Chapter 8 Adenocarcinoma

Overview

In Japan, the proportion of squamous cell carcinoma among all cervical cancers has been declining every year. In a recent survey, non-squamous cell carcinoma accounted for approximately 20% of overall cervical cancer. Approximately 90% of non-squamous cell carcinomas are adenocarcinoma or adenosquamous carcinoma.[1] Outcomes for adenocarcinoma and adenosquamous carcinoma are considered to be worse than for squamous cell carcinoma. Some modifications to treatments are therefore necessary for adenocarcinoma and adenosquamous carcinoma. Only a few studies have been conducted with subjects with non-squamous cell carcinoma of the cervix, however, and high level evidence is difficult to obtain. In this chapter, adenocarcinoma and adenosquamous carcinoma are grouped together as "adenocarcinoma."

Unlike squamous cell carcinoma, early-stage adenocarcinoma sometimes does not show characteristic colposcopic features. This can make it difficult to accurately evaluate the spread and depth of invasion of lesions. Cervical cone biopsy is generally performed to enable an accurate diagnosis. In the early stages, adenocarcinoma can be present within the cervical canal, necessitating resection of more tissue on the sides of the cervical canal than for squamous cell carcinomas.

For adenocarcinoma in situ, residual cancer is reported in 20% of patients with clear surgical margins in the cone biopsy specimens. Therefore, caution is required if the uterus is to be preserved, due to differences to the standard treatment of cone biopsy for squamous cell carcinoma in situ.

For microinvasive adenocarcinoma (stage Ia), radical hysterectomy, or modified radical hysterectomy with lymphadenectomy, is recommended. Cytoreductive surgery without lymphadenectomy is sometimes performed if the invasion is shallow. If the patient expresses a strong desire for fertility preservation, treatment can comprise cervical cone biopsy alone if careful case selection is performed.

Invasive adenocarcinoma has a higher rate of lymph node metastasis than squamous cell carcinoma, and is also considered to have a low sensitivity to radiotherapy and chemotherapy. Treatment selection follows that for squamous cell carcinoma, although surgery is considered more effective than radiotherapy in early stage adenocarcinoma. A Japanese study compared cervical adenocarcinoma and squamous cell carcinoma. The subjects were patients with stage Ib or II disease who underwent postoperative radiotherapy, and stage III disease who underwent definitive radiotherapy. The 5 year survival rate for patients with adenocarcinoma was 20%-40% lower than for those with squamous cell carcinoma.[2] Burke et al.[3] performed radical hysterectomy in patients with stage Ib disease. The recurrence rate was high at 17% for adenocarcinoma, and 9% for squamous cell carcinoma. Eifel et al.[4] performed radiotherapy on patients with stage Ib disease, yielding a 5 year survival rate of 81% for squamous cell carcinoma, while that for adenocarcinoma tended to be lower at 72%. For patients with tumor diameters of ≥4 cm, the 5 year survival rates for squamous cell carcinoma and adenocarcinoma were 73% and 59%, respectively, representing a significant difference. The pelvic recurrence rates were 13% and 17%, respectively, with no significant

difference. The distant metastasis rates were 21% and 37%, respectively, representing a significant difference. Huang et al.[5] performed neoadjuvant chemotherapy + radical hysterectomy for patients with stage Ib2 and IIa disease. Adenocarcinoma had a high relative risk for recurrence and death of 2.6 in comparison to squamous cell carcinoma. Many studies have demonstrated worse outcomes for adenocarcinoma than for squamous cell carcinoma. One study examined patients with stage Ib disease who underwent radical hysterectomy. No significant differences were seen in the 5 year survival rates between the squamous cell carcinoma group, adenocarcinoma group, and adenosquamous carcinoma group.[6]

Several possible reasons have been raised for the poor prognosis for adenocarcinoma compared to squamous cell carcinoma. First, there is a difference in the lymph node metastasis rates. In stage I, the lymph node metastasis rates for both adenocarcinoma and squamous cell carcinoma are 5-10%, with no difference seen. In stage II, the rate is 20-30% for squamous cell carcinoma, and considerably higher at 30-50% for adenocarcinoma.[7,8] Second, many studies have shown that the pelvic control rate using radiotherapy is lower for adenocarcinoma than squamous cell carcinoma.[2,9-12] However, some studies have reported no difference in pelvic control rates.[4,13,14] A definite conclusion can therefore not be reached. Numerous studies have examined differences in outcomes and prognostic factors between adenocarcinoma and squamous cell carcinoma. At present, there is no clear evidence as to what treatments are effective for adenocarcinoma, and whether outcomes can be improved by implementing different treatments than for squamous cell carcinoma.[15]

The ovarian metastatic rate for squamous cell carcinoma is almost negligible at <1%, but significantly higher for adenocarcinoma at 2-14%.[16-20] Generally, ovarian preservation at hysterectomy is performed only for squamous cell carcinoma. Extra caution is required for ovarian preservation in patients with adenocarcinoma.

Chemotherapy is considered effective for advanced and recurrent adenocarcinoma. However, there is no globally established standard regimen. The efficacy of neoadjuvant therapy is unclear for adenocarcinoma.

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CQ27
What treatments are recommended for stage 0 adenocarcinoma?

Recommendations

(1) Total hysterectomy is recommended (Grade B).
(2) In patients who desire to have children, uterus preservation can be considered with cervical cone biopsy only and careful management (Grade C).

Background and Objectives

We examined appropriate treatments for stage 0 (adenocarcinoma in situ).

Explanations

Adenocarcinoma in situ can be located in the cervical canal or deep in the cervical glands, and conventional cytological examination may give a false negative result. It has been reported that 24-75% of adenocarcinoma in situ also has squamous cell lesions.[1] It is therefore not uncommon to see adenocarcinoma in situ in specimens from cone biopsy performed with the presumptive diagnosis of cervical intraepithelial neoplasia (CIN). Unlike squamous cell carcinoma in situ, adenocarcinoma in situ sometimes does not exhibit characteristic colposcopic features, making it difficult to evaluate the spread of the lesion and depth of invasion. Therefore, if atypical glandular cells are detected at cervical cytology and a lesion more advanced than adenocarcinoma in situ is suspected, cervical cone biopsy should be performed to obtain an accurate diagnosis. Some are of the opinion that cervical cone biopsy alone is adequate treatment.[2] However, residual lesions are found on the uterine side in approximately half of patients with positive surgical margins.[3-5] Skip lesions may also be present in the endocervical membrane.[6] In addition, residual lesions are found in approximately 20% of the patients with negative surgical margins.[3,4] From these findings, with careful management uterus preservation is thought possible by cervical cone biopsy for patients who desire to have children. Total hysterectomy is indicated for patients who have no desire to have a child.[7] The presence of glandular residual lesions on the uterine side can be predicted by performing endocervical curettage at cervical cone biopsy.[6] Laser ablation and cryotherapy are not recommended since they do not allow pathological evaluation of the lesion.

Note: Management of glandular dysplasia

Glandular dysplasia is considered to be a precursor lesion of adenocarcinoma. Management strategies for glandular dysplasia have not yet been established. According to the literature, it takes 1.5-3 years for the progression from glandular dysplasia to adenocarcinoma in situ,[8] and glandular dysplasia is not considered to require treatment.[9] If slightly atypical glandular cells are observed, repeat cytology is recommended after an interval of 3-6 months. If glandular dysplasia is suspected, then endocervical curettage after an interval of 1-3 months is recommended.[7,10] If the extent of the lesion is unknown,

the interval between examinations is increased gradually. If there are findings of increased atypia, and adenocarcinoma in situ or a more advanced lesion is suspected, diagnostic cervical cone biopsy should be performed.[7,10]

References

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CQ28
What treatments are recommended for stage Ia adenocarcinoma?

Recommendations

(1) In cases with deep invasion, radical hysterectomy or modified hysterectomy with pelvic lymphadenectomy is recommended(Grade C).
(2) In cases with shallow invasion, hysterectomy without pelvic lymphadenectomy (total hysterectomy or modified hysterectomy) may be performed (Grade C).
(3) If the patient strongly desires fertility preservation, with careful case selection cervical cone biopsy can be performed to preserve the uterus (Grade C).

Background and Objectives

We examined appropriate treatments for stage Ia (microinvasive) adenocarcinoma as classified in the Guidelines for the Clinical and Pathological Study of Uterine Cervical Cancer in Japan.

Explanations

The National Comprehensive Cancer Network (NCCN) guidelines for cervical cancer recommend radical hysterectomy for cases with deep invasion (stage Ia2). Total hysterectomy is recommended for cases with shallow invasion (stage Ia1). If surgery is not feasible or fertility preservation is desired, cervical cone biopsy can be performed. If the resection margins are negative, preservation of the uterus is possible.[1] However, it should be noted that the above guidelines do not differentiate between adenocarcinoma and squamous cell carcinoma.

Adenocarcinoma of the cervix is considered to have a higher biological malignancy than squamous cell carcinoma. In many cases, an accurate pathological diagnosis cannot be obtained by colposcopic biopsy. There is no consensus on the assessment of depth of invasion (where to set the origin of invasion).[2] In the Guidelines for the Clinical and Pathological Study of Uterine Cervical Cancer in Japan, stage Ia adenocarcinoma is defined as adenocarcinoma with microinvasion confined to the region of the normal endocervical glands. Subtyping is not performed.[3] In these guidelines, for convenience and to avoid terminological confusion related to staging, we have used the terms ‘adenocarcinoma with shallow invasion’ and ‘adenocarcinoma with deep invasion’. Shallow invasion corresponds to a depth of ≤3 mm and deep invasion ≤5 mm. In Japan, stage Ia adenocarcinoma refers to a lesion contained within the existing endocervical gland region. It must be noted that the Japanese definition differs from that used by International Federation of Gynecology and Obstetrics (FIGO), in which stage Ia refers to a depth of invasion of ≤5 mm.

For microinvasive adenocarcinoma with deep invasion, modified radical hysterectomy with pelvic lymphadenectomy, or more extensive surgery, is generally required.[4,5] For microinvasive adenocarcinoma with shallow invasion, metastasis to the

pelvic lymph nodes is very rare. Some are therefore of the opinion that total hysterectomy without lymphadenectomy is sufficient.[6,7] Others recommend cytoreductive surgery, such as total hysterectomy without pelvic lymphadenectomy, regardless of the depth of invasion.[8,9] The pathological criteria for microinvasive adenocarcinoma are not clear, and there are many unknowns regarding its natural history. As with microinvasive squamous cell carcinoma, caution is required in selecting cytoreductive surgery.

If the patient strongly desires fertility preservation, some are of the opinion that cervical cone biopsy alone is sufficient with careful follow-up, and that it can be curative if the following conditions are met: "sufficient resection of the cervical canal is performed in cervical cone biopsy, the spread is fully confirmed, and the existing lesion does not go beyond the region of the cervical glands."[6,10]

Ostor[11] reviewed 26 literature articles, finding that no ovarian metastases were detected in 155 patients with cervical adenocarcinoma with invasion ≤5 mm. Caution is required for ovarian preservation for all patients with stage Ia adenocarcinoma, but is at least reasonable in patients with stage Ia1 disease with shallow invasion.

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CQ29
What primary treatments are recommended for invasive adenocarcinoma?

Recommendations

(1) In principle, surgery is recommended for stage I and II disease (Grade B).
(2) Definitive radiotherapy or concurrent chemoradiotherapy (CCRT) are recommended for stage III and IVa disease (Grade B).

Background and Objectives

Invasive adenocarcinoma is considered to have a worse prognosis and lower radiosensitivity than squamous cell carcinoma. We examined primary treatments for invasive adenocarcinoma.

Explanations

The results of some retrospective studies indicated that surgery led to better outcomes than definitive radiotherapy for stage I and II invasive adenocarcinoma.[1,2] No randomized controlled trials (RCTs) have compared surgery and definitive radiotherapy for cervical adenocarcinoma. However, in a subanalysis of a RCT on stages Ib and IIa, the adenocarcinoma surgery group had significantly better outcomes (survival and disease-free survival).[3] From the above findings, in principle surgery is recommended for stage I and II disease. One study found that radiotherapy as primary treatment provided good outcomes if the diameter of the primary lesion was no larger than 3 cm.[4] Definitive radiotherapy should be considered for patients in whom surgery cannot be performed for some reason, such as the elderly and patients with concurrent diseases.

Definitive radiotherapy can be considered for stage III and IVa disease. For adenocarcinoma, the addition of a low dose rate of intracavitary irradiation was reported to provide better local control than using a high dose rate alone.[5]

The U.S. National Comprehensive Cancer Network (NCCN), National Cancer Institute (NCI), and American College of Obstetricians and Gynecologists (ACOG) guidelines do not mention the histological type in consideration of the use of definitive radiotherapy.[6,8]

As with squamous cell carcinoma, CCRT is generally administered to patients with stage I and II adenocarcinoma with large tumor diameters, or ≥stage III adenocarcinoma with locally advanced lesions. However, there is a lack of evidence on the efficacy of CCRT in the treatment of adenocarcinoma, and the optimal regimen has not been determined.

CQ30
Is neoadjuvant chemotherapy (NAC) useful?

Recommendation

NAC cannot be recommended since its usefulness has not been determined (Grade C).

Background and Objectives

The usefulness of NAC in the treatment of squamous cell carcinoma is unclear. In this section, we will examine the usefulness of NAC in the treatment of adenocarcinoma.

Explanations

First, we examined evidence on the response rates of adenocarcinoma to various anticancer agents. reported response rates from studies with a relatively large number of patients in early stages of adenocarcinoma were 50-80% .[1-3] Reported response rates were 20-50% for cases with advanced, recurrent, and metastatic disease.[4-6] Overall, response rates for patients with early stage disease tended to be high, although low compared to those with squamous cell carcinoma. No agent has been found that is as effective for adenocarcinoma as for squamous cell carcinoma.

Next, we examined outcomes when NAC was administered. Outcomes were good for cases in which the tumor size was reduced by NAC, followed by radical surgery. For patients who did not respond to NAC, there was a high likelihood of a worse outcome. The only past studies showing efficacy of NAC were from case series at individual institutions, so the level of evidence is not high.

As mentioned previously, there is no evidence that overall outcomes are improved in patients with cervical adenocarcinoma by treatment with NAC.

CQ31
What postoperative adjuvant therapies are recommended for the high risk group for recurrence?

Recommendation

Whole pelvis irradiation is recommended, in which case concurrent chemotherapy should also be considered (Grade C).

Background and Objectives

Adjuvant therapies following radical surgery for cervical adenocarcinoma include radiotherapy, chemotherapy, and concurrent chemoradiotherapy (CCRT). As with squamous cell carcinoma, we examined whether CCRT can be recommended for adenocarcinoma.

Explanations

If radical surgery is performed for adenocarcinoma, surgery alone yields poor outcomes in the group with the following risk factors for recurrence: positive lymph node metastasis, large tumor diameter, deep stromal invasion, vascular infiltration, and lymphatic infiltration.[1,2]

In a randomized controlled trial (RCT), Peters et al. performed radical hysterectomy on patients with stage Ia2, Ib, and IIa disease.[3] Adjuvant therapy was administered to patients in the high risk group for recurrence: 116 patients underwent radiation monotherapy (96 with squamous cell carcinoma and 20 with adenocarcinoma or adenosquamous carcinoma), and 127 patients CCRT (97 with squamous cell carcinoma and 30 with adenocarcinoma or adenosquamous carcinoma). The 4 year disease-free survival rates were 63% for radiation monotherapy and 80% for CCRT. The 4 year survival rates were 71% and 81%, respectively. These results represent significantly better outcomes for patients who received CCRT. A similar difference between the two treatments was also seen with adenocarcinoma and adenosquamous carcinoma. In other words, CCRT is more effective than radiation monotherapy as adjuvant therapy.

It is not clear whether CCRT data from Western countries can be applied as is to Japanese women. There have been few studies of CCRT for Japanese women, examining agents used, dosage and administration, efficacy, or incidence of adverse events. Therefore, special attention should be paid to the usefulness and safety of CCRT when it is to be used in Japan, even if its efficacy has been demonstrated in Western countries.

CQ32
What regimens are recommended for chemotherapy against stage IVb or recurrent carcinoma?

Recommendation

A platinum-based agent, as monotherapy or in combination (Grade C).

Background and Objectives

The global trend is for treatment strategies for adenocarcinoma to follow those for squamous cell carcinoma. However, adenocarcinoma has a worse prognosis than squamous cell carcinoma, and the incidence of adenocarcinoma is on the rise. Therefore, some are of the opinion that treatment strategies for adenocarcinoma should be considered separately from those of squamous cell carcinoma. The demand for a systemic approach is expected to increase, including concurrent chemoradiotherapy (CCRT), neoadjuvant chemotherapy (NAC), and adjuvant chemotherapy. We examine the appropriate agents for patients with metastatic or recurrent adenocarcinoma.

Explanations

The reported response rate of adenocarcinoma to cisplatin is 20%.[1] Response rates for ifosfamide, 5-fluorouracil (+leucovorin), and oral etoposide monotherapy are 15%,[2] 14%,[3] and 12%[4], respectively. These response rates are all slightly lower than for squamous cell carcinoma. The response rate of adenocarcinoma to paclitaxel monotherapy was 31%, representing a better rate than for the other agents.[5]

There have been only a few phase II clinical trials conducted on combination therapy for adenocarcinoma. In TEP therapy, epirubicin (70 mg/m^2) is followed by paclitaxel (175 mg/m^2, over 3 hours) and cisplatin (50 mg/m^2). This combination is administered every 3 weeks. The response rate was 62% for locally advanced cervical adenocarcinoma.[6] However, toxicity was high, and the necessity of combining three drugs is questionable.

Docetaxel, a taxane like paclitaxel, is also gaining interest. A study of the combination of docetaxel and carboplatin in advanced and recurrent cervical cancer found that although 7 out of 17 patients had adenocarcinoma, the overall response rate was high at 76%.[7]

In Japan, a regimen using drugs other than taxanes is an important option when considering insurance coverage. In particular, valuable evidence has been published in Japan regarding MEP therapy. MEP therapy involves a combination of cisplatin (50 mg/m^2, day 1), etoposide (100 mg/m^2/day, days 1, 3, and 5), and mitomycin C (10 mg/m^2, day 1). In this trial, the overall response rate was 16% for stage IVb and recurrent adenocarcinoma. The response rate was 27% if subjects were limited to those who had not previously undergone chemotherapy.[8] Another study indicated a response in 5 out of 7 patients who underwent nedaplatin + irinotecan combination therapy.[9] Since this

combination is covered by Japanese medical insurance, it should be considered for the treatment of stage IVb or recurrent cervical adenocarcinoma.

The U.S. clinical trial GOG 204, a phase III randomized controlled trial (RCT) on stage IVb and recurrent cervical cancer, commenced in May 2003. In this trial, the combination of cisplatin and paclitaxel (TP regimen) was used as the standard treatment for patients with cervical cancer, and patients with adenocarcinoma and adenosquamous carcinoma were included for the first time. Presently, high expectations are held for the TP regimen as the most effective chemotherapy for adenocarcinoma.

As indicated in CQ26, all results from RCTs published until now have been on squamous cell carcinoma. It will probably require some time to establish a standard chemotherapy targeting adenocarcinoma.