

Definitive and palliative radiotherapy for cervix cancer in the elderly

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Summary

The elderly population is increasing in number. Aggressive therapeutic intervention in this patient group may not always be possible because of age, the presence of co-morbidity, and poor functional status. Hence, individualized management of cervix cancer (CC) in the elderly is often practiced. Because of the preceding consideration, the cases of 79 women 65 years of age and older with CC treated with radiation over the last 20 years were reviewed. The cases were classified into two groups – those who were aggressively irradiated (group 1: 43 patients) and those managed less intensively for palliation (group 2: 36 patients). Local tumor control, complications, and survival were assessed. There were fewer extremely aged (≥ 75 years of age) women ($p = 0.006$) with advanced stage disease ($p = 0.012$) in group 1 than in group 2. Also, group 1 women experienced fewer treatment failures ($p < 0.0003$) and more of them were alive and well at last follow-up ($p < 0.005$) than those from group 2. The median survival periods for groups 1 and 2 were 60 months and 11 months, respectively ($p < 0.0001$); the corresponding 5-year crude survival rates were 54% and 19%, respectively ($p = 0.002$). Two women required remedial surgery for bowel obstruction/perforation after irradiation, and one patient sustained chronic radiation cystitis.

Key words: Uterine cervix; Cancer; Radiotherapy.

Introduction

The literature is replete with reports of cervical cancer (CC) in the elderly, focusing on the risk of non-treatment [1,2], effects or usefulness of radiotherapy (RT) [3, 4], outcome of patients with Stage IIIB disease [5], prognosis mostly [6], or their tolerance to RT compared to younger women [7]. Because not all elderly patients are deemed suitable for definitive/aggressive RT, we compared all women in our experience who were irradiated to such a full course of treatment with those who were treated for palliation with an abbreviated radiotherapeutic regimen. The current study was designed to investigate the outcomes of older patients with CC managed with such radiation treatment objectives (reports of which are sparse [8]).

Materials and Methods

Out of 1,316 patients diagnosed with CC at our institution between May 1980 and December 1999, we retrospectively identified and studied 79 elderly (65 years of age and older) women who had been treated by radiation. Their records were reviewed to obtain the following data: age, tumor histology, disease stage, hemoglobin values (the mean value if more than one was recorded), the presence of comorbid illnesses, radiation therapy and follow-up information. All patients' disease was staged according to the American Joint Committee on Cancer system [9]. Investigative studies included chest radiography (33 patients); computed tomography of the chest, abdomen, and pelvis (21 patients); intravenous pyelogram (40 patients); barium enema (20 patients); cystoscopy (25 patients); and proctoscopy (17 patients).

The patients were assigned to a group depending on the therapeutic intent: group 1 (definitive/radical RT, 43 patients) or group 2 (palliative RT, 36 patients). For the purpose of this study, radical RT (the technique of which is similar to that previously reported [10]) was defined as megavoltage external beam pelvic irradiation with intracavitary tandem and ovoids brachytherapy or vaginal cuff brachytherapy in posthysterectomy situations (e.g., early stage cervix for tumor-positive resection margins or cervical stump carcinomas), or the application of continuous pelvic teleirradiation to total doses exceeding 60 Gy using the "shrinking field" technique; such a technique consisted of whole pelvis irradiation to a total dose of 45 Gy, and then an additional dose (ranging from 16 to 23 Gy) to a smaller area – the true pelvis. On the other hand, RT was defined as being given with a palliative intent when the total dose with external beam pelvic irradiation alone was less than 40 Gy, or was 60 Gy using the shrinking-field technique but given in a split-course/protracted manner; and when the additional dose (after external beam irradiation) from intracavitary (ovoids alone) brachytherapy use was considered insufficient for Stage IIIB disease. The mean dose for pelvic teleirradiation in groups 1 and 2 were $44 \pm$ (standard deviation) 3.3 Gy (range 40 to 50 Gy) and 37 ± 12.7 Gy (range 12 to 50 Gy), respectively. There were only two women whose disease was also treated with chemotherapy (either cisplatin or 5-fluorouracil).

Follow-up ranged from 3 to 153 (median 22) months. Survival was calculated from the diagnosis of CC until death or the date when the patient was last known to be alive. The patient data of the two treatment groups were compared using the chi-square test (for categorical variables) and the Wilcoxon rank sum test (for the numeric variables, e.g., age, hemoglobin values). A non-parametric test rather than a parametric one such as the t-test was employed to compare the numeric variables of the two cohorts due to the observed non-normality of age and hemoglobin information.

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Results

The mean age at diagnosis was 74 ± 6.9 years. Most of the patients possessed well differentiated tumors and comorbid illnesses as well as lower hemoglobin values (Table 1). Also, there were fewer extremely aged (≥ 75 years of age) women ($p = 0.006$) with advanced stage disease ($p = 0.012$) in group 1 than in group 2 patients.

Hypertension was the most common coexisting illness (with 33 affected patients) followed by heart disorders (14 patients), diabetes mellitus (10 patients), cerebrovascular disease (6 patients), another primary malignant tumor of the breast/bladder/lung (4 patients), and other significant maladies such as Hashimoto's thyroiditis, diverticulosis, or peripheral vascular disease (3 patients).

Of the 30 women with Stage IIIB CC, ten had bilateral pelvic wall involvement. Six patients had Stage IVA disease because of bladder (3 patients), proximal urethra (1 patient), rectal (1 patient), or bladder with rectal (1 patient) invasion by neoplasm. Seven women possessed Stage IVB CC due to extrapelvic nodal metastatic lesions in the paraaortic/mediastinal/supraclavicular sites (4 patients); imaging-demonstrated spread to the lungs (2 patients); and confirmed metastasis to the umbilicus - Sister Mary Joseph's nodule (1 patient).

Radical RT was not applied in 36 (46%) of the 79 studied patients for varying reasons: patient/family refusal, severe concomitant health problems, restrictive anatomy, and/or extremely frail condition. The frequency with which palliative versus aggressive RT was executed was greater in the ≥ 75 years of age group (Table 1).

Table 1. — Demographic Data.

| Feature | Radiotherapy | |
|--|---------------------|------------------------|
| | Radical (n = 43) | Palliative (n = 36) |
| Histology: | | |
| Squamous cell carcinoma | | |
| Well differentiated | (23) | (26) |
| Moderately differentiated | (8) | (1) |
| Poorly differentiated | (10) | (6) |
| Adenocarcinoma | (2) | (2) |
| Adenosquamous carcinoma | — | (1) |
| Age: | | |
| 65-74 yrs | (30) | (14) |
| ≥ 75 yrs | (13) | (22) |
| Stage ^a | | |
| IB | (12) | (4) |
| IIA-IIIB | (12) | (6) |
| IIIA-IIIB | (17) | (16) |
| IVA | (2) | (4) |
| IVB | — | (6) |
| Other illness ^b | (29) | (25) |
| Hemoglobin ^c ≥ 12 g/ml | (10) | (10) |

^aAmerican Joint Committee on Cancer staging system; ^bHypertension, diabetes mellitus, peptic ulcer, congestive heart failure, Hashimoto's thyroiditis, rheumatic valvular/Alzheimer's/cerebrovascular/coronary artery disease, diverticulosis, bladder/breast/lung cancer; ^c65 evaluable patients.

The overall 5-year crude survival rates for Stages I, II, III, and IV were 41%, 47%, 30%, and 11%, respectively; accordingly, the median periods of survival were 58 months, 57 months, 18 months, and 7.5 months.

At last follow-up (Table 2), more patients from group 1 were alive and well than women from group 2 ($p < 0.005$). Moreover, the majority of the patients tolerated their RT course. The median survival periods for groups

Table 2. — Results.

| Variable | Radiotherapy | |
|------------------------------|---------------------|------------------------|
| | Radical (n = 43) | Palliative (n = 36) |
| Status ^a | | |
| ANED | 35% ^b | 8% ^c |
| DNED | 49% | 31% |
| DWD | 16% | 61% |
| Acute morbidity ^d | 30% ^e | 31% ^f |
| Complication ^g | 7% | — |

^aANED = Alive without cancer; DNED = Died without cancer; DWD = Died with cancer; ^bSurvival ranging from 10 to 153 months; ^cSurvival ranging from 20 to 80 months; ^dGastrointestinal, genitourinary, or dermal manifestations; ^e27 evaluable patients; ^f16 evaluable patients; ^genteric or bladder radiation injury.

1 and 2 were 60 months and 11 months respectively, $p < 0.0001$; the corresponding survival rates at 5 years were 54% and 19%, respectively ($p = 0.002$). Fewer treatment failures were observed in group 1 than group 2 ($p < 0.0003$); the local relapse rates for groups 1 and 2 were 12% (5/43) and 56% (20/36) respectively ($p < 0.0001$); the corresponding extrapelvic and distant failure rates were 7% (3/43) and 8% (3/36), $p > 0.99$.

Long-term complications were observed in three women from group 1. A patient who experienced radiation cystitis six years after RT is still alive and free of cancer another six years later. Two women underwent corrective surgery for bowel perforation or obstruction that was noted immediately after treatment in one patient and more than five years post-irradiation in the other. These two women lived five and nine years respectively, following therapy. All three patients had known risk factors (e.g., significant illness like hypertension and previous surgery/total colectomy for diffuse colonic diverticulosis) which predisposed them to radiation injury.

Univariate analysis (Table 3) shows that younger age, early stage CC, radical RT, and the non-occurrence of any type of treatment failure favorably affected prognosis to a significant degree. However, after multivariate analysis, the intent of RT and the absence of disease relapse proved to be the only independent predictors of long-term survival.

Table 3. — Prognostic Factors.

| Variable | | Median survival in months | p value |
|----------------------------|-----------------|------------------------------|---------|
| Age | < 75 yrs | (44) ^a | 57 |
| | ≥ 75 yrs | (35) | 25 |
| Disease stage ^b | 1-2 | (34) | 58 |
| | 3-4 | (45) | 16 |
| Other illness | Absent | (25) | 33 |
| | Present | (54) | 24 |
| Hemoglobin level | < 12 Gm/dl | (45) | 28 |
| | ≥ 12 Gm/dl | (20) | 57 |
| Treatment failure | Absent | (50) | 61 |
| | Present | (29) | 6 |
| Treatment | Radical | (43) | 60 |
| | Palliative | (36) | 11 |

^a() Number of evaluable patients; ^bAmerican Joint Committee on Cancer staging system.

Table 4. — Literature review of the effects of radiotherapy for cervix cancer in the elderly.

| Author | No. of patients | Age in yrs. (mean/median) | Stage | Morbidity rate ^a | Complication rate | 5-year Survival rate | | |
|-------------------------------|-----------------|---------------------------|--------|-----------------------------|-----------------------------|--------------------------|------------|------|
| Chapman [6] | 300 | 73 | I | 53 | NS ^b | NS | I | 34% |
| | | | II | 110 | | | II | 25% |
| | | | III | 95 | | | III | 25% |
| | | | IV | 42 | | | IV | 12% |
| Lindegaard <i>et al.</i> [3] | 114 | 75 | I | 25 | 5% | Grade 3 11% | I | 61% |
| | | | II | 32 | | | II | 34% |
| | | | III | 55 | | | III | 25% |
| | | | IV | 2 | | | | |
| Mitchell <i>et al.</i> [7] | 60 | 77 | I B | 26.7% | Grade 2-3 < 1% to 7% | Grade 2-3 5% to 8% | I B -II A | 68% |
| | | | IIA-B | 50% | | | II B- IV A | 32% |
| | | | IIIA-B | 23.3% | | | | |
| Mitsuhashi <i>et al.</i> [4]] | 126 | 75.8 | I | 13 | 1 | Grade 3-4 10% | I | 100% |
| | | | II | 26 | | | II | 81% |
| | | | III | 69 | | | III | 73% |
| | | | IV | 18 | | | IV | 54% |
| Minagawa <i>et al.</i> [5] | 102 | 67 | III B | | NS | NS | III B | 48% |
| Sablinska [8] | 85 | 76.7 | I | 5 | - | 41% | I | 3 |
| | | | II | 40 | | | II | 48% |
| | | | III | 40 | | | III | 43% |
| This series | 79 | 74 | I | 16 | Grade 2 30% ^c | Grade 3 4% | I | 41% |
| | | | II | 18 | | | II | 47% |
| | | | III | 33 | | | III | 30% |
| | | | IV | 12 | | | IV | 11% |

Numbers refer to number of patients unless specified.

^aGastrointestinal, genitourinary, and cutaneous side effects; Gynecology Oncology Group toxicity criteria (McGonigle *et al.* [20]);

^bNS=Not stated; ^cThirteen of 43 evaluable patients experienced treatment-related side effects.

Discussion

It is estimated that by the year 2030 one in five of the American population will be an elderly person [11], and women will be predominant in this group [12]. Sixty percent of all cancer happens in the elderly [11]. Carcinogenesis in this select age group can perhaps be ascribed to their prolonged exposure to carcinogenic substances and the known fact that increased oncogen activation occurs with the ageing of cells and tissues [13].

The biology of aging is a complex process. There is deterioration of immune function and a progressive decline in physiologic reserves in older individuals [14]. These phenomena can decrease the quality of life, increase toxicity with the application of treatment, and further reduce life expectancy.

In CC, the natural history of the disease argues for aggressive therapy. Moreover, uncontrolled malignancy can be associated with a poor quality of life and lead to death [15]. On the other hand, the fact that cancer becomes a less prominent cause of death [16, 17] as age increases would lend support for a less intensive, palliative course of treatment. Although cure is also the preferred outcome for this particular group of people, its benefits may be tempered by competitive causes of death and the risk of therapeutic complications [18].

A recent report by Trimble and colleagues [1] evaluated the treatment patterns among women with CC in the United States. The study (which was composed of 13,715 patients from the National Cancer Institute's Surveillance, Epidemiology, and End Results program) found that as the age at diagnosis increased, the percentage of women receiving RT alone increased (compared to treatment by surgery alone or surgery combined with irradiation).

Also, in another patterns of care analysis of 1,582 women comparing those age < 70 years with those ≥ 70 years, Wright *et al.* [2] noticed that there was a strong bias toward treating younger patients surgically and older individuals with RT.

Advanced age is perhaps deemed unsuitable for aggressive treatment because significant coexisting illnesses are present in 24% to 63% of elderly patients with CC [4, 7, 8]. However, this viewpoint can be questioned because of the fact that those individuals who reach 65 years of age can expect another 17 years of life [12].

Attitudes among the oncology staff concerning the selection of the type of radiotherapeutic management of disease in this cohort are likely to be multifactorial and reflect both physician and patient preferences [2]. Therapy decisions, especially those made between radical or palliative courses of treatment, should be based on medical judgment, a humanistic appreciation of the patient's needs and wishes [16] and the patient's functional status.

The development of CC in older patients is not necessarily tantamount to a terminal event (Table 4). The most striking findings of the present study were the survival and local relapse differences depending upon the radiotherapeutic intent. These observations correspond to reports confirming that aggressive RT is associated with improved survival [7,8,19] and pelvic tumor control [19]. Overall treatment-related acute morbidity was usual and complications not exceedingly high in this limited experience. For several years now, we have also applied chemoradiation to our CC patients. However, our combined therapy patient population has been mostly of the younger age group.

We recognize that the retrospective design and the

present patients (mostly treated with radiation alone) representing a selected group are some of the limitations of the present study. Nonetheless, the observed acceptable toxicity and reasonable tumor control as well as survival in this series seem to legitimize RT (with an intent to cure) even though it may be restricted to certain cases. The cautious administration of both tele- and brachyradiotherapy in this particular patient group should ordinarily be considered unless the tumor is very small or such treatment is precluded by peculiar anatomy, debility, severe co-morbid illness, and extreme age.

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