Two things become apparent to the reader of this excellent article. First, the National Cancer Institute clearly had great foresight in 1970, when they began funding the Gynecologic Oncology Group (GOG) so that phase I, II, and III trials could be conducted in a systematic manner. Second, the authors have written a thorough review of over 3 decades of research into the biology and clinical aspects of cervical and vulvar cancer. In this short space, it would be impossible to adequately comment on the 50 studies reviewed by the authors. However, based on these studies, I would posit the rationale for a paradigm shift in the staging of cervical cancer, and would add (to paraphrase Mark Twain), "the report of the complete demise of hydroxyurea as a radiation sensitizer may be an exaggeration."

Like the GOG, since 1971, we have been researching many of the same issues in cervical and vulvar carcinoma: the importance of the size of the cervical lesion and lymph node metastasis in the survival of patients with stage IB cervical cancer[1]; the importance of surgical staging by para-aortic lymphadenectomy in locally advanced stage IIB, III, or IVA cervical cancer[2]; the use of para-aortic radiation in cervical cancer patients with documented para-aortic lymph node metastasis[3]; the use of the radiation sensitizer hydroxyurea in locally advanced cervical cancer[4]; the value of pelvic lymphadenectomy in central lesions of the vulva[5]; and the rates of survival, recurrence, and inguinal lymph node metastasis in vulvar cancer.[6]

Because of the rarity of vulvar cancer in the United States—only 3,800 cases and 800 deaths are predicted for 2002[7]—new advances in the treatment of this disease will be slow and probably only result from well-designed studies conducted by cooperative groups such as the GOG. Moreover, with the 5-year survival in early-stage (IB) cervical cancer being greater than 90%, studies documenting improvement will be difficult. However, progress in the treatment of locally advanced (ie, stage IIB-IVA) cervical cancer is essential if survival is to be improved in the 21st century.

Surgical Staging

Because endometrial, ovarian, and vulvar cancer (and almost all other solid tumors) are surgically staged prior to decisions being made about postoperative therapy, it would appear that this same rationale would lead to progress in locally advanced cervical cancer if the full extent of disease is surgically documented prior to initiating radiation therapy. This is particularly germane given the lack of sensitivity and specificity of radiologic imaging studies in the diagnosis of para-aortic lymph node metastasis from cervical cancer.

In 1977, I reported on 100 consecutive patients with stage IIB, IIIB, and IVA cervical cancer who underwent preradiation para-aortic lymphadenectomy.[2] Of these, 28% had metastasis to the para-aortic lymph nodes, which are outside the field of standard pelvic radiation: 13.6% of stage IIB, 36.7% of stage IIIB, and 57.1% of stage IVA patients had para-aortic lymph node metastasis (Table 1). Looking at these percentages in another way, the highest possible cure rate for all 100 patients would be 72%, in the unlikely possibility that all such patients had their localized disease eradicated. For patients found to have para-aortic node metastasis, more uniform extended-field therapies may eventually lead to improved survival even in women with a poor prognosis.

Radioresistance
How to overcome the radioresistance of large cervical tumors remains the most critical issue in improving the cure rate. Nearly 35 years ago, in their seminal report on radiation therapy in locally advanced cervical cancer, Fletcher and Rutledge demonstrated that significantly increasing the energy of the radiation therapy unit (from kilovoltage in 1948-1954 to megavoltage in 1954-1963) did not improve 5-year survival in patients with stage IIB, III, or IVA cervical cancer (Table 2).[8]

Thus, it became apparent that the higher megavoltage radiation did not overcome the radioresistance of these large tumors. Furthermore, increasing the dose of pelvic irradiation was not an option because the radiation dose is limited by the tolerance of the normal tissue, ie, the bladder and intestinal tract.

**Hydroxyurea**

For decades, researchers looked for agents that could be combined with radiation therapy to improve survival rates. One method of radiation sensitization was to synchronize cells within the mitotic cycle so that they received radiation during a radiosensitive portion of the cell cycle. Sinclair first proposed a basis for the possibility that hydroxyurea preferentially destroys the relatively radioresistant cells synthesizing DNA (S phase) and collects the surviving cells in their radiosensitive G1/S phase.[9]

Using X-HeLa cells, Phillips and Tolmach subsequently demonstrated that hydroxyurea prevents the repair of sublethally damaged irradiated cells.[10] Finally, using human cervical carcinoma cells, Kuo et al concluded that the radiation sensitization of cervical carcinoma is more significant with postirradiation exposure to clinically achievable concentrations of hydroxyurea.[11]

In 1983, my colleagues and I conducted a small prospective double-blind randomized study of hydroxyurea vs placebo administered during radiation therapy and for 4 weeks postirradiation in surgically staged (negative para-aortic lymph nodes), stage IIB cervical cancer patients. We reported a statistically significant improvement in survival among those who received hydroxyurea plus pelvic irradiation vs those who received placebo plus pelvic irradiation.[4]

In 1993, GOG-56, a phase III trial in 294 surgically staged patients with stage IIB, III, and IV disease and negative para-aortic lymph nodes, found a 5-year progression-free survival of 52.8% for the hydroxyurea arm vs 42.4% for the misonidazole arm (P = .05). The investigators concluded that among patients with locally advanced carcinoma of the cervix, "hydroxyurea continues to be the agent of choice with radiation."[12] This study is notable for the fact that all patients had negative para-aortic nodes confirmed by surgical staging and had been followed for at least 5 years until death. However, hydroxyurea was given only during external radiotherapy, arguably negating one of the major mechanisms of action of the agent—ie, postirradiation exposure to hydroxyurea to prevent repair of sublethally damaged cancer cells.

**Cisplatin as a Radiation Sensitizer**

Cisplatin is the single most active cytotoxic agent against metastatic squamous cell carcinoma of the cervix. However, only a small body of preclinical data demonstrate that cisplatin is actually a radiation sensitizer. In fact, after studying 19 cloned human cervical tumor cell lines, Britten and coauthors concluded “that concomitant cisplatin/radiotherapy regimens may result in higher level of local control, but primarily through additive toxicity and not through radiation sensitization.”[13]

In GOG-120, a phase III trial in surgically staged patients with a median follow-up of less than 3 years, 65% of those who received weekly cisplatin or hydroxyurea, fluorouracil, and cisplatin during radiation survived, compared with 47% of those who received only radiation therapy (P = .002).[14] This trial and four others reported improved survival with cisplatin-based chemotherapy plus radiation vs radiation therapy alone.

These findings resulted in a paradigm shift when the National Cancer Institute in 1999 notified all US physicians of the superiority of cisplatin-based chemotherapy plus radiation therapy vs radiation therapy alone in locally advanced cervical cancer. Notably, in the one trial that required cisplatin-based chemotherapy during radiation and for two cycles post-radiation therapy, only patients who received the four cycles of chemotherapy (which included the two cycles of chemotherapy after completion of radiation therapy) showed a survival benefit.[15]

**Conclusions**

The reported median follow-up in GOG-120—the trial of cisplatin-based chemotherapy plus radiation—was 2.9 years. With a longer follow-up, the 65% survival seen in that trial might approach the 53% survival seen in the earlier GOG-56 trial of hydroxyurea plus radiation (in which patients were followed for 5 or more years until death), notwithstanding the fact that hydroxyurea was given only during radiotherapy.

At the beginning of the 21st century, most patients with locally advanced cervical cancer will and should receive cisplatin-based chemotherapy during radiation therapy. However, it is clear that we
are still searching for the best radiation potentiator in this setting and that there may still be a role for agents with a mechanism of action similar to that of hydroxyurea.

References:


Source URL:
http://www.physicianspractice.com/review-article/advances-treatment-gynecologic-malignancies-2

Links: