Treatment	Clinical outcome		
Zhou et al. (2017a)	8751	I-IV	Radiotherapy	SCC: better CSS and OS compared with AC (HR = 1.514,95% CI = 1.359–1.687 and HR = 1.354, 95 %CI = 1.232–1.489) and with AD (HR = 1.326, 95%C I = 1.111–1.582 and HR = 1.355, 95%CI = 1.164–1.578).		
Grigsby et al. (1988)	1004	I-III	Radiotherapy		5-year DFS	p
				SCC all stages (n.925)	68.0%	ns
				AC all stages (n.79)	64.9%	
				SCC stage IB (n.302)	87.7%	ns
				AC stage IB (n.38)	84.2%	
				SCC stage IIA (n.103)	70.9%	ns
				AC stage IIA (n.9)	55.6%	
				SCC stage IIB (n.249)	66.3%	ns
				AC stage IIA (n.18)	55.6%	
				SCC stage III (n.226)	36.7%	0.007
				AC stage III (n.12)	25.0%	
Chen et al. (2014)	229	IIb-IV	Radiotherapy or		5-year DFS	5-year-OS
				SCC (n.194)	47.6%	58.1%
			Chemoradiation	AC/AD (n.35)	30.0%	41.3%
					p = 0.044	p = 0.09

Legend: SCC, squamous cell carcinoma; CSS, cancer specific survival; OS, overall survival; AC, adenocarcinoma;HR, hazard ratio; CI,confidence interval; AD, adenosquamous carcinoma; DFS, disease-free survival.

95% CI = 1.30–1.50, respectively). Oka et al. (1996) assessed immunohistochemical expression of MIB-1 in 196 biopsies from 14 patients with cervical adenocarcinoma and 62 patients with cervical squamous cell carcinoma before and after radiotherapy. The mean MIB-1 indices before and after radiotherapy at 9 Gy and 27 Gy were 28%, 21% and 26%, respectively, in adenocarcinomas, and 38%, 53% and 26%, respectively, in squamous cell carcinomas. Therefore, adenocarcinomas had a low cycling cell population and no relevant MIB-1 change during radiotherapy, whereas squamous cell carcinomas had a higher cycling cell population and showed a transient MIB-1 increase at 9 Gy of radiotherapy. These findings could suggest a different radiosensitivity of these two histological type. A Chinese randomized trial assigned 880 patients with FIGO stages IIb-IVa cervical adenocarcinoma to receive either concurrent chemoradiation alone or concurrent chemoradiation plus one cycle of chemotherapy with paclitaxel (135 mg/mq (Shoji et al., 2013)) + cisplatin (75 mg/mq (Shoji et al., 2013)) before chemoradiation and two cycles of the same regimen after chemoradiation (Tang et al., 2012). Patients who received chemoradiation plus neo-adjuvant and adjuvant chemotherapy experienced a lower distant and pelvic failure rate ($p < 0.05$), a longer DFS ($p < 0.05$) and a longer OS ($p < 0.05$).

3.4. Concurrent chemoradiation followed by surgery

Very few data are currently available in the literature about neoadjuvant concurrent chemoradiation followed by surgery in adenocarcinoma of the uterine cervix (Shibata et al., 2009; Poujade et al., 2010; Zhang et al., 2015). This neoadjuvant treatment obtained a clinical complete response and a pathological complete response in 33.5–48.0% and 26.3–33.5% of the patients, respectively (Shibata et al., 2009; Poujade et al., 2010). Mucinous subtype appeared to be less responsive to chemoradiation in a French retrospective study (Poujade et al., 2010).

4. Prognostic factors

4.1. Clinical-pathological variables

The most investigated clinical-pathological factors for adenocarcinoma of the uterine cervix are FIGO stage (Eifel et al., 1990; Park et al., 2010; Benedetti-Panici et al., 1996; Baalbergen et al., 2004; Alfsen et al., 2003; Nosaka et al., 2015; Suzuki et al., 2004), nodal status (Park et al., 2010; Baalbergen et al., 2004; Nosaka et al., 2015; Lu et al., 1998), tumor size (Eifel et al., 1990; Park et al., 2010; Nosaka et al., 2015), tumor grade (Eifel et al., 1990; Baalbergen et al., 2004; Alfsen et al., 2003; Lu et al., 1998), patient age (Baalbergen et al., 2004; Alfsen et al., 2003), depth of cervical invasion (Park et al., 2010; Baalbergen et al., 2004), LVSI (Park et al., 2010; Baalbergen et al., 2004; Alfsen et al., 2003) and parametrial involvement (Park et al., 2010; Lu et al., 1998) (Table 4). The retrospective analysis of the patients who received radiotherapy with curative intent at the M. D. Anderson Cancer Center between 1965 and 1985 revealed that 5-year DFS was 73% for the 223 patients in stage I and 32% for the 60 in stage II (Eifel et al., 1990). Among stage I patients, 5-year DFS was 88% when tumor size was < 3 cm, 64% when size was 3–5.9 cm, and 45% when size was > 6 cm ($p = 0.002$). Decreased DFS correlated also with poorly differentiated tumor grade ($p = 0.0014$). Among stage II patients, those with bulky disease did worse with a 5-year DFS of 15%, and 73% of the relapsed patients died of distant metastases. A retrospective Dutch study assessed the 305 cervical adenocarcinomas diagnosed between 1989 and 1999 in the Rotterdam area (Baalbergen et al., 2004). Patients with early disease usually underwent radical hysterectomy and pelvic lymphadectomy, followed by adjuvant radiotherapy in presence of histologically positive nodes, positive surgical margins or involved parametria, whereas patients with more advanced disease received definitive radiotherapy. Five-year OS was 79% in stage I, 37% in stage II, and < 9% in stage III-IV ($p < 0.001$) (Williams et al., 2015). Beside stage, tumor grade (G1 = 92% *versus* G2 = 66% *versus* G3 = 53%, $p < 0.001$), patient age (< 35 years = 83% *versus* 35–65 years = 69% *versus* > 65 years = 46%, $p < 0.001$) and histological subtype (adenocarcinoma = 73% *versus* adenosquamous carcinoma = 57% *versus* clear cell carcinoma = 53%, $p < 0.005$) were significant prognostic factors. As far as stage I-IIa disease is concerned, OS was significantly better when primary treatment was surgery opposed to radiotherapy ($p = 0.002$). Among the 200 stage I-IIa patients who underwent surgery, lymph node status (negative = 91% *versus* positive = 34%, $p < 0.001$), LVSI (no = 89% *versus* yes = 50%, $p < 0.001$) and depth of stromal invasion (≤ 10 mm = 85% *versus* > 10 mm, = 53%, $p < 0.001$) were significant prognostic variables. In multivariate analysis, only tumor stage ($p < 0.001$), tumor grade, $p < 0.001$) and nodal status ($p < 0.003$) retained independent prognostic relevance. In the study of (Lu et al., 1998) including 40 patients with stage !b-IIb cervical adenocarcinoma who underwent surgery, parametrial involvement and moderately or poorly differentiated tumor grade

Table 4
Adenocarcinoma of the uterine cervix: prognostic relevance of clinical–pathological variables.

Variable	Prognostic relevance	
	Univariate	Multivariate
	Eifel et al. (1990)	
	Park et al. (2010)	
	Benedetti-Panici et al. (1996)	
Stage	Baalbergen et al. (2004)	Baalbergen et al. (2004)
	Nosaka et al. (2015)	Nosaka et al. (2015)
	Alfsen et al. (2003)	
	Suzuki et al. (2004)	Suzuki et al. (2004)
Nodal status	Park et al. (2010)	Park et al. (2010)
	Baalbergen et al. (2004)	Baalbergen et al. (2004)
	Nosaka et al. (2015)	
	Lu et al. (1998)	Lu et al. (1998)
Size	Eifel et al. (1990)	
	Park et al. (2010)	
	Nosaka et al. (2015)	
Tumor grade	Eifel et al. (1990)	
	Baalbergen et al. (2004)	Baalbergen et al. (2004)
	Alfsen et al. (2003)	
	Lu et al. (1998)	
Age	Baalbergen et al. (2004)	
	Alfsen et al. (2003)	Alfsen et al. (2003)
LVSI	Park et al. (2010)	
	Baalbergen et al. (2004)	
	Alfsen et al. (2003)	Alfsen et al. (2003)
Depth of stromal invasion	Park et al. (2010)	
	Baalbergen et al. (2004)	
Parametrial infiltration	Park et al. (2010)	
	Lu et al. (1998)	
Tumor/stroma ratio	Pongsuvareeyakul et al. (2015)	

Table 5
Adenocarcinoma of the uterine cervix: prognostic relevance of biological variables.

Variable	prognostic relevance	
	Yes	No
p16	Alfsen et al. (2003)	
p27	Alfsen et al. (2003)	Suzuki et al. (2004); Hellberg et al. (2009)
p21	Lu et al. (1998)	Alfsen et al. (2003); Suzuki et al. (2004)
Cyclin D1		Suzuki et al. (2004)
P53	Suzuki et al. (2004); Tsuda et al. (1995)	Lu et al. (1998)
COX2	Kim et al. (2004)	
NM23/ NDP	Mandai et al. (1995)	Kristensen et al. (1996)
HER2	Mandai et al. (1995)	
	Ueda et al. (2017)	
Maspin	Nosaka et al. (2015)	
PD-L1	Harrison et al. (1993)	
C-MET	Tsai et al. (2006)	
	Ueda et al. (2017)	
EGFR	Ueda et al. (2017)	

correlated with poor prognosis in univariate analysis, whereas nodal status was related to the clinical outcome in both univariate and multivariate analysis. The review of 222 surgically-treated patients with stage Ia2-IIa disease found that FIGO stage, nodal status, tumor size, depth of cervical invasion, parametrial involvement, surgical margin status, and LVSI correlated significantly with both DFS and OS in univariate analysis, and that nodal status and parametrial involvement were independent prognostic factors for both DFS (OR = 2.45, 95%CI = 1.14–5.30, p = 0.022, and respectively, OR = 3.46, 95%CI = 1.46–8.19, p = 0.005) and OS (OR = 2.79, 95%CI = 1.25–6.25, p = 0.012, and respectively, OR = 6.17, 95%CI = 2.55–14.95, p = 0.002) (Park et al., 2010). The univariate analysis of 46 patients with stage I-IV disease treated with different therapeutic approaches revealed that DFS was related to FIGO stage ($p < 0.001$) and nodal status (p = 0.002) and OS was related to FIGO stage ($p < 0.001$), nodal status ($p < 0.001$) and tumor size ($P = 0.005$) (Nosaka et al., 2015). FIGO stage was the only independent prognostic factor for both DFS (p = 0.001) and OS (p = 0.002). FIGO stage was a strong prognostic variable in both a Japanese study on 53 patients with stage I-IV disease treated with definitive radiotherapy (Suzuki et al., 2004) and an Italian study on 42 patients with stage Ib2-IIIb disease scheduled for NACT followed by radical hysterectomy (Benedetti-Panici et al., 1996). The tumor-stroma ratio [TSR] represents an estimation of the percentage of neoplastic cells compared to the combined area of neoplastic cells and tumor-associated stroma (Mesker et al., 2007). In a recent study, 29% of 131 surgically- treated early stage patients had a low TSR and experienced decreased OS in univariate analysis (HR 2.7; 95% CI 1.0–7.0; p = 0.041) but not in multivariate analysis (Pongsuvareeyakul et al., 2015). As far as histological subtypes are concerned, villo-glandular papillary carcinoma has a more favorable clinical outcome (National Cancer Comprehensive Network, 2019; Young and Scully, 1989; Collinet et al., 1999; Heatley, 2007; Zhou et al., 2016; Zhao et al., 2016; Jones et al., 1993), conversely, gastric-type adenocarcinoma (Karamurzin et al., 2015; Kojima et al., 2007; McCluggage, 2013; Nakamura et al., 2018; Park et al., 2018a, b), adenoma malignum (National Cancer Comprehensive Network, 2019; Wilbur et al., 2014) and signet - ring cell carcinoma (Haswani et al., 1998; Insabato et al., 2007) have worse prognosis compared with usual- type endocervical adenocarcinoma.

4.2. Biological variables

Some studies have investigated potential biological biomarkers in cervical cancer, but their results have been often conflicting and inconclusive (Table 5).

Low expression of p16, p21 and p27 was found in 27.5%, 12.9% and 18.3% of 142 patients with stage I–II adenocarcinoma of the uterine cervix treated with different therapeutic approaches (Alfsen et al., 2003). In multivariate analysis, low p27 expression and high p16 expression were strong predictors of poor prognosis. The expression of p21 was an independent predictor of favorable clinical outcome in the study of Lu et al. (1998). Conversely, other authors failed to detect any relationship between p27, p21 and cyclin D1 and clinical outcome in patients with stage I–IV disease treated with radiotherapy (Suzuki et al., 2004; Hellberg et al., 2009). The systematic review of 27 studies aimed to investigate p53 mutational status in cervical cancer evidenced a p53 mutation in 32 of 241 (13.3%) adenocarcinomas compared with 39 of 657 (5.9%; p = 0.0003) squamous cell carcinomas (Tornesello et al., 2013). The proportion of adenocarcinomas with mutated p53 ranged from 4% in North America to 19% in Asia. (Suzuki et al., 2004) found that p53 status had a prognostic relevance for cervical adenocarcinoma treated with definitive radiotherapy. In their series 5-year DFS was 30% for the 24 p53-positive patients *versus* 62% for the 29 p53-negative patients (p = 0.02). As far as surgically- treated cases are concerned, OS was significantly better in the 12 p53- positive patients than in the 14 p53- negative patients ($p < 0.002$) assessed by Tsuda et al. (1995) whereas p53 expression had no prognostic relevance in the series of Lu et al. (1998). An Italian investigation detected p53 mutations in 36% of 28 cervical adenocarcinomas, 16% of 55 cervical squamous cell carcinomas, and 13% of 31 cervical intraepithelial neoplasias (p = 0.035) (Tornesello et al., 2014). It is noteworthy that p53 mutations were found in 54% of 11 endocervical adenocarcinomas, 50% of 4 serous adenocarcinomas, 25% of 8 endometrioid

adenocarcinomas, and 0% of the other 4 adenocarcinomas (2 clear cell, 1 intestinal and 2 mixed). The prognostic relevance of p53 in the different subtypes of adenocarcinoma is unknown. Kim et al. (2004), who assessed tissues samples from stage IIb cervical cancer patients treated with definitive radiotherapy or concurrent chemoradiation, detected positive immunostaining for Cyclooxygenase-2 [COX-2] in 57% of 21 adenocarcinomas *versus* 24% of 84 squamous cell carcinomas ($p = 0.007$). COX-2 expression was a strong predictor of treatment response regardless of the histologic type. When patients were stratified into four groups according to histology and COX-2 status, 5-year OS was 49% for adenocarcinoma /COX-2-positive, 78% for adenocarcinoma /COX-2-negative, 62% for squamous cell carcinoma /COX-2-positive and 84% for squamous cell carcinoma /COX-2-negative ($p = 0.007$). The prognostic relevance of human nonmetastatic clone 23 type 1 [nm23], a gene encoding a protein identical to nucleoside diphosphate [NDP] kinase, is still debated in cervical cancer (Mandai et al., 1995; Kristensen et al., 1996; Chen et al., 2001; Tee et al., 2007; Hsu et al., 2008). Kristensen et al. (1996) assessed immunohistochemical expression of nm23/ NDP in surgical specimens from 176 stage Ib cervical cancer patients who underwent radical hysterectomy. Positive immunostaining for this kinase was found in 73.5% of squamous cell carcinomas, 78.5% of adenosquamous carcinomas and 53.3% of adenocarcinomas. In univariate analysis, patients with squamous cell carcinoma and adenosquamous carcinoma staining positive for nm23/NDP kinase had a lower DFS than those with negative immunostaining ($p = 0.046$), while no difference was detected for patients with adenocarcinoma. (Mandai et al., 1995), who assessed 88 cervical cancers, found immunohistochemical expression of nm23 and HER2 in 46% and 49%, respectively, of adenocarcinomas, and 36% and 38%, respectively, of squamous cell carcinomas. Negative expression of nm23, positive expression of HER2, and combined nm23- negative and HER2-positive expression correlated with poor prognosis ($p = 0.034$, $p = 0.014$, $p = 0.00008$, respectively) among patients with adenocarcinoma, but not among those with squamous cell carcinoma. Positive staining of c-MET was detected in 21 of 69 (30.4%) patients with cervical adenocarcinoma treated with primary radical hysterectomy and this biological variable was found to be an independent predictor of OS ($p = 0$ .022) (Tsai et al., 2006). Ueda et al. (2017), who examined the expression profile of epidermal growth factor receptor [EGFR], HER2 and c-Met in 43 cervical adenocarcinomas, noted that 20 (46%) of these tumors were positive for double or triple tyrosine kinases. Double positivity for EGFR and HER2 (EGFR+/HER2+/c-Met + and EGFR+/HER2+/c-Met-) correlated with node involvement ($p = 0.013$), advanced stage ($p = 0.007$) and worse DFS ($p = 0.029$). Maspin is a member of the serpin family of protease inhibitors, and its cytoplasmic expression is a poor prognostic factor in several malignancies (Umekita et al., 2002; Tsuji et al., 2007; Takagi et al., 2015). A Japanese investigation found positive immunostaining for maspin in 69.2% of 46 patients with stage I–IV cervical adenocarcinoma treated with different therapeutic approaches (Nosaka et al., 2015). In univariate analysis, 5- year DFS and OS were significantly worse in maspin-positive than in maspin-negative cases ($p = 0.023$ and $p = 0.043$, respectively). Heeren et al. (2016) assessed programmed death-ligand [PD-L1] expression in primary tumor samples from 156 patients with squamous cell carcinoma and 49 patients with adenocarcinoma of the uterine cervix. Squamous cell carcinomas were more frequently positive for PD-L1 and contained more PD-L1-positive tumor-associated macrophages when compared with adenocarcinomas (both $P < 0.001$). Disease-specific survival was significantly poorer in squamous cell carcinoma patients with diffuse PD-L1 expression compared with those with marginal PD-L1 expression, whereas disease-specific survival was significantly worse in adenocarcinoma patients with PD-L1-positive tumor-associated macrophages compared with those without PD-L1-positive tumor-associated macrophages. These findings would seem to point differences in immunological microenvironments and tumor escape mechanisms between the two histological types of cervical cancer.

5. Conclusions

Adenocarcinoma accounts for 10–25% of all cervical cancers, and its relative and absolute incidence has gradually increased in the last years. Although most studies have shown that adenocarcinoma carries a worse prognosis, other investigations have failed to detect significant differences in DFS and OS between squamous cell and non- squamous cell carcinomas, especially in patients with early stage disease. Therefore the prognostic relevance of histologic type is still debated. Moreover, adenocarcinoma is a very heterogenous disease including different histopathologic subtypes. The current guidelines suggest the same therapeutic approach in squamous cell carcinoma and adenocarcinoma. However, whereas radical hysterectomy and definitive radiotherapy achieve the same clinical outcome in patients with early stage squamous cell carcinoma, surgery seems to obtain better locoregional control rate, DFS and OS compared with definitive radiotherapy in those with early stage adenocarcinoma. The analysis of a series of patients with stage Ia2-IIa cervical adenocarcinoma treated with radical hysterectomy detected no significant difference in 5-year DFS (88.7% *versus* 84.1%), 5-year- OS (93.0% *versus* 86.9%) and pattern of recurrence between the 186 patients treated by laparoscopy and the 107 treated by laparotomy (Park et al., 2016). However the interim analysis of the prospective phase III Laparoscopic Approach to Cervical Cancer [LACC] study enrolling 631 patients with stage Ia1- Ib1 cervical squamous cell, adenocarcinoma, or adenosquamous carcinoma showed a 4.5-year DFS rate of 96.5% in the laparotomy arm and 86.0% in the mini-invasive, (laparoscopic or robotic) arm (HR = 3.74, 95% CI: 1.63–8.58, $P = 0.002$) (Society of Gynecologic Oncology, 2018). Therefore, radical hysterectomy for cervical squamous cell or adenocarcinoma should be performed by laparotomic approach. Cisplatin-based chemoradiation is the standard treatment for locally advanced disease, although NACT followed by radical surgery may be an interesting therapeutic option for stage Ib2-II patients. The meta-analysis of 18 trials comparing NACT followed by definitive radiotherapy *versus* the same radiotherapy alone showed a trend to a better OS for NACT arm when chemotherapy cycle length was $\leq$ 14 days or cisplatin dose-intensity was $\geq$ 25 mg/m^2/week (Neoadjuvant Chemotherapy for Cervical Cancer Meta-Analysis Collaboration (NACCCMA) Collaboration, 2004). The NCT01566240 randomized trial will assess whether NACT with paclitaxel (80 mg/m^2) plus carboplatin (area under curve [AUC]2) weekly for 6 cycles followed by concurrent chemoradiation offers a clinical benefit *versus* concurrent chemoradiation alone in patients with locally advanced cervical cancer. Few randomized trials appear to suggest a positive impact of adjuvant chemotherapy after concurrent chemoradiation, and this adjuvant treatment deserves to be further investigated especially in patients with high risk disease (Chemoradiotherapy for Cervical Cancer Meta-analysis Collaboration (CCCMAC), 2010; Kumar and Gupta, 2016; Dueñas-González et al., 2011; Abe et al., 2012). A large randomized Chinese trial has suggested that incorporating paclitaxel/cisplatin- based NACT and adjuvant chemotherapy into concurrent chemoradiation may be a very promising approach for advanced cervical adenocarcinoma (Tang et al., 2012). FIGO stage, nodal status and tumor size significantly correlate with DFS and OS of patients with this malignancy, whereas the prognostic relevance of biological variables is still under investigation. Palliative chemotherapy is the only treatment option for patients with persistent or recurrent cervical adenocarcinoma not amenable with surgery and radiotherapy, and several single drugs have been shown to be active in this clinical settings (Thigpen et al., 1986; Sutton et al., 1993; Look et al., 1997; Curtin et al., 2001; Rose et al., 2003). A GOG phase III randomized trial of four cisplatin-containing doublets in 434 patients with stage IVb, recurrent, or persistent squamous and non-squamous cervical carcinoma showed a trend in objective response rates, DFS and OS favoring paclitaxel (135 mg/m^2 day 1) + cisplatin (50 mg/m^2 day 2) every 3 weeks compared with vinorelbine + cisplatin, gemcitabine + cisplatin, and topotecan + cisplatin (Monk et al., 2009).

Another GOG trial randomly allocated 452 patients belonging to the same clinical setting to receive either paclitaxel + cisplatin or topotecan + paclitaxel with or without bevacizumab (15 mg/kg on day 1) every 3 weeks (Tewari et al., 2017). The chemotherapy plus bevacizumab groups showed a longer OS compared with the chemotherapy-alone groups (HR = 0·77, 95%CI = 0·62-0·95, p = 0·007). Immunohistochemical expression of PD-L1 has been detected in both squamous cell and non squamous cell carcinoma of the uterine cervix but not in benign cervical tissues (Heeren et al., 2016; Reddy et al., 2017). Therefore the use of immune checkpoint inhibitors should be explored in patients with PD-L1-positive persistent or recurrent disease not amenable with other treatments (Martínez and Del Campo, 2017). Moreover a therapeutic strategy targeting cell surface tyrosine-kinases should be adequately investigated. EGFR-targeting agents (*e.g.*, cetuximab and panitumumab) or HER2-targeting agents (*e.g.*, trastuzumab) might have efficacy in cervical adenocarcinoma (Nakamura et al., 2018; Ueda et al., 2017). In particular HER2 may be an attractive target for gastric- type mucinous carcinoma of the uterine cervix. No data are currently available about the use of trastuzumab in this malignancy, although this monoclonal antibody has been found to be effective in HER2-positive stomach cancer.

Conflict of interest statement

The authors indicated no potential conflict of interest including any financial or personal relationships with other people or organizations that could inappropriately influence (bias) this work.

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