[Review]

Strategies for the Treatment of Cervical Cancer with Bulky Pelvic Lymph Nodes: An Overview of the Current Evidence

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Abstract **:** Cervical cancer commonly metastasizes first to the pelvic lymph nodes and then subsequently spreads to distant organs, making lymph node metastases the most significant prognostic factor in cervical cancer, and the strategy for its treatment directly influences prognosis. This review focuses on the treatment strategies for cases of cervical cancer with bulky pelvic lymph nodes. Concurrent chemoradiotherapy is the standard treatment modality for patients with pelvic lymph node metastases, but it is inadequate for bulky pelvic lymph nodes. Accordingly, surgical resection of the bulky lymph nodes has been attempted, and its therapeutic significance has been reported. If the bulky lymph nodes are unresectable, definitive concurrent chemoradiotherapy is performed. If it yields an inadequate degree of lymph node shrinkage, boosted radiation should be considered. The addition of chemotherapy after concurrent chemoradiotherapy has also been reported to be effective in patients with lymph node metastases and is currently being evaluated in clinical trials.

Keywords **:** debulking surgery, bulky lymph node metastasis, concurrent chemoradiotherapy, boost irradiation, cervical cancer.

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Introduction

Uterine cervical cancer is both the fourth most commonly diagnosed cancer and cause of cancer-related death in women worldwide [1]. Surgery and radiotherapy (RT) are equally effective for cervical cancer and have comparable outcomes for stage I－II (early locally advanced) invasive cancer [2]. Decision on the treatment is based on a risk-benefit analysis of each treatment modality to obtain a cure with minimum complications. The optimal approach to treatment for each patient should consider clinical factors such as menopausal status, age, medical illness, histological type, and tumor size [2]. Surgery, particularly radical hysterectomy (RH), as the primary treatment modality for locally advanced cervical cancer has the advantages of 1) enabling a histopathological diagnosis, thereby allowing accurate identification of tumor spread and personalized postoperative treatment; 2) avoidance of radiation-specific complications if no adjuvant RT is performed; and 3) the possibility of the preservation of ovarian function.

Lymph node status is the most important prognostic factor for survival in cervical cancer. Patients with positive lymph node metastasis have shorter survival than those without metastasis, with a 3-year survival rate of only 64% compared with 94% of those with negative metastasis [3]. Apparently, a positive lymph node in-

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dicates a worse survival prognosis than a negative one. Those with a higher number of metastases and larger metastatic lymph nodes have a poorer prognosis. With respect to size, "bulky" indicates large for its weight, or too big to handle. Although there is no clear definition of a "bulky lymph node" for gynecologic malignancies, it generally refers to a swelling of ≥2 cm.

Radiation therapy for uterine cervical cancer generally involves a radiation dose of around 50 Gy, which is insufficient to control bulky lymph nodes. Higher doses are not feasible, however, because of the risk of serious or fatal toxicity to adjacent organs. Concurrent chemoradiation therapy (CCRT), a combination of external and intracavity RT with cisplatin-based chemotherapy, has been shown to yield a higher overall survival than RT alone in both the primary definitive and postoperative adjuvant setting [4, 5]. CCRT yields better outcomes than RT alone in invasive cervical cancer, including in patients with lymph node metastases, but it is inadequate for patients with bulky lymph nodes. The Cochrane review reported better outcomes of CCRT than radiation alone for postoperative node-positive patients with stage IB/II lymph nodes [6]. While radiation alone is sufficient for treatment in cases of a single, small lymph node metastasis, CCRT yields better outcomes than radiation alone in cases of multiple positive lymph nodes or bulky disease [7]. The efficacy of CCRT, however, is reduced in cases of lymph nodes swollen larger than 2 cm, and thus it is becoming increasingly common to remove these bulky nodes before CCRT treatment. This review focuses on the strategies for the treatment of cases of cervical cancer with bulky pelvic lymph nodes.

Cervical cancer is classified according to the International federation of gynecology and obstetrics (FIGO) guidelines. Previous versions did not consider lymph node metastases, but cases with pelvic lymph node metastases are classified as stage IIIC in the revised FIGO 2018 classification [8]. Because all the references quoted in the present study use the FIGO 2008 classification or previous versions, the FIGO 2018 classification is not applied in this review.

1. Pretreatment debulking surgery of bulky lymph nodes

The performance of pretreatment debulking surgery is based on the idea that metastatic lymph nodes too large for radiation treatment should be removed first. Table 1 summarizes the reports on outcomes of pre-

Table 1. Summary of reported lymph node debulking in cervical cancer

Author (year)	Stage (FIGO 2008)	Total Subjects	Patients with bulky nodes	Approach for bulky LN resection	Main therapy for bulky LN case	5-y survival with negative nodes	5-y survival with microscopic nodes	5-y survival with macroscopic nodes debulked	5-y survival with macroscopic nodes unresected	Reference
Downey *et al* (1989)	IB2-IIIB	156	57	EXP	RT	85%	57%	51%	0%	[9]
Potish *et al* (1989)	IB-IIIB	159	58	EXP	RT	86%	56%	57%	0%	[10]
Hacker *et al* (1995)	IB-IVA	34	34	Abdominal	S+RT	NA	80%	82−90%	NA (all resected)	[11]
Cosin *et al* (1998)	IB-IV	266	74	EXP	RT	75%	50%	46%	0%	[12]
Morice *et al* (1999)	IB-II	421	52	Abdominal	S+CCRT	94% (3-y)	64% (3-y)	40% (3-y)	NA (all resected)	[3]
Suprasert *et al* (2005)	IB-IIA	242	23	Abdominal	CCRT	NA	93% (2-y DFS)	58% (2-y DFS)	NA (all resected)	[13]
Richard *et al* (2008)	IB	3,116	55	Abdominal	RT	NA	69%	71%	NA (all resected)	[14]
Cheung *et al* (2011)	IB-IIA	110	16	Laparoscopic	CCRT	85%	40−50%	40−50%	NA (all resected)	[15]
Cheung *et al* (2011)	IB2-IV	85	29	Laparoscopic	CCRT	70−80%	NA	30−40%	NA (all resected)	[15]

FIGO: International federation of gynecology and obstetrics, LN: lymph node, EXP: extraperitoneal, RT: radiotherapy, CCRT: concurrent chemoradiotherapy, S: surgery, NA: not applicable, DFS: disease free survival

treatment debulking surgery of bulky pelvic lymph nodes. Survival information has been reported for patients with negative lymph nodes, microscopic metastatic lymph nodes, and bulky (macroscopic) metastatic lymph nodes surgically removed. Most studies showed similar survival rates between patients with microscopic lymph node metastases and those with bulky lymph node metastases that were resected. Meanwhile, no long-term survivors have been reported in patients with unresected macroscopic lymph nodes. Unfortunately, macroscopic or bulky disease is undefined in most reports. In general, most studies indicate that surgical resection of the bulky lymph nodes may improve similar survival rates to be comparable to that of cases with microscopic metastases. Therefore, surgical removal of pelvic nodal metastases before radiation therapy is recommended.

Downey first recommended surgical resection of pelvic lymph node metastases prior to RT in 1989. In their study, 156 patients who underwent pelvic lymph node resection for metastases were divided according to pelvic node status. The 5-year survival rates were similar for 48 patients with resected bulky lymph node metastases and 18 patients with only microscopic metastases (51% and 57%, respectively). Meanwhile, none of the 9 patients whose bulky nodes were unresectable survived [9]. In the same year, Potish *et al* reported an analysis of 159 patients with cervical cancer who underwent surgical staging by extraperitoneal lymphadenectomy followed by radiation therapy. The 5-year recurrence-free rate for women who were microscopically positive for pelvic nodal metastases was substantially the same (56%) as that for women who were positive for completely resected metastases (57%) [10].

In 1995, Hacker *et al* reported that after bulky lymph node resection of 34 patients, 23 patients underwent radical hysterectomy, 33 patients underwent extra-pelvic irradiation, 28 underwent pelvic and aortic irradiation, and 23 underwent four cycles of cisplatin chemotherapy. The bulky lymph nodes could be resected in all the patients. Bulky nodules were confined to the pelvis in 17 cases, to the common iliac region in 9 cases, and to the supra-aortic region in 8 cases. The survival rate of patients with completely resected bulky lymph nodes was similar to that of patients with only microscopic metastases in the lymph nodes [11].

In 1998, Cosin *et al* evaluated 266 patients with cervical cancer who underwent extraperitoneal pelvic and aortic lymphadenectomy before receiving radiation therapy. Among the metastasis-positive patients, the 5-year survival rate was comparable at 50% versus 46% for those with microscopic metastases and those with bulky, metastasis-positive lymph nodes who achieved complete lymph node resection. The results showed the possibility of improving survival by removing the bulky lymph nodes before the main treatment [12].

In 1999, Morice *et al* conducted a prospective study of 421 patients with cervical cancer treated with systematic pelvic and aortic lymphadenectomy in combination with radiation therapy and surgery. Pelvic lymph node metastases were detected in 106 patients (26%), and bulky metastasis-positive lymph nodes were found in 52 (12%). The 3-year survival rate was 64% in patients with positive microscopic lymph node metastases and 40% in patients with resected bulky lymph nodes. These results confirm the therapeutic value of complete resection of bulky-positive lymph nodes [3].

When a radical hysterectomy is withdrawn because of positive pelvic lymph nodes found during surgery, it is called an "abandoned hysterectomy." In these cases, the therapeutic strategy generally involves removal of only the lymph nodes followed by CCRT. Thus, the bulky lymph nodes are removed before treatment. In 2005, Suprasert *et al* described 23 cases of grossly positive lymph nodes among 242 hysterectomies. In these 23 cases, RH was discontinued and only total pelvic lymphadenectomy was performed. Of the 23 cases, 22 received CCRT, and the remaining one received radiation therapy. Although there were no significant differences in complications between the 23 patients and the 35 patients who completed the hysterectomy and had a positive microscopic lymph node detection after surgery, the 2-year disease-free survival rate was significantly lower in the abandoned hysterectomy group than that in the completed surgery group, i.e., the microscopic metastasis group (58% vs. 93%). This indicates that those with abandoned RH may have a worse prognosis than those with complete surgery [13].

In 2008, Richard *et al* compared the 5-year survival

rates between women who completed a RH and those with abandoned hysterectomy, using the Surveillance, Epidemiology, and End Results database. From a cohort of 3,116 women diagnosed with stage IB cervical cancer, 265 (8.7%) were pelvic lymph node positive and underwent total pelvic and aortic lymphadenectomy. Of these, 163 had a completed RH and 55 had an abandoned hysterectomy. The results showed that, among patients with positive pelvic lymph node at the time of RH, the 5-year survival rate was comparable between the completed and abandoned RH groups, at 69% and 71%, respectively [14].

In 2011, Cheung *et al* laparoscopically removed the lymph nodes in patients with positive lymph nodes in pre-treatment imaging and evaluated metastasis on intraoperative pathology. If there was metastasis, the hysterectomy was discontinued, and CCRT become the main treatment afterwards, while hysterectomy was performed for patients with negative lymph node metastasis. In total, 16 of the 110 patients with early stage cervical cancer and 37 of the 97 patients with advanced stage cervical cancer underwent resection of enlarged metastatic nodules before receiving RT. After radical hysterectomy, a further six patients had microscopic lymph node metastases, four of whom underwent postoperative adjuvant radiation therapy. After a median follow-up of 62 months, the rate of intra-pelvic recurrence was not significantly different between node-positive and node-negative patients, regardless of early or advanced stage of disease. However, extra-pelvic recurrence occurred in 59.1% of the early node-positive patients and 44.8% of the advanced stage node-positive patients and was the main cause of poor survival. The authors concluded that removal of bulky lymph nodes may help reduce pelvic recurrence, but it is less effective for improving survival [15].

Lymph node enlargement can be caused by factors other than metastasis. The major advantage of surgery is that it enables a histopathological diagnosis of the resected lymph nodes. Zighelboim *et al* retrospectively evaluated 104 patients with suspected lymph node metastases presenting enlarged lymph nodes (≥2 cm) on computed tomography (CT) or magnetic resonance imaging (MRI). Of them, 25 patients (24%) were found to have no metastases histologically [16], indicating that in cases of suspected lymph node metastasis that are treated with CCRT without resection, more than a few cases are actually negative for lymph node metastasis.

Resection of bulky lymph nodes is not always successful. Zighelboim *et al* reported that the most common reason for failure was tight adherence of the enlarged lymph nodes to the vessels and bone invasion. They also analyzed the influencing factors of the failure of complete resection of bulky lymph nodes, and found that, among 62 cases of surgical debulking for bulky lymph nodes, 16 cases (26%) were unresectable. Body mass index had no effect on the success of lymph node resection. In univariate analysis, age and the size and location of the bulky lymph nodes were associated with the resection rate. Logistic regression confirmed that the probability of successful resection decreased with age and increasing maximum lymph node size [16]. There is also a risk of complications with bulky lymph node excision, so strict patient selection is necessary. Patients in whom control of primary tumor is unlikely or those who have a high risk of potential distant metastases have no prognostic benefit from bulky lymphadenectomy. Conversely, patients with small metastatic lymph nodes (less than 2 cm) may be successfully treated with CCRT. In these cases, surgical debulking of the lymph nodes has little benefit for survival.

Pretreatment lymph node resection in patients with cervical cancer involves four basic approaches: extraperitoneal laparotomy, transperitoneal laparotomy, extraperitoneal laparoscopy, and transperitoneal laparoscopy. Although there is no significant difference in the frequency of operative complications between these approaches, the transperitoneal approach has been associated with a higher incidence of bowel complications as side effects after CCRT than the extraperitoneal approach (11.5% vs. 3.9%) [17]. Thus, the extraperitoneal approach is preferred when performing surgical lymph node debulking. In another study of 168 patients who were randomly assigned to classical open transperitoneal, open extraperitoneal, or laparoscopic transperitoneal pelvic lymphadenectomy before scheduled radical hysterectomy, open extraperitoneal and laparoscopic transperitoneal lymphadenectomy showed similar effectivity and complication rates as did classical open transperitoneal approach [18]. In summary, although all approaches have shown similar effectiveness, the retroperitoneal approach has the ad-

vantage of fewer intestinal complications from CCRT treatment per lymphadenectomy.

Figure 1 shows a representative case of cervical cancer, stage IB, squamous cell carcinoma with bulky pelvic lymph nodes treated at our institution. On pretreatment MRI and PET/CT imaging, the left pelvic lymph node was enlarged in multiple masses, measured 8 cm at maximal diameter, and formed a large mass. In this case, the cervical tumor was less than 2 cm in size and was at stage IB1. During surgery, the bulky lymph node was strongly adherent to the left external iliac vein and could be removed grossly, but the microscopic tumor remained. The pelvic lymph nodes were systematically dissected. The cervical tumor was small, and the patient preferred resection of the uterus rather than definitive CCRT, therefore a succeeding radical hysterectomy was performed. Postoperative pathological examination revealed metastasis of the squamous cell carcinoma in the enlarged lymph nodes, but not in the other small lymph nodes. The TNM classification was pT1bN1M0. There were no metastases in her common iliac lymph node and biopsied paraaortic lymph nodes. This case was a good candidate for debulking because the primary tumor was small and well-controlled, and there was no metastasis in the lymph node located higher than the common iliac lymph node, thus the possibility of distant metastasis was low. She received adjuvant CCRT without any severe complications.

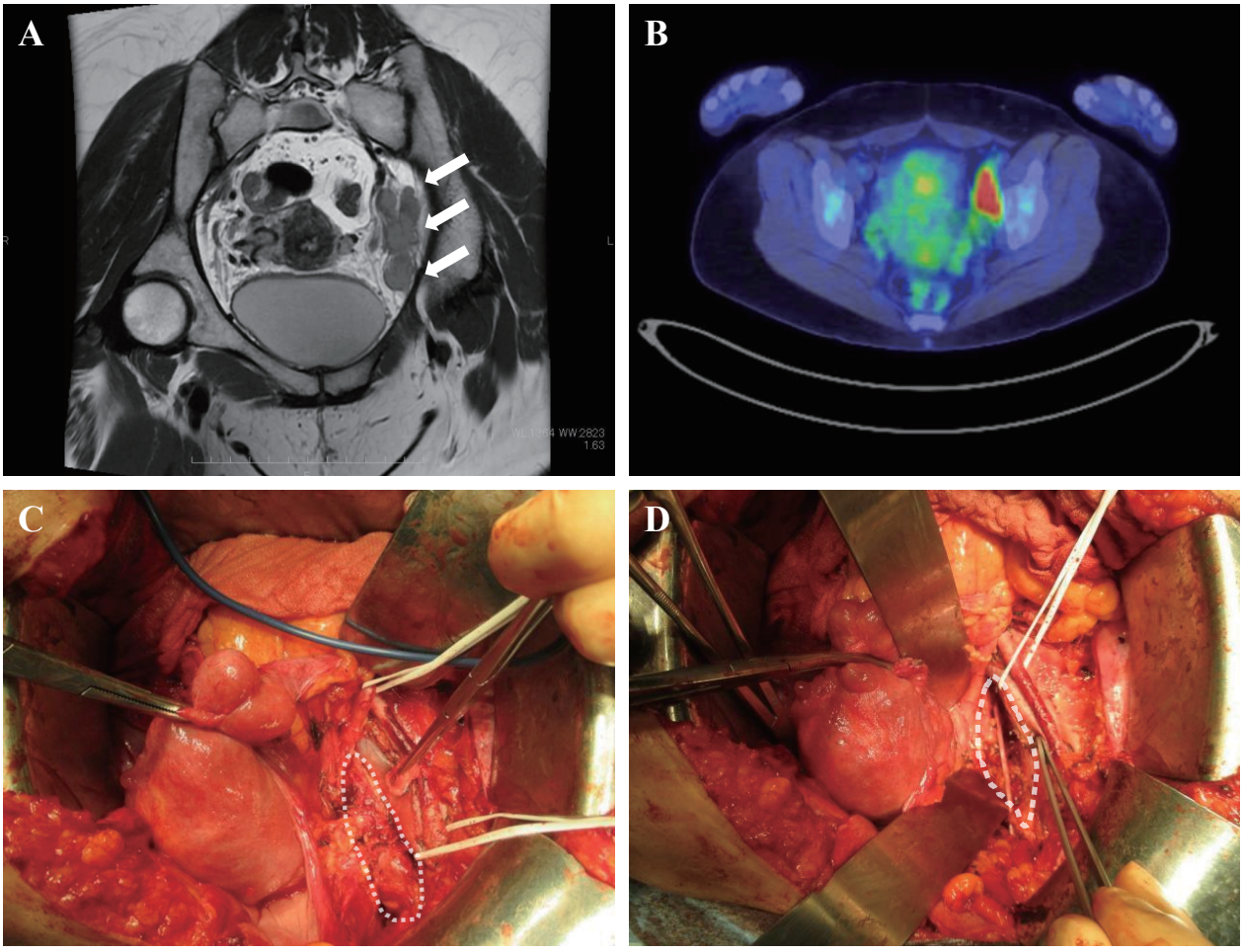

Figure 1. Multiple left metastatic pelvic lymph nodes that formed a bulky node. A, B: Arrows indicate the bulky node. C: The bulky node indicated by a white dotted line was tightly adherent to the vascular wall of the external iliac vein. D: The operative field after careful resection of the bulky node. The obturator nerve is preserved and visible.

2. Boosted external beam radiotherapy to bulky node

Boosted external beam radiotherapy (EBRT) is an alternative strategy for cases with unresectable bulky lymph node. Ariga *et al* retrospectively analyzed the outcomes of boosted EBRT for bulky metastasis-positive pelvic lymph nodes in patients with cervical cancer, and found that boosted EBRT to positive pelvic nodules achieves excellent nodal control without increasing late complications. The study population comprised 174 patients with cervical cancer of FIGO stages IB1-IVA who received definitive RT or CCRT in combination with high-dose-rate intracisternal brachytherapy. The median diameter of the target lymph node was 15 mm (range, 10−60 mm), and the median number of positive lymph nodes was 2 (range, 1−4). In total, 52 of 57 patients (91%) with positive lymph nodes received boosted EBRT. The median dose of the EBRT for nodules was 56 Gy. The 5-year overall survival rates for node-positive and node-negative patients were 73% and 92%, respectively, and the pelvic control rates were 83% and 92%, respectively. There was no significant difference with respect to late complications between the boosted EBRT group and the no-EBRT group [19].

Although higher radiation doses increase effectiveness, they also increase complications. In a report by Hata *et al* 111 swollen pelvic lymph nodes (median, 25 mm; range, 11−56 mm) in 62 cervical cancer patients were initially treated with RT. Forty-six of those patients received concurrent chemotherapy. The total radiation dose ranged from 45 to 61.2 Gy (median, 50.4 Gy). All 33 metastatic lymph nodes measuring ≥30 mm in diameter were controlled by irradiation at a median dose of 55.8 Gy. The 3-year lymph node-progression free rate was 98.0% in 111 metastatic lymph nodes. Of those, 2 patients developed grade ≥3 treatment-related toxicity, one patient developed ulcers, and another patient developed sigmoid colon perforation [20].

RT-induced shrinkage of metastatic lymph nodes is closely associated with disease control. Wakatsuki *et al* reported that the degree of lymph node shrinkage after RT was a more significant predictor of recurrence than the size of the pre-RT lymph nodes. They found that poorly shrunken lymph nodes needed a total dose of >58 Gy of boosted radiation. In their study of 245 patients with squamous cell carcinoma of the cervix who had received radiation therapy, 129 had large pelvic lymph nodes that were diagnosed as metastases. The pelvic lymph node control rate at 5 years was 79.5% for positive cases and 95.8% for negative cases, and there was a significant correlation between the size of the pelvic lymph node after 50 Gy of RT (<10 mm: 96.7%, ≥10 mm: 75.7%). Overall, 9 of the 16 patients who received less than 58 Gy of RT developed recurrence, whereas none of the 21 patients who received more than 58 Gy RT developed recurrence. These findings suggested that the control rate of nodules correlated significantly with the dose of RT [21].

Meanwhile, Wujanto *et al* reported that EBRT boost to pelvic lymph nodes have no survival or recurrence benefit in patients with locally advanced cervical cancer who present with lymph node involvement on diagnosis. In an evaluation of 139 patients with locally advanced cervical cancer who received RT (EBRT doses: 45−50.4 Gy; nodal boosts: 3.6−19.8 Gy), 67 were positive for pelvic lymph node metastases, of which 53.7% had received a nodal boost. The 5-year recurrence-free survival rate was lower than that without a nodal boost at 48.6% versus 64.5%. Furthermore, the 5-year overall survival rate was higher for the boost group at 74.3% versus 80.6%, while there was no significant difference in toxicity. They concluded that EBRT boost to the pelvic lymph nodes does not reduce recurrence or improve survival [22]. It should be noted, however, that the total irradiation dose in their study was relatively lower than that in other studies, and this may have caused the unfavorable results of EBRT.

3. Strategy for treatment of cervical cancer with bulky pelvic lymph node

Figure 2 shows the strategy for the treatment of cervical cancer patients diagnosed with a bulky pelvic lymph node (≥2 cm) on pre-treatment imaging. Removal of the bulky lymph nodes can be considered if the following 4 conditions are met: 1) absence of distant metastases, 2) primary cervical tumor can be controlled by CCRT or RH, 3) the bulky lymph nodes are

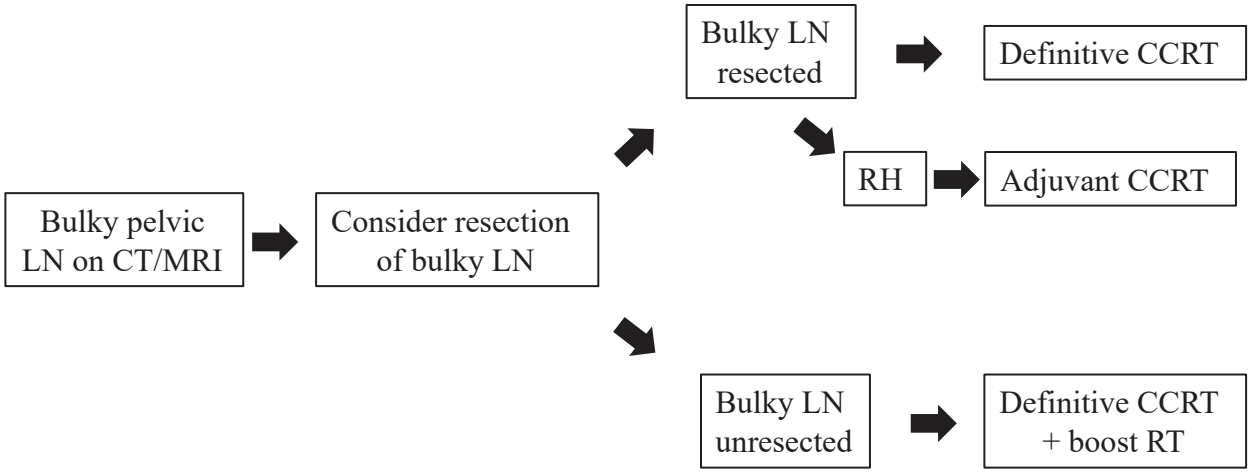

Figure 2. Treatment strategy for cervical cancer with bulky pelvic lymph nodes. Resection of the bulky nodes should be considered in cases with bulky pelvic lymph nodes detected on pretreatment imaging. Thereafter, the standard practice is to perform definitive CCRT, but if the cervical tumor is relatively small, radical hysterectomy is also acceptable. If the bulky lymph nodes are unresectable, definitive CCRT should be performed, and boosted radiation should be considered when it does not adequately reduce the lymph node. RH: radical hysterectomy, CCRT: concurrent chemoradiotherapy.

not involved in major blood vessels, and 4) the bulky lymph nodes are not accompanied by bone infiltration (although these findings cannot be accurately determined until during surgery) (Figure 3). An extraperitoneal route is recommended as an approach that can reduce serious complications from radiation. After removal of bulky lymph nodes, the standard practice is to perform definitive CCRT, but if the cervical tumor is relatively small, radical hysterectomy is also acceptable. This reduces vaginal adhesions and improves the maintenance of sexual function because intracavitary irradiation is not performed. Meanwhile, in cases of unresectable bulky lymph nodes, definitive CCRT should be performed. If CCRT does not adequately reduce the lymph node size, boosted radiation should be considered.

As stated at the beginning of this review, lymph node metastasis is the most significant influencing factor in the prognosis in cervical cancer. Depending on the number and size of the metastases, bulky lymph nodes are usually associated with multiple metastasis-positive lymph nodes. Although these cases are currently treated mainly with adjuvant CCRT without further consolidation, surgery plus CCRT is still inadequate. Therefore, various strategies are being devised to overcome this problem. The most realistic

1) Absence of distant metastases
2) Primary cervical tumor can be controlled
3) The bulky lymph nodes are not involved in major blood vessels
4) The bulky lymph nodes are not accompanied by bone infiltration

Figure 3. Indications for pretreatment resection of bulky pelvic lymph nodes.

and promising strategy is the addition of consolidation chemotherapy after adjuvant CCRT. A meta-analysis of randomized controlled trials showed the need for randomized trials to validate the additional benefit from adjuvant chemotherapy [23]. The hazard ratio for survival was 0.46 in patients who received chemoradiotherapy plus adjuvant chemotherapy, which indicated a 54% reduction in the risk of death. A phase II study reported the effectiveness and acceptable side effects of paclitaxel+carboplatin (TC) therapy as consolidation chemotherapy after CCRT in patients with multiple positive postoperative lymph nodes [24]. The efficacy of the addition of platinum-based consolidation chemotherapy after CCRT is also being evaluated

in a phase III trial named RTOG0724 [8]. This randomized controlled trial aims to show that adjuvant therapy after CCRT prolongs the prognosis of patients at high risk of recurrence after cervical cancer surgery; i.e., patients with paracervical tissue invasion or lymph node involvement. Thus, in patients with surgically treated bulky lymph node-positive cervical cancer, postoperative CCRT followed by TC chemotherapy is expected to improve the prognosis.

Conclusions

The strategy for the treatment of cervical cancer with pelvic lymph node metastases must be carefully determined. In patients with small tumor size and a small number of metastatic lymph nodes, CCRT can control the disease, but in those with bulky, metastatic-positive lymph nodes, pretreatment lymph node resection should be considered. For unresectable lymph nodes, the extent of bulky lymph node shrinkage is determined at the end of CCRT. In these cases, a radiation boost should also be considered. It is currently unclear, however, whether pretreatment resection of the bulky lymph nodes is superior to radiation boost to the bulky lymph nodes without resection for prolonging patient prognosis. A randomized controlled trial will be necessary.

Conflicts of Interest

The authors declare that there is no conflict of interest.

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