Analysis of Failures in Patients with FIGO Stage IIIc₁-IIIc₂ Endometrial Cancer

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Abstract. Aim: To assess the pattern of failures in patients with FIGO stage IIIc₁-IIIc₂ endometrial cancer. Patients and Methods: Data were retrospectively analyzed for 34 patients with this malignancy who underwent extra-fascial total hysterectomy, bilateral salpingo-oophorectomy and pelvic/para-aortic node dissection. Postoperative treatment consisted of radiotherapy in 5 patients, 6 cycles of chemotherapy in 9, and 3-4 cycles of chemotherapy followed by radiotherapy in 20. The median follow-up of survivors was 33 months (range, 6 to 133 months). Results: Tumour relapsed in 14 out of 34 patients (41.2%). Median time to recurrence was 17 months (range, 9.5-42 months). Vaginal recurrence developed in 2 patients (5.9%), distant recurrence in 5 (14.7%), pelvic node recurrence in 3 (8.8%) and para-aortic recurrence in 7 (20.6%). Two patients had multiple sites of recurrence. Distant failure occurred in 11.1% of the patients who received 6 cycles of chemotherapy versus 20.0% of those who had 3-4 cycles of chemotherapy followed by radiotherapy. Five-year overall survival was 60.5%, and, in particular, it was 62.5% for stage IIIc₁ and 57.0% for stage IIIc₂. Conclusion: FIGO stage IIIc₁-IIIc₂ endometrial cancer relapses in approximately 40% of cases, and distant sites and para-aortic nodes represent the most common sites of failure.

Surgery is the primary treatment of endometrial cancer and consists of extra-fascial total hysterectomy and bilateral salpingo-oophorectomy, with or without pelvic and para-aortic lymphadenectomy (1). Unsolved controversy exists regarding the selection of patients who may benefit from lymphadenectomy and the magnitude of such benefit (2-12).

Outside clinical trials, this surgical procedure is usually performed for women with non-endometrioid histology or those with endometrioid histology with poorly differentiated grade (assessed on preoperative biopsy) and/or deep myometrial invasion (assessed on preoperative magnetic resonance imaging or intraoperative frozen sections). Conversely, lymphadenectomy can be omitted in patients with well or moderately differentiated endometrioid carcinoma and superficial myometrial invasion.

Among the 7990 surgically staged endometrial cancer patients reported in the International Federation of Gynecology and Obstetrics (FIGO) Annual Report n. 26, 356 (4.5%) had stage IIIc disease, characterized by the presence of metastases to pelvic and/or para-aortic lymph nodes, and their 5-year overall survival was 57.3% (13). The FIGO staging system has recently been updated (FIGO 2009) (14). Pelvic and para-aortic lymph node metastases have been separated, and stage IIIc is now categorized as IIIc₁ (positive pelvic lymph nodes) and IIIc₂ (positive para-aortic lymph nodes with or without positive pelvic lymph nodes). Radiotherapy and chemotherapy have been widely used as postoperative treatment in this clinical setting, but no definite conclusion regarding the optimal adjuvant therapy can be drawn from the available literature (6, 7, 9, 12, 15-20).

The aim of this retrospective study was to assess the pattern for failures of patients with FIGO stage IIIc₁-IIIc₂ endometrial cancer.

Materials and Methods

Between May 1987 and December 2010, 327 patients underwent peritoneal washing, extra-fascial total hysterectomy, bilateral salpingo-oophorectomy and pelvic/para-aortic lymphadenectomy for endometrial cancer at the Department of Gynecology and Obstetrics of the University of Pisa. Two hundred and sixty-eight patients were operated by laparotomy, and 59 by laparoscopy or robotics. Patients who underwent laparotomy or laparoscopic hysterectomy without lymphadenectomy, vaginal hysterectomy, those with synchronous endometrial and ovarian cancer, and those with clinical or surgical-pathological stage IV disease were excluded from the present analysis.
According to Mariani et al. (7), an adequate pelvic lymphadenectomy was defined as the removal of more than 10 pelvic lymph nodes, and adequate para-aortic lymphadenectomy was defined as the removal of 5 or more para-aortic lymph nodes.

Patients were staged retrospectively according to the FIGO 2009 classification (14).

The histological classification was performed according to the World Health Organization classification (13). The architectural grade was defined as grade 1 (G1), ≤5% of a nonsquamous or nonmucinous solid growth pattern; G2, 6-50% of nonsquamous or nonmucinous solid growth pattern; and G3, >50% of nonsquamous or nonmucinous solid growth pattern. Notable nuclear atypia, inappropriate for the architectural grade, raised the grade of G1 or G2 tumour by one.

Lymphvascular space involvement (LVSI) was defined as the presence of tumour cells within or attached to the wall of a blood vessel or lymphatic space using morphological and immunohistochemical analyses.

The present investigation analyzed the 34 patients who had FIGO stage IIIc1 or IIIc2 disease and who were periodically followed-up until July 2011 or until death. Adjuvant therapy has been changed over the duration of the study.

External pelvic beam irradiation was performed with a 15 MV beam and with a four-field technique (gantry angles at 0°, 90°, 180° and 270°). A 45-50.4 Gy dose was given in daily fractions of 1.8 Gy in 5-6 weeks. The pelvic target volume was outlined on a computed tomographic (CT) scan. When performed, 45 Gy para-aortic irradiation was planned in daily fractions of 1.8 Gy in 5 weeks. A portal image was obtained once per week and compared with the reference image in order to verify the accuracy of the treatment.

Vaginal cuff high-dose rate (HDR) brachytherapy was added in selected cases with isthmus or stromal cervical involvement after external beam irradiation with a cylinder applicator. The treatment planning was performed on a CT scan. The prescribed dose was 10-15 Gy in 5 Gy fractions. Rectal and bladder doses were estimated from dose volume histogram on CT-based plan and were evaluated to the dose points specified by the International Commission on Radiation Unit and Measurements (21).

The median follow-up of survivors was 33 months (range, 6 to 133 months).

Statistical analysis. Patient age, FIGO substage, histological type, tumour grade, myometrial invasion and LVSI were assessed for their relation to disease-free survival and overall survival.

The time from surgery to recurrence was defined as disease-free survival. The time from surgery to death or last observation was defined as overall survival.

SAS statistical package (release 8.2; SAS Institute, Cary, NC, USA) was used for the computations.

The cumulative probability of disease-free survival and overall survival was estimated by the product-limit method. The log-rank test was used to compare the homogeneity of disease-free survival and overall survival functions across strata defined by categories of prognostic variables.

Results

The median age of women was 62 years (range, 39 to 74 years). FIGO substage was IIIc1 and IIIc2 in 27 (79.4%) and 7 (20.6%) women, respectively. Histological type was endometrioid in 26 (76.5%) cases and nonendometrioid in 8 (23.5%). Tumour grade was G1 in 3 cases (8.8%), G2 in 17 (50.0%), and G3 in 14 (41.2%). Myometrial invasion was ≤50% in 6 (17.6%) women and >50% in 28 (82.4%). LVSI was positive in 20 cases (58.8%) and negative in 14 (41.2%).

Pelvic lymphadenectomy was performed in all 34 women and the median number of removed lymph nodes was 15 (range, 5 to 50). Pelvic lymphadenectomy was adequate (>10 removed nodes) in 27 out of the 34 (79.4%) patients, and inadequate in 7 (20.6%). Tumour positive pelvic nodes were found in 32 patients; the corresponding para-aortic nodes were tumour negative in 11 of these patients, positive in 6, and unknown (not removed) in 15. Among the 32 patients with histologically proven pelvic lymph node involvement, the median number of tumour positive pelvic nodes was 2 (range, 1 to 11).

Para-aortic lymphadenectomy was performed in 18 out of the 34 patients and the median number of removed lymph nodes was 6 (range, 1 to 27). Para-aortic lymphadenectomy was adequate (≥5 removed nodes) in 10 patients (29.4%), inadequate in 8 (23.5%), and not performed in 16 (47.1%). Tumour positive para-aortic nodes were found in 7 out of the 18 patients who underwent para-aortic lymphadenectomy; the corresponding pelvic nodes were negative in two of these patients, and positive in five (71.5%). Among the seven patients with histologically proven para-aortic lymph node involvement, the median number of positive para-aortic nodes was 5 (range, 1 to 13).

Postoperative treatment consisted of 6 cycles of platinum-based chemotherapy for 9 women, 3-4 cycles of platinum-based chemotherapy followed by external pelvic beam irradiation for 20 women (one of these had additional brachytherapy), and external pelvic beam irradiation in 5 women (of these, two received additional para-aortic irradiation and one received additional brachytherapy).

The chemotherapy regimen consisted of paclitaxel plus carboplatin in 9 patients, epidoxorubicin plus paclitaxel plus cisplatin in 6, epidoxorubicin plus cisplatin in 12, and cyclophosphamide plus epidoxorubicin plus cisplatin in 2.

Tumour relapsed in 14 out of the 34 patients (41.2%), with a median time to recurrence of 17 months (range, 9.5-42 months). The primary relapse involved distant sites in four patients (lung: 2, peritoneum: 1, lung and liver: 1), retroperitoneal lymph nodes in eight patients (para-aortic in 6, pelvic in 2), and multiple sites in two patients (vagina, peritoneum and pelvic lymph nodes in one, and vagina and para-aortic lymph nodes in one). Vaginal recurrence therefore developed in 5.9% of the patients (2/34), distant recurrence in 14.7% (5/34), pelvic lymph node recurrence in 8.8% (3/34), and para-aortic lymph node recurrence in 20.6% (7/34). Distant failure occurred in one (11.1%) of the 9 patients who received six cycles of chemotherapy versus 4
(20.0%) out of 20 patients who received 3-4 cycles of chemotherapy followed by irradiation.

Five-year disease-free survival was 45.3% (Table I).

Treatment at recurrence was as follows. Of the four women with distant recurrence, two received chemotherapy and died of disease after 3 and 6 months, respectively, one died of lung embolism within one week, and the remaining patient one underwent surgery (lung resection) plus chemotherapy and is still alive with no evidence of disease after 12 months. As far as the eight women with lymph node failure are concerned, four underwent chemotherapy and died of disease after 6, 9, 10 and 17 months, respectively; one patient had chemotherapy plus radiotherapy and died of disease after 8 months; one patient received radiotherapy and died of cardiovascular disease after 45 months, one patient refused any treatment and is still alive with disease after 2 years, and the remaining patient is currently under evaluation. The two women with multiple recurrences underwent surgery plus chemotherapy and died of disease after 12 and 61 months, respectively.

Five-year overall survival was 60.5% (Table II).

Discussion

Different surgical procedures can be performed to assess the retroperitoneum, ranging from biopsies of enlarged lymph nodes, to selective lymph node sampling from multiple sites, to systematic pelvic and para-aortic lymphadenectomy (3-8, 12). Retroperitoneal lymph node metastasis is a critical prognostic factor for endometrial cancer, and therefore staging lymphadenectomy allows a better prediction of the clinical outcome. However, its therapeutic potential is still matter of debate. Two randomized trials failed to detect any significant advantage in terms of disease-free survival and overall survival for patients who underwent pelvic lymphadenectomy compared to those who did not (10, 11). However, the conclusions of these studies have been criticized because of several biases (22-24). According to the FIGO Annual Report n.26, 5-year survival was 57.3% for stage IIIc (FIGO 1988) endometrial cancer, and, in particular, it was 61.0% for G2 stage IIIc disease and 51.4% for G3 stage IIIc disease (13).

Many authors have investigated the role of adjuvant radiotherapy and/or chemotherapy for early-stage, high-risk or advanced-stage endometrial cancer, but only few have analyzed the efficacy of postoperative treatment selectively for stage IIIc disease (6, 7, 9, 12, 15, 16). Early papers reported that extended-field (pelvic plus para-aortic) irradiation achieved long-term disease-free survival in about 50% of women with para-aortic lymph nodal involvement (25, 26). Mariani et al. (7) reviewed 122 patients with node-positive endometrial cancer, of whom 94 (77%) had adequate pelvic lymphadenectomy (removal of ≥10 lymph nodes) and 47 (39%) had adequate para-aortic lymphadenectomy (removal of ≥5 lymph nodes). Pelvic and para-aortic
radiotherapy was administered to 78% and 29% of patients, respectively. The five-year pelvic sidewall failure rate was 57% for women who had inadequate pelvic lymphadenectomy and/or no radiotherapy versus 10% for those who had both adequate pelvic lymphadenectomy and radiotherapy (p<0.001). The 5-year para-aortic failure rate was 34% after adequate para-aortic lymphadenectomy without para-aortic radiotherapy, 69% after para-aortic radiotherapy without adequate para-aortic lymphadenectomy, and 0% after adequate para-aortic lymphadenectomy and radiotherapy. However, extended-field irradiation is sporadically used in clinical practice due to both the risk of severe bowel complications and the suggestion that para-aortic node involvement is associated with systemic spread of disease. In recent years, some authors have investigated the role of chemotherapy in patients with node-positive endometrial cancer (6, 9, 12, 15, 17, 27). Fujimoto et al. (9) reported a 5-year overall survival of 62.6% in 63 women with stage IIIc disease who underwent systematic pelvic lymphadenectomy with or without para-aortic lymphadenectomy followed by 5-6 cycles of platinum-based or platinum/paclitaxel-based chemotherapy. Five–year overall survival was 43.5% and 82.4% for women with and without para-aortic metastases, respectively (p=0.039). Similarly, Watari et al. (6) reported a 5-year overall survival of 79.6% among 55 patients with tumour positive nodes who underwent pelvic and para-aortic lymphadenectomy followed by platinum-based chemotherapy. Five-year overall survival was 86.4% for women with negative para-aortic nodes, 60.4% for those with one positive para-aortic node, and 20.0% for those with two or more positive para-aortic nodes, and these differences were statistically significant. In the study of Randall et al. (16), comparing whole-abdominal irradiation versus platinum/doxorubicin–based chemotherapy for advanced endometrial cancer, the analysis of the subset of women with stage IIIc disease showed that chemotherapy was superior to radiotherapy in terms of both progression–free survival (p=0.040) and overall survival (p=0.044). The addition of paclitaxel to platinum-based chemotherapy has been found to improve progression survival and overall survival of women with advanced endometrial cancer (28).

In our study, pelvic and para-aortic lymphadenectomy were carried out in 34 (100%) and 18 (52.9%) of the 34 women, respectively, whereas adjuvant chemotherapy, chemotherapy followed by radiotherapy, and radiotherapy were used in 9 (26.5%), 20 (58.8%), and 5 (14.7%) women, respectively. The rate of adequate pelvic lymphadenectomy (79.4%) was similar to that of Mariani et al. (7), whereas the rate of adequate para-aortic lymphadenectomy was slightly lower (29.4%). After a median follow-up of 33 months, vaginal, distant, pelvic node, and para-aortic node recurrence were 5.9%, 14.7%, 8.8% and 20.6%, respectively. Five-year overall survival was 60.5% (62.5% for stage IIIc1 and 57.0% for stage IIIc2). These results compare favorably with those of the literature (6, 7, 9, 13).

In conclusion, FIGO stage IIIc1-IIIc2 endometrial cancer relapses in approximately 40% of cases, and distant sites and para-aortic nodes represent the common sites of failure. The retrospective, non-randomized nature of the study and the limited number of women do not allow us to draw any conclusions regarding the impact of postoperative treatment on the pattern of recurrences. Recent studies have suggested a possible role for the combination of adjuvant chemotherapy and radiotherapy in women with high-risk endometrial cancer, including those with node-positive disease (12, 20, 29, 30).

References