

Management of Recurrent Cervical Cancer

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Approximately 30% of cervical cancer patients will ultimately fail after definitive treatment. The reported 5-year survival rates of patients with treatment failure are between 3.2% and 13%. Management of recurrences depends on the extent of disease, primary treatment, and performance status/comorbidity. Primary treatment, relapse pattern, and characteristics at presentation are determinants for prognosis after recurrence. Concurrent chemoradiation achieves significantly better outcome than radiation alone in patients with recurrences after primary radical hysterectomy. Isolated paraaortic lymph node metastasis and local recurrence confined to cervix were associated with better outcome in failure after definitive radiotherapy. When definitive radiotherapy or surgery plus adjuvant radiotherapy has failed, pelvic exenteration is usually necessary for those had central relapse with clear pelvic sidewall and free of distant metastasis. Radical hysterectomy with or without pelvic node dissection is considered feasible for small uterine and/or vaginal recurrences with high operative morbidity. For patients who have recurrences involving the irradiated pelvic wall, pelvic exenteration is usually not an option for curative intent. Intraoperative radiotherapy, combined operative radiotherapeutic treatment, and laterally extended endopelvic resection have been used in such situations with some success. Chemotherapy alone is basically palliative. Generally, combination chemotherapy could attain higher response rates with no significant improvement in overall survival than cisplatin alone. Recent investigations indicated benefits of positron emission tomography in more accurate restaging of recurrent disease. The impact of various post-treatment surveillance strategies to early detect treatment failure remains to be evaluated. (*Chang Gung Med J* 2004;27:711-7)

Key words: recurrent cervical carcinoma, posttherapy surveillance, restaging, salvage therapy.

Cervical cancer remains the leading female malignancy in Taiwan. The incidence including invasive carcinoma (n = 2720) and carcinoma in situ/cervical intraepithelial neoplasia grade 3 (n = 3556) (International Federation of Gynecology and Obstetrics [FIGO] stage 0) was 53.8 per 100,000 women in the Taiwan Cancer Registry annual report 2000.^(1,2) Early-stage (IB and IIA) cervical cancer can be cured on an average rate of 80% with either radical surgery or definitive radiation, yet 30-50% of patients with stage IIB to IV will ultimately fail.⁽³⁻⁵⁾ Recurrent cervical carcinoma remains a tough clinical

problem. The prognosis of recurrent cervical carcinoma is grim regardless of the mode of primary treatment except those with isolated small vaginal or cervical relapse. The reported 5-year survival rates of patients who recur after radical surgery or radiotherapy are between 3.2% and 13%.⁽⁶⁻¹¹⁾

Prevent Recurrences

Generally, optimizing primary treatment could be more rewarding than a deliberate post-treatment surveillance or aggressive salvage therapy.

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Multimodality approaches have recently been investigated extensively in managing cervical cancer.⁽¹²⁻¹⁸⁾ Concurrent chemotherapy in combination with radiotherapy has significant benefit over radiotherapy alone (decreased relative risk of failure or death) in several randomized controlled trials for locally advanced cervical cancer.⁽¹²⁻¹⁴⁾ Adjuvant therapy for early-stage patients undergoing radical surgery with high risk of treatment failure has been relatively inconclusive.⁽¹⁶⁻¹⁸⁾

Posttherapy Surveillance

Regardless of treatment modalities, the median time to recurrence is usually short, >75% of recurrences occur within 3 years from diagnosis.⁽⁶⁻¹¹⁾ Purposes of posttherapy surveillance are to early detect recurrences, assess outcome, and also to care complications.⁽⁸⁾ Our protocol of posttherapy surveillance consists of 3-monthly visits for 2 years, 4-monthly for the third year, 6-monthly between 3-5th year, and yearly thereafter. Clinical history, physical and pelvic examination, Pap smear, and serum tumor markers (squamous cell carcinoma antigen [SCC-Ag] and carcinoembryonic antigen [CEA] for squamous cell carcinoma; CA125 and CEA for adenocarcinoma; and SCC-Ag, CEA, CA125 for adenosquamous carcinoma) are checked on every visit.^(7,11,17) Yearly chest X-ray studies are advised in asymptomatic patients, while CT-MRI scans are performed yearly for first 3 consecutive years for high-risk groups or when clinically indicated (suspicious symptoms/signs, or elevated tumor markers).^(5,7,11,17,19)

There has been no consensus regarding appropriate follow-up items and intervals. Soisson et al. investigated clinical parameters in the detection of recurrent cervical carcinoma after radical hysterectomy (n = 31), and they found vaginal cytology had a sensitivity and specificity of 13 and 100%, pelvic and physical examination 58 and 96%, and the presence of suspicious symptoms 71 and 95%, respectively. Only 3 patients (10%) were successfully salvaged, and two of which was detected exclusively by vaginal cytology. Vaginal cytology might not be sensitive or cost-effective, however, it is the technique most likely to detect recurrences while it is curable. The utility of serum tumor markers is also controversial.^(11,19-25) The reasons against routine use are that few recurrences are detected by serum tumor mark-

ers alone and that salvage rates remain low in those patients.^(21,22) In contrast, others suggest that monitoring serum tumor markers help to early identify asymptomatic potentially curable local or distant failures.^(19,23-25)

Prognostic Factors after Failed Primary Treatment

For those with persistent or recurrent cancer after primary radical surgery or radiotherapy, salvage therapy^(7,11) (surgery, radiotherapy with or without chemotherapy, or both) to resectable pelvic or localized extrapelvic metastasis could lead to a secondary cure in selected patients. Primary treatment, relapse pattern, and characteristics at presentation (initial stage, histologic type, or lymph node metastasis) are recognized determinants for prognosis after recurrence.^(7-11,22,26,27) In our previous study, we found that median survival after diagnosis of recurrence was 9.8 months in patients (n = 177) with recurrent cervical cancer after primary radical surgery. Of the 13 patients who survived > 5 years after recurrence, all had squamous tumors and 7 had an isolated vaginal relapse. A direct comparison of chemoradiation and radiation alone resulted in no difference in survival after recurrence. When those with isolated vaginal metastasis were excluded, patients receiving chemoradiation (5-year survival 30%) had significant better outcomes than those receiving radiotherapy alone (5-year survival 9.7%).⁽⁷⁾ Longer time to recurrence was noted to be associated with better prognosis by some^(9,10,26,27) but was found unrelated to outcome by others.^(7,11) In a large retrospective review, of 1292 cervical cancer patients underwent definitive radiotherapy at our hospital between 1990 and 1999, 375 (29%) developed treatment failure. In the 162 patients with local failure, 44% had persistent disease and 56% had a relapse after complete remission. Isolated paraaortic or supraclavicular lymph node metastasis salvaged with radiotherapy/chemoradiation and local recurrence confined to cervix receiving salvage surgery were associated with better outcome in failure after definitive radiotherapy. The 3-year survival rates after recurrence were 34%, 28%, 29%, respectively.⁽¹¹⁾ Selected patients who had a distant relapse at sole site could be successfully salvaged by targeted chemoradiation, surgery plus radiotherapy or surgery alone.^(7,9,11,19,28-30)

Pelvic Exenteration

When definitive radiotherapy or surgery plus adjuvant radiotherapy has failed, pelvic exenteration is usually necessary for those who had central pelvic relapse with clear pelvic sidewall and free of distant metastasis.⁽³¹⁻³³⁾ Outcome results vary according to patient selection. Continent urinary diversion is feasible with acceptable short-term and long-term complications.⁽³³⁾ Multiple pelvic and/or paraaortic nodal metastasis, peritoneal disseminations, upper abdominal tumor extensions and distant metastasis are recognized contraindications to exenteration.^(32,34) Nevertheless, exploration for exenteration is aborted in significant proportions of candidates who have been evaluated by deliberate preoperative studies. The reasons for aborting the procedure include peritoneal disease, nodal metastasis, parametrial fixation, and so forth.⁽³⁵⁾ Occasionally, re-irradiation is feasible for superficial late recurrences in the cervix or vagina.⁽³⁵⁾ Radical hysterectomy with or without pelvic node dissection is considered feasible for small uterine and/or vaginal recurrences with high operative morbidity.⁽³⁶⁻³⁸⁾ For patients whose initial FIGO stage \geq IIB, there is high failure rate in the pelvis, and such patients cannot be salvaged by further exenteration.⁽³²⁾

Intraoperative Radiotherapy (IORT) and Other Alternatives

For patients who have recurrences involving the pelvic wall and have been irradiated (primarily or adjunctively) in the pelvis after operation, pelvic exenteration is conventionally not an option for curative intent. However, various approaches such as combined operative and radiotherapeutic treatment (CORT),⁽³⁹⁾ IORT,⁽⁴⁰⁻⁴²⁾ or laterally extended endopelvic resection (LEER)⁽⁴³⁾ have been attempted. The preliminary local control and survival rates were higher, yet long-term survival tends to decline with time. Monge-Martinez et al. reported outcomes in 67 patients (36 primary, 31 recurrent) treated with intraoperative electron beam radiotherapy. The 10-year in-field control rates were 92.8% (primary) and 46.4% (recurrent), and 10-year overall survival were 58% and 14%, respectively. The 10-year overall survival was 0% for patients with gross residual disease.⁽⁴²⁾

Role of Chemotherapy in Recurrent Cervical Cancer

Chemotherapy alone is basically palliative. The most active single agent remains to be cisplatin. Other agents such as 5-fluorouracil, doxorubicin/epirubicin, ifosfamide, dibromodulcitol, CPT-11, paclitaxel, gemcitabine, topotecan, etc., are also active in cervical carcinoma.^(32,44-47) Generally, combination chemotherapy could attain higher response rates and progression-free intervals with no significant improvement in overall survival than cisplatin alone.^(32,44,47) However, anecdotal long-term survivors (>5 years) have been reported in a patient with multiple lung metastases and the other with supraclavicular lymph node metastasis by chemotherapy alone.⁽³²⁾

New Approaches

Positron emission tomography (PET) is a molecular imaging technique that uses radiolabeled molecules to image molecular interactions of biological processes in vivo. [18F]fluoro-2-deoxy-D-glucose (18F-FDG) PET has improved the accuracy of detection and staging from 8% to 43% over conventional work-ups in patients with lung, colorectal cancer, lymphoma, melanoma, breast cancer, and thyroid cancer, depending on the clinical question.⁽⁴⁸⁾

The clinical value of FDG-PET for primary staging in cervical cancer seems promising.⁽⁴⁸⁻⁵²⁾ A few retrospective studies⁽⁵³⁻⁵⁷⁾ have investigated FDG-PET as routine post-treatment surveillance or to determine whether various clinical situations suspicious of recurrence are true recurrences (Table 1). These studies are difficult to interpret because of poorly defined high-risk group or suspicious of recurrence. Grigsby et al. analyzed pre- and post-treatment PET scans in 76 cervical cancer patients. Among the 11 patients who developed new abnormal FDG uptakes, there were no survivors at 2 years.⁽⁵⁶⁾ Ryu et al. performed PET as routine post-therapy surveillance, in which 80 of 249 patients showed positive PET scanning, yet only 28 had recurrence confirmed (false positive rate of 65%).⁽⁵⁷⁾ We have prospectively investigated the role of PET in 27 patients with unexplained elevation of SCC-Ag levels (MRI and/or CT normal or inconclusive).⁽⁵⁸⁾ PET findings were positive for 19 of them, of which 17 were confirmed to have recurrences, and such expe-

dited detection of recurrent cervical cancer led to positive effects on patient survival (Table 1).

In another prospective trial (n = 40),⁽⁵⁹⁾ we evaluated the diagnostic efficacy and benefit of PET restaging in documented recurrent cervical cancer. A total of 55% patients had treatment modified due to PET findings. For those receiving primary surgery, a significantly better 2-year overall survival rate was noted for study patients when compared with a group of historical controls who were restaged without

PET. We also investigated the prognostic features of recurrent cervical cancer patients, in which study⁽⁶⁰⁾ a serum level of SCC-Ag > 4 ng/mL at relapse, primary radiation, and presence of symptoms at recurrence were significant predictors of poor survival. A scoring system using these 3 covariates defined 3 distinct prognostic groups. Our results suggest that we may select appropriate candidates for PET scanning using this risk-score, and PET scans may offer maximal benefits with precise restaging information (Table 2).

Table 1. FDG-PET after Definitive Treatment in Cervical Cancer

Authors	Year	Study	Patient number	Purpose	Gold std	Results
Grigsby ⁽⁵⁶⁾	2003	Retrospective	76	Pre- & Post-therapy surveillance	Clinical follow-up	Persistent abnormal FDG uptake: cervix 18%, PLN 16%, PALN 45%, SLN 75%; 11 pts with new lesions, 2-year survival 0%
Ryu ⁽⁵⁷⁾	2003	Retrospective	249	Detect asymptomatic early recurrence	Histology or clinical follow-up	80 pts with PET-positive PPV 35% Sv 90.3%, Sp 76.1%
Chang ⁽⁵⁸⁾	2004	Prospective	27	Detecting site of recurrence when SCC-Ag elevation and CT-MRI (-)	Histology or clinical follow-up	Sv 94% (17/18), Sp 86% (6/7), PPV 89% (17/19), NPV 88% (7/8)

Abbreviations: Gold std: gold standard; FDG: [¹⁸F]fluoro-2-deoxy-D-glucose; PET: positron emission tomography; PALN: para-aortic lymph node; PLN: pelvic lymph node; SLN: supraclavicular lymph node; Sv: sensitivity; Sp: specificity; PPV: positive predictive value; NPV: negative predictive value; pts: patients; SCC-Ag: squamous cell carcinoma antigen; CT-MRI: computed tomography and/or magnetic resonance imaging.

Table 2. FDG-PET after Documented Recurrence in Cervical Cancer

Authors	Year	Study	Patient number	Purpose	Gold std	Results
Lai ⁽⁵⁹⁾	2004	Prospective	40, potentially curable	Primary end point: % improvement in restaging Secondary end point: 2-y OS (restaging with vs without PET)	Histology or clinical follow-up	55% modified treatment due to PET Detecting metastatic lesion: dual-phase PET vs MRI-CT, AUC= 0.962 vs 0.771 (<i>p</i> < 0.0001) 2-y OS: PET vs without PET: HR, 0.21 (95% CI, 0.05-0.83) <i>p</i> = 0.020
Yen ⁽⁶⁰⁾	2004	Prospective	55, potentially curable	Defining prognostic groups	Histology or clinical follow-up	65% modified treatment due to PET 3 poor prognostic covariates identified: primary radiation, SCC-Ag > 4 ng/mL, and presence of symptoms A risk scoring system formulated: score ≤ 1, HR 1.0; score = 2, HR, 6.91 (95%CI [1.49-32.14]); score = 3: HR, 60.46 (95% CI [9.68-378.09])

Abbreviations: Gold std: gold standard; FDG: [¹⁸F]fluoro-2-deoxy-D-glucose; PET: positron emission tomography; AUC: area under the curve; HR: hazard ratio; CI: confidence interval; OS: overall survival; SCC-Ag: squamous cell carcinoma antigen.

Conclusions

Generally, optimizing primary treatment could be more rewarding than a deliberate posttherapy surveillance or salvage therapy on recurrence. Management of recurrences depends on the extent of disease, primary treatment, and performance status/comorbidity. Primary treatment, relapse pattern, and characteristics at presentation are determinants for prognosis after recurrence. Recent investigations indicated benefits of PET scan by more accurate restaging recurrent disease. The cost-effectiveness of various post-treatment surveillance strategies after definitive therapy to early detect treatment failure remains to be evaluated.

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