Radiotherapy Research in Gynecologic Cancer

Antonio P. G. Vigliotti, MD, 
David H. Hussey, MD, 
B-Chen Wen, MD, 
Shirish K. Jani, PhD, and 
J. Fred Doornbos, MD

University of Iowa College of Medicine
Iowa City, Iowa

There has been significant improvement in the treatment for gynecologic cancers over the years, and radiation therapy has played a major role in these advances. These improvements result in part from a better knowledge of the biologic behavior of gynecologic tumors and in part from the development of new radiation therapy equipment and a refinement of brachytherapy techniques. Nevertheless, many patients with advanced gynecologic malignancies still are not cured. To improve the results of radiotherapy, many clinical trials have been performed during the last several decades.

This article reviews many of the major radiotherapy research programs performed for gynecologic cancer over the last 15 years. These have been directed mainly at 1) the management of locally advanced gynecologic tumors, and 2) the treatment of areas of regional metastasis.

Research Aimed at Locally Advanced Cancers

In general, the two biologic factors that determine the probability of local control by irradiation are 1) the number of clonogenic malignant cells, and 2) the proportion of malignant cells in a hypoxic state. As the volume of cancer increases, the probability of control diminishes when irradiation is the sole treatment modality. Although control rates can be improved by increasing the dose of irradiation, this result is achieved at the cost of significant irradiation sequelae. In the past 15 years, a variety of clinical studies have been performed to evaluate ways to improve the local control of bulky gynecologic cancers. These have included combinations of radiotherapy and hyperbaric oxygen or hypoxic cell sensitizers, fast neutron radiotherapy, and combined radiotherapy and surgery.

Hyperbaric Oxygen

The radiosensitizing properties of oxygen have been known for many years. How-
However, it was first proposed for clinical use in 1953 by Gray et al., who noted that radiosensitization was greater for tumors than for normal tissues. Subsequently, Thomlinson and Gray found indirect histologic evidence for hypoxic regions in human tumors. Based on these observations, radiotherapists began clinical trials of hyperbaric oxygen (HBO) and radiotherapy in the late 1950s.

The HBO studies involved placing patients in hyperbaric chambers and pressurizing them to 3–4 atmospheres of oxygen for 30–45 minutes before irradiation. The rationale was that one could saturate the plasma and tissue fluids with oxygen under pressure so that it would diffuse greater distances through respiring tissue to reach hypoxic tumor cells. With 3 atmospheres pressure, oxygen diffuses1,000 μ through respiring tissue instead of the usual 150–200 μ.

The results of the HBO trials for cervical carcinoma are summarized in Table 1. A variety of fractionation schedules were used for these studies. Some institutions selected abbreviated fractionation for both the HBO and the control groups because radiobiologic data showed a greater therapeutic gain for HBO when relatively few large fractions of radiation were used. Others chose conventional daily fractionation for both groups because this was considered the best standard form of treatment. In one study, abbreviated fractionation was used for the HBO arm and conventional fractionation for the control arm.

In general, the studies in which abbreviated fractionation schedules were used reported the greatest benefit from HBO. For example, the British series from Portsmouth and Oxford showed a threefold improvement in local tumor control with the use of HBO and almost twice the patient survival. However, the local control and survival rates for the patients treated in air were significantly lower than one would expect with well-fractionated radiation therapy, indicating that abbreviated fractionation was suboptimal.

The results of the trials in which conventional fractionation schedules were used for both arms were less impressive. The study that showed the greatest advantage was a British study from Mount Vernon and Glasgow. In that study, an 18–24% improvement in local tumor control and 10–15% improvement in patient survival was noted. However, there was also a significantly greater number of complications in the group for which HBO was used, so that the therapeutic gain with HBO was less than these figures would indicate.

Most of the other trials in which conventional fractionation was used failed to show an advantage with HBO. The largest series was reported from M. D. Anderson Hospital, where 233 patients with stage IIB, III, or IVA uterine cervix cancer were treated with conventional fractionation in HBO or in air, usually followed by intra-cavitary radium. The local tumor control rate was 82% in HBO, compared with 74% in air. The morbidity was slightly greater with the use of HBO (33% complications in HBO versus 28% in air), and patient survival was less (33% in HBO versus 41% in air).

In the mid-1970s the Radiation Therapy Oncology Group (RTOG) initiated a randomized clinical trial using a different schedule for each arm. Abbreviated fractionation was used for the patients for which HBO was used because the greatest therapeutic gain with HBO had been reported from studies in which abbreviated fractionation schedules were used. Conventional fractionation was used for the control patients because the best results in air had been achieved with well-fractionated irradiation. In both treatment arms therapy was completed with intra-cavitary radium when indicated. The RTOG study showed no improvement with
### TABLE 1. Clinical Trials of Hyperbaric Oxygen and Radiotherapy for Locally Advanced Carcinoma of the Uterine Cervix

<table>
<thead>
<tr>
<th>Investigator</th>
<th>No. Patients</th>
<th>Dosage Schedule</th>
<th>Local Control</th>
<th>Complications</th>
<th>Survival</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Studies using abbreviated fractionation schedules</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Bates and Churchill-Davidson²</td>
<td>43</td>
<td>3,600 rads/6Fx/18 days</td>
<td>12% HBO</td>
<td>36% HBO</td>
<td>@ 5-yr follow-up (nonrandomized)</td>
<td></td>
</tr>
<tr>
<td>2. Wiernik and Perrins*</td>
<td>30</td>
<td>4,250 rads/10Fx/31 days ± radium or hysterectomy</td>
<td>46% HBO vs 32% air</td>
<td>@ 2-yr follow-up</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Ward et al.*</td>
<td>45</td>
<td>3,150 rads/10Fx/29 days</td>
<td>60% HBO vs 68% air</td>
<td>74% HBO vs 76% air</td>
<td>@ 1-yr follow-up</td>
<td></td>
</tr>
<tr>
<td>4. Watson et al.²⁶ (Portsmouth)</td>
<td>37</td>
<td>3,500–3,600 rads/6–7Fx/18–22 days</td>
<td>58% HBO vs 18% air</td>
<td>42% HBO vs 17% air</td>
<td>@ 3-yr follow-up</td>
<td></td>
</tr>
<tr>
<td>5. Watson et al.²⁶ (Oxford)</td>
<td>34</td>
<td>4,250 rads/10Fx/31 days ± radium</td>
<td>45% HBO vs 13% air</td>
<td>35% HBO vs 24% air</td>
<td>@ 3-yr follow-up</td>
<td></td>
</tr>
<tr>
<td><strong>Studies using conventional fractionation</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6. Watson and Banerjee²⁷</td>
<td>16</td>
<td>25Fx/5wks</td>
<td>1/11 HBO</td>
<td>4/11 HBO</td>
<td>@ 2-yr follow-up (nonrandomized)</td>
<td></td>
</tr>
<tr>
<td>7. Johnson and Walton⁸</td>
<td>71</td>
<td>~6,000 rads/30Fx/6wks</td>
<td>39% HBO vs 16% air</td>
<td>35% HBO vs 16% air</td>
<td>@ 5-yr follow-up (nonrandomized)</td>
<td></td>
</tr>
<tr>
<td>8. Tobin et al.*</td>
<td>14</td>
<td>Conv. fractionation</td>
<td>22% HBO vs 6% air</td>
<td>35% HBO vs 16% air</td>
<td>@ 5-yr follow-up (nonrandomized)</td>
<td></td>
</tr>
<tr>
<td>9. Watson et al.*⁹</td>
<td>80</td>
<td>4,250 rads/20Fx/4 wks + radium</td>
<td>Early results favor HBO</td>
<td>3/7 HBO vs 4/7 air</td>
<td>Early results same</td>
<td></td>
</tr>
<tr>
<td>10. Dische et al.*¹¹</td>
<td>77</td>
<td>5,500 rads/27Fx/5½wks + radium</td>
<td>68% HBO vs 55% air</td>
<td>41% HBO vs 43% air</td>
<td>Unlimited follow-up</td>
<td></td>
</tr>
<tr>
<td>11. Glassburn et al.*¹²</td>
<td>40</td>
<td>5,000–6,000 rads/20–24Fx/5–6wks + radium</td>
<td>55% HBO vs 48% air</td>
<td>47% HBO vs 39% air</td>
<td>@ 27-month follow-up</td>
<td></td>
</tr>
<tr>
<td>12. Fletcher et al.*¹³</td>
<td>233</td>
<td>4,000–6,500 rads/20–35Fx/4–7wks ± radium</td>
<td>82% HBO vs 74% air</td>
<td>37% HBO vs 28% air</td>
<td>Unlimited follow-up</td>
<td></td>
</tr>
<tr>
<td>13. Watson et al.⁸⁶ (Mt. Vernon)</td>
<td>127</td>
<td>4,250–4,500 rads/20Fx/28 days + radium</td>
<td>85% HBO vs 61% air</td>
<td>55% HBO vs 40% air</td>
<td>@ 3-yr follow-up</td>
<td></td>
</tr>
<tr>
<td>14. Watson et al.⁸⁶ (Glasgow)</td>
<td>56</td>
<td>5,500 rads/27Fx/38 days + radium</td>
<td>70% HBO vs 52% air</td>
<td>42% HBO vs 32% air</td>
<td>@ 3-yr follow-up</td>
<td></td>
</tr>
<tr>
<td><strong>Study using abbreviated HBO and conventional fractionation in air</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15. Brady et al.*¹⁴ (RTOG)</td>
<td>48</td>
<td>4,000 rads/10Fx/5wks + radium in HBO 5,000 rads/25Fx/5wks + radium in air</td>
<td>74% HBO vs 76% air</td>
<td>32% HBO vs 24% air</td>
<td>Unlimited follow-up</td>
<td></td>
</tr>
</tbody>
</table>

* Randomized studies.
† Twenty percent complications in HBO vs 9% in air (Pooled results from Portsmouth, Oxford, Glasgow, and Mount Vernon).
HBO. The group treated in HBO had a 74% local control rate, compared with 76% for those treated in air; and complications developed in 32% of the group treated in HBO, compared with 24% for those treated in air. At the time of analysis 41% of the patients treated in HBO and 37% of the control patients were alive.

In summary, the value of HBO as an adjunct to radiation therapy for uterine cervix cancer remains unproven. It appears to add something when suboptimal abbreviated fractionation schedules are employed, but it adds little to what can be achieved with well-fractionated external beam irradiation and well-planned brachytherapy. Fractionating the irradiation permits more opportunity for reoxygenation between dose fractions, and brachytherapy delivers a much higher dose to the central, presumably hypoxic, part of the tumor. These results may indicate that hypoxia is not an important cause of local failure in cervical cancer when good radiotherapy techniques are employed. On the other hand, it may be that oxygen is not reaching the hypoxic cells even under hyperbaric conditions and perhaps other means of circumventing the hypoxic cell problem will be more successful.

**Hypoxic Cell Sensitizers**

Another approach to the problem of the hypoxic tumor cell is the use of drugs that mimic oxygen in its ability to sensitize hypoxic cells. Because hypoxic cells are confined to tumors, these drugs specifically sensitize tumor cells, while not affecting the radiation response of normal tissues.

The hypoxic cell sensitizers first were proposed by Adams in the early 1960s. He noted that oxygen sensitizes cells to radiation by binding electrons in free radicals and suggested that other electron affinic compounds would be effective radiosensitizers. Theoretically, these drugs have an advantage over oxygen in that they are not rapidly metabolized by tumor cells. To develop a clinically useful drug, Adams et al.\(^\text{15}\) screened many compounds and classified them according to their electron affinity and pharmacologic properties.

At present, the compounds showing the most potential for clinical application are the nitroimidazoles.\(^\text{16}\) Of these, metronidazole (Flagyl, Searle Pharmaceuticals, Chicago, Ill.) and misonidazole have been studied most extensively. Many drugs of this type are being tested in the laboratory, and several have considerable potential for clinical application.\(^\text{17,18}\)

The misonidazole studies\(^\text{16,19-23}\) for uterine cervix cancer are listed in Table 2. Pilot studies had shown that cumulative doses greater than 12 g/m\(^2\) resulted in significant neurotoxicity, and yet the effectiveness of the drug is directly related to the amount of misonidazole administered with each radiation fraction. In formulating these protocols, one had to choose between 1) delivering small, but less effective drug doses with conventional radiotherapy fractionation, which is well tolerated by normal tissues, or 2) using larger and more effective drug doses in combination with abbreviated radiotherapy fractionation, which is poorly tolerated by normal tissues. Although abbreviated fractionation schedules were used in several pilot studies, conventional fractionation with small daily doses of misonidazole was used in all of the randomized trials.

The largest randomized trial was a cooperative study performed in the Scandinavian countries.\(^\text{21}\) At last report, 341 patients with stages IIB, III, and IVA cervical cancer had been entered into this trial and treated with 5 weeks of external beam irradiation and brachytherapy, with or without daily misonidazole (total: 12 g/m\(^2\)). Although a final report has not been published, the preliminary results showed no benefit from the addition of misonidazole.

In Great Britain, the Medical Research Council randomized 153 patients with Stage III cervical cancer.\(^\text{22}\) A minimum tumor dose of 4,200 rads was given in 20
**TABLE 2. Clinical Trials of Misonidazole and Radiotherapy for Locally Advanced Carcinoma of the Uterine Cervix**

<table>
<thead>
<tr>
<th>Study</th>
<th>Radiation Dosage Schedule</th>
<th>No. Patients</th>
<th>Misonidazole Dose</th>
<th>Local Tumor Status</th>
<th>Radiotherapy Complications</th>
<th>Misonidazole Complications</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonrandomized studies</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phillips et al.(^16)* (RTOG 79-05)</td>
<td>27</td>
<td>1,000 rads × 3</td>
<td>4 g/m²Fx (total: 12 g/m²)</td>
<td>27% complete regression</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Phillips et al.(^16) (RTOG 79-06)</td>
<td>17</td>
<td>400 rads × 10 + external boost</td>
<td>1.25 g/m²Fx (Max: 12.5 g/m²)</td>
<td>41% complete regression</td>
<td>—</td>
<td>71% peripheral neuropathy</td>
<td>—</td>
</tr>
<tr>
<td>Girinski et al.(^19)</td>
<td>29</td>
<td>5,000 rads/5½ wks + brachytherapy</td>
<td>0.5–0.6 g/m²Fx for 1st and last 2 wks of treatment (total: 11–14 g/m²)</td>
<td>62% local control</td>
<td>—</td>
<td>18% peripheral neuropathy</td>
<td>70% @ 3 yr</td>
</tr>
<tr>
<td>Thomas et al.(^20)</td>
<td>58</td>
<td>4,500 rads/20 Fx/4 wks + brachytherapy</td>
<td>Randomized doses: no drug 0.15 g/m²Fx × 22 0.30 g/m²Fx × 22 0.45 g/m²Fx × 22</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Randomized studies</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Scandinavian Study(^21)</td>
<td>341</td>
<td>25 fractions + brachytherapy</td>
<td>Daily (total: 12 g/m²) Control group (no drug)</td>
<td>No benefit</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Medical Research Council(^22)</td>
<td>139</td>
<td>4,200 rads/20 Fx/4 wks + brachytherapy</td>
<td>0.5 g/m²Fx (total: 12 g/m²) Control group (no drug)</td>
<td>64% complete regression 68% complete regression</td>
<td>15%</td>
<td>36% neurotoxicity</td>
<td>51% @ 2 yrs</td>
</tr>
<tr>
<td>Leibel et al.(^23) (RTOG 80-05)</td>
<td>119</td>
<td>4,600 rads/4½–5 wks + brachytherapy or external boost</td>
<td>0.4 g/m²Fx (Max: 12 g/m²) Control group (no drug)</td>
<td>38% local control 48% local control</td>
<td>5%</td>
<td>3% GI toxicity</td>
<td>52% @ 1½ yrs</td>
</tr>
</tbody>
</table>

*Clinical material for RTOG 79-05 included massive pelvic cancers of any site.*
fractions over 4 weeks, followed by intra-
cavitary radiation to a dose of 3,500 rads at
Point A. The patients were randomized to
receive or not receive 500 mg/m² miso-
nidazole (total: 12 g/m²). Again, no im-
provement in results was observed. The
complete response rate was 64% with miso-
nidazole, compared with 68% with radio-
therapy alone. Complications developed in
15% of the patients treated with miso-
nidazole, compared with 17% of those
treated with radiotherapy alone; and 51% of
the patients treated with misonidazole
were alive 2 years later, compared with
55% of those treated with radiotherapy
alone.

The RTOG recently reported a random-
ized trial of 119 patients with stage IIB, III,
or IVA squamous carcinoma of the cervix. A
dose of 4,600 rads in 23 frac-
tions over 4½ weeks was delivered to the
whole pelvis, followed by a 1,000-rad boost
to the parametria and an intracavitary
application or an external beam boost to
the primary tumor. The experimental
group received 400 mg/m² misonidazole
before each treatment (maximum: 12 g/m²).
The addition of misonidazole to irradi-
ation not only failed to improve the survival
for these patients, but may have in fact
been detrimental (Table 2). The local tu-
mor control rate was 38% for the group
treated with misonidazole compared with
48% for the group treated with radio-
therapy alone. Furthermore, only 52% of
the patients receiving misonidazole were
alive 18 months later, compared with 70%
of those treated with radiotherapy alone.

In summary, the studies of combined
radiotherapy and misonidazole for uterine
cervix cancer have not shown a benefit
from the addition of the drug. This is
largely because of drug toxicity, which
limits the misonidazole dose to levels
that are relatively ineffective in a well-
fractionated treatment schedule. The
search for new and better hypoxic cell sen-
sitizers continues, and new drugs may be
developed that are less toxic and more ef-
fective clinically.

Fast Neutron Therapy

Neutrons are nuclear particles that, like x-
rays, deposit their energy exponentially as
they pass through tissue. Neutrons have no
physical dose distribution advantage over
x-rays and gamma rays. They do produce
more dense ionizations than x-rays or
gamma rays, however, and this results in
different biologic properties. Most im-
portantly, fast neutrons are less dependent
on oxygen for their biologic effect. Other
important differences include a dimin-
ished capacity to repair sublethal radiation
damage with neutrons and less depend-
ence of radiosensitivity on the phase of
the cell cycle. Theoretically, fast neutrons
should be more efficient than x-rays or
gamma rays in treating slowly proliferat-
ing, relatively hypoxic cancers.

Over the past decade, several clinical
trials of fast neutron therapy have been
performed for gynecologic malignancies—
one at the National Institute of Radi-
ological Sciences (NIRS) in Chiba, Japan, and
another at M. D. Anderson Hospital
using the Texas A&M Variable Energy
Cyclotron (TAMVEC). In both of these
institutions, a combination of neutrons and
high-energy x-rays has been employed,
usually followed by intracavitary irra-
diation.

The NIRS clinical trial was a non-
randomized study of 98 patients with stage
IIB squamous carcinoma of the uterine
cervix. In that study, patients treated with
a mixed beam of neutrons and photons
were compared with a similar group of pa-
tients treated with photons alone when the
cyclotron was not available for neutron
therapy. The patients treated with a mixed
beam received neutron treatments twice a
week and photon treatments three times a
week for 5 weeks (720 rads in 10 fractions
with neutrons and 2,550 rads in 15 frac-
tions with photons), whereas the patients
treated with photons received 5,000–5,500 rads in 25–28 fractions over 5–5 ½ weeks. These doses are approximately equivalent because neutrons are approximately three times more effective biologically than photons. All patients were treated subsequently with high-dose-rate intracavitary irradiation to a dose of 1,100–1,300 rads at Point A.

No significant improvement in results was achieved with mixed-beam irradiation (Table 3). Mixed-beam irradiation produced a 73% local control rate, compared with 66% with photons alone; and major complications developed in 6% of the patients treated with a mixed beam, compared with 10% of the photon group. The actuarial 5-year survival rates were identical for both groups (49%).

At M. D. Anderson Hospital, a series of pilot studies was performed in the early 1970s, and these led to a randomized clinical trial in 1977. The pilot studies evaluated 1) neutrons only, 2) a neutron boost following photon irradiation, 3) a mixed beam of neutrons and photons, and 4) photons only. The randomized trial compared mixed-beam and photon irradiation, the treatment regimens that had given the best pilot study results. The aim for all of these studies was to deliver a dose biologically equivalent to 5,000 rads photon irradiation in 5 weeks to the whole pelvis and then reevaluate for completion of treatment with intracavitary radium or an external beam boost. The clinical material included mainly patients with stage IIIB, III, or IVA squamous carcinoma of the cervix.

A comparison of the pilot study results showed a greater local control rate with mixed-beam irradiation (61%) than with photons only (48%), but there was no improvement in the complication rate (7% with mixed beam versus 8% with photons) or survival rate (56% with mixed beam versus 55% with photons alone) (Table 3). The worst results were achieved with neutrons only (29% local tumor control, 12% complications, and 6% patient survival), although the clinical material for this group of patients was slightly more advanced and they were treated in an earlier phase of the program, when dosage schedules were not well established.

An analysis of the randomized clinical trial failed to show an advantage with either mixed-beam irradiation or photons only (Table 3). In that study, mixed-beam irradiation resulted in a 58% local control

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**TABLE 3. Clinical Trials of Fast Neutron Therapy for Locally Advanced Carcinoma of the Uterine Cervix**

<table>
<thead>
<tr>
<th>Study Type</th>
<th>No. Patients</th>
<th>Local Control</th>
<th>Complications</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>NIRS pilot studies</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mixed beam + cathetron</td>
<td>45</td>
<td>73%</td>
<td>6%</td>
<td>49%†</td>
</tr>
<tr>
<td>Photons + cathetron</td>
<td>53</td>
<td>66%</td>
<td>10%</td>
<td>49%†</td>
</tr>
<tr>
<td>TAMVEC pilot studies</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutrons only ± radium</td>
<td>17</td>
<td>29%</td>
<td>12%</td>
<td>6%</td>
</tr>
<tr>
<td>Neutron boost ± radium</td>
<td>20</td>
<td>55%</td>
<td>20%</td>
<td>45%</td>
</tr>
<tr>
<td>Mixed beam ± radium</td>
<td>59</td>
<td>61%</td>
<td>7%</td>
<td>56%</td>
</tr>
<tr>
<td>Photons ± radium</td>
<td>40</td>
<td>48%</td>
<td>8%</td>
<td>55%</td>
</tr>
<tr>
<td>TAMVEC random study</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mixed beam ± radium</td>
<td>43</td>
<td>58%</td>
<td>9%</td>
<td>53%</td>
</tr>
<tr>
<td>Photons ± radium</td>
<td>32</td>
<td>59%</td>
<td>6%</td>
<td>59%</td>
</tr>
</tbody>
</table>

*Five-year follow-up.
†Unlimited follow-up.
‡Actuarial 5-year survival.
rate, compared with 59% with photons alone. There was a 9% incidence of complications with mixed-beam irradiation compared with 6% with photons alone and a 53% survival rate with mixed-beam irradiation, compared with 59% with photons only.

The failure of neutron therapy to improve the control rate of gynecologic cancers may have resulted from technical problems associated with the cyclotrons used in these studies or to the poor dosimetric properties of neutron beams. However, neutron therapy also has failed to improve the local control rate for cancers of other sites, e.g., head and neck, where technical problems and dosimetric properties are not as critical. The negative results of these studies are more likely due to inherent properties of neutrons, e.g., a greater absorption in fat, or a greater biologic effectiveness for normal tissue injury.

**Radiotherapy and Surgery**

One of the most effective ways to circumvent the problem of the hypoxic tumor cell is through the use of combined surgery and radiation therapy. Surgery is used to remove gross masses that are too large to be eradicated by moderate doses of irradiation, and radiation therapy is used to eradicate microscopic extensions of tumor that cannot be excised. In some situations the surgery is more conservative than would be used if it were the sole treatment modality, and the radiation therapy dose is less than would be employed with radical irradiation alone.

Combined therapy has been used for a variety of gynecologic cancers, including certain carcinomas of the endometrium, ovary, vulva, and cervix. In cervical carcinoma it has been used to manage bulky endocervical cancers. These tumors tend to be infiltrative and necrotic and would be expected to have a large hypoxic cell compartment. Furthermore, they are less well suited for treatment with brachy-therapy because the peripheral part of the tumor is located remotely from the intracavitary sources. If there is no parametrial extension, endocervical cancers are amenable to treatment with an extracavitary hysterectomy and radiotherapy because they are encapsulated within the uterus.

The results of combined hysterectomy and radiation therapy for bulky and/or "barrel-shaped" carcinomas of the uterine cervix are shown in Table 4. In these studies, the results of surgery and radiation therapy are compared with those achieved with radiation therapy alone in the same institutions.

At M. D. Anderson Hospital, combined extracavitary hysterectomy and radiotherapy has been used for selected barrel-shaped endocervical cancers since the mid 1950s. A recent analysis shown that the addition of an extracavitary hysterectomy did not improve the control rate for tumors less than 6 cm in diameter, but for lesions more than 6 cm in diameter surgery reduced the incidence of central failures from 16 to 2%. Survival rates were not improved, however, because of a high incidence of distant metastasis. Initially, 11% (9 of 79) of patients treated with combined hysterectomy and radiation therapy had major complications develop. Since 1970 the surgical technique has been modified and the radiation dose has been limited to 4,000-rad whole pelvis irradiation and no more than 5,000 mg hours with intracavitary radium. With this regimen the complication rate has been reduced to 3% (2 of 78).

In 1979 Van Nagell et al. analyzed the results for stage IB squamous carcinoma at the University of Kentucky. The recurrence rate with radiation therapy alone was low for lesions smaller than 5 cm in size. For tumors larger than 5 cm in size, however, six of seven patients treated with radiotherapy alone had recurrent cancer develop, while none of the five patients treated with combined hysterectomy and
TABLE 4. Clinical Trials of Radiation Therapy Plus Hysterectomy for Carcinoma of the Uterine Cervix

<table>
<thead>
<tr>
<th>Institution</th>
<th>Stage/Size</th>
<th>Pelvic Failures</th>
<th>Complications</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Radiotherapy</td>
<td>Radiotherapy</td>
<td>Radiotherapy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Only</td>
<td>+ Hysterectomy</td>
<td>Only</td>
</tr>
<tr>
<td>M. D. Anderson&lt;sup&gt;27, 28&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>&lt;6 cm</td>
<td>6% (12/217)*</td>
<td>4% (4/95)*</td>
<td>11% before 1970</td>
</tr>
<tr>
<td></td>
<td>&gt;6 cm</td>
<td>16% (10/63)*</td>
<td>2% (1/48)*</td>
<td>3% after 1970</td>
</tr>
<tr>
<td>Univ. of Kentucky&lt;sup&gt;29&lt;/sup&gt;</td>
<td>IB, &lt;5 cm</td>
<td>7% (3/44)&lt;sup&gt;†&lt;/sup&gt;</td>
<td>—</td>
<td>7% (6/92)</td>
</tr>
<tr>
<td></td>
<td>IB, &gt;5 cm</td>
<td>6/7&lt;sup&gt;†&lt;/sup&gt;</td>
<td>0/5&lt;sup&gt;†&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Mallinkrodt Institute of Radiology&lt;sup&gt;30&lt;/sup&gt;</td>
<td>IB, nonbarrel</td>
<td>3% (7/279)</td>
<td>11% (10/90)</td>
<td>88% @ 5 yrs</td>
</tr>
<tr>
<td></td>
<td>IB, barrel</td>
<td>17% (7/41)</td>
<td>7% (1/14)</td>
<td>63% @ 5 yrs</td>
</tr>
<tr>
<td>Univ. of Florida&lt;sup&gt;31&lt;/sup&gt;</td>
<td>IB-II B, 6-8 cm</td>
<td>30% (15/50)</td>
<td>36% (10/28)</td>
<td>68% @ 3 yrs</td>
</tr>
<tr>
<td></td>
<td>IB-II B, &gt;8 cm</td>
<td>45% (5/11)</td>
<td>29% (4/14)</td>
<td>43% @ 3 yrs</td>
</tr>
<tr>
<td>NewYork Medical College&lt;sup&gt;32&lt;/sup&gt;</td>
<td>11B</td>
<td>—</td>
<td>—</td>
<td>5% (1/20) fistulae</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>15% (3/20 uropathy</td>
</tr>
</tbody>
</table>

* Central failures.
† Tumor recurrence, site not specified.
§ Nineteen of 21 patients with radiotherapy and hysterectomy (11 extrafascial and 10 radical) had surgical specimens with negative results.
<sup>†</sup> Four of 19 patients with radical hysterectomy and 0 or 5 patients treated with extrafascial hysterectomy had major complications develop.
radiotherapy had recurrent cancer develop.

At the Mallinkrodt Institute of Radiology, combined irradiation and hysterectomy resulted in no significant improvement in patient survival for patients with stage IB non–barrel-shaped cancers, compared with those treated with radiation therapy alone (Table 4). However, the pelvic failure rate for the barrel-shaped tumors was reduced from 17 to 7% with the addition of surgery. The principal site of failure for these bulky cancers was distant metastasis, which ranged from 32 to 40% for barrel-shaped tumors, compared with 10 to 25% for non–barrel shaped tumors.

The usefulness of combined extraperitoneal hysterectomy and radiation therapy has been challenged recently by several authors. Weems et al. found no improvement in local control for patients with stages IB–IIIA carcinomas measuring 6–8 cm in diameter. Furthermore, Rotman et al. found no evidence of tumor in the surgical specimens of 90% (19 of 21) of patients treated with the combined approach. Because of this, and because of a greater complication rate with adjunctive surgery and a significant metastasis rate with bulky cancers, they concluded that combined therapy is not routinely indicated.

In 1984 the Gynecologic Oncology Group (GOG) and the RTOG initiated a prospective randomized trial to evaluate the role of adjunctive extraperitoneal hysterectomy and radiation therapy in uterine cervix cancer. In this study, patients with bulky stage IB carcinomas of the uterine cervix and negative lymph nodes have been randomized to receive radiation therapy alone or combined radiation therapy and extraperitoneal hysterectomy.

In summary, the results of retrospective studies show a decreased incidence of central failures with the combination of extraperitoneal hysterectomy and radiation therapy, but patient survival has not been improved, largely because of a high incidence of distant metastasis. In the early years combined therapy resulted in a significant complication rate, but the morbidity has been reduced as surgical techniques have been improved and radiotherapy doses limited.

Research Aimed at Regional Metastasis

The decision to treat sites of regional metastasis should take into account the relative probabilities of regional and hematogenous metastasis and the likelihood of controlling the regional metastasis without serious complications. In general, tumor size is the principal feature determining the effectiveness of irradiation for the eradication of a cancer. Other factors being equal, regional metastases are no less radiosensitive than the cancer at the primary site. However, the irradiation of sites of regional spread often requires large portals, and the volume of normal tissues included in these portals limits the dose that can be delivered safely.

A variety of clinical studies have been performed over the past 15 years to evaluate ways to control regional metastases from gynecologic cancers. These have included the use of extended-field irradiation for uterine cervix cancer and whole abdominal irradiation for ovarian cancer.

Extended Field Irradiation

In the early 1970s, researchers at several institutions performed studies to evaluate the effectiveness of paraaortic irradiation in selected patients with uterine cervix cancer. These studies were based on the observation that carcinoma of the cervix tends to spread in an orderly fashion, first to the pelvic lymph nodes, and then to the paraaortic nodes, with distant metastases occurring relatively late. The rationale was that paraaortic treatment could cure a subset of patients, if the disease was confined to the regional nodes but small enough to be eradicated with moderate doses of radiotherapy.
The clinical trials varied considerably with regard to the extent of the tumor and the surgical and radiotherapy techniques employed (Table 5). Some institutions treated patients with gross disease in the common iliac and/or paraaortic areas with radiation, whereas others resected all gross tumor before radiation therapy was started. Several studies included all patients, regardless of nodal status. Transperitoneal lymphadenectomy was performed in most institutions, although the standard procedure was an extraperitoneal lymphadenectomy in several hospitals. In a few institutions staging was determined by lesser surgical procedures such as a biopsy or node sampling, or clinically by lymphangiography. The radiotherapy dose usually ranged between 4,500 and 5,000 rads in 4½–5½ weeks, but some patients received doses as high as 6,000 rads. Intracavitary brachytherapy was employed to secure control of the disease within the pelvis after completion of the external beam irradiation.

The results are shown in Table 5. Patient survival ranged from 10 to 71%, but usually averaged 20–30%. The wide range in survival is not surprising, because some patients had early-stage pelvic disease, while others had extensive pelvic disease and gross metastasis in the paraaortic lymph nodes.

In 1979 the RTOG initiated a randomized trial of localized versus extended field irradiation for patients with bulky stage IB, IIA, or IIB squamous carcinomas of the uterine cervix with clinically negative or unevaluated paraaortic lymph nodes. This study is ongoing, but the preliminary results show no difference in survival for the two treatment arms.

The major problem with extended field irradiation has been a high incidence of complications. Not unexpectedly, complication rates were influenced by the type of surgical procedure, the total dose of radiation, and the volume irradiated. In general, there was a higher incidence of complications with transperitoneal lymphadenectomies. For example, Piver reported a 45% incidence of major complications, and Berman a 30% incidence of small bowel damage following transperitoneal lymphadenectomies. On the other hand, a retroperitoneal approach by Berman resulted in only a 2.5% (1 of 39) incidence of major complications, and Ballon had no problems with small bowel obstruction in 18 patients staged by extraperitoneal lymphadenectomy.

In the M. D. Anderson series, the total dose to extended fields and the volume irradiated were the major factors determining complication rates. In that series, most patients were staged by lymphangiography and received no lymphadenectomy. El Senoussi et al. reported a 24% complication rate with 4,000–4,500 rads, a 44% complication rate with ~5,000 rads, and a 57% complication rate with 5,500–6,000 rads.* They concluded that 4,500 rads in 5 weeks was the maximum dose that could be delivered safely to extended fields. Wharton et al. reported a 4% (1 of 23) complication rate when the fields were extended to L4, compared with 19% (5 of 26) when the paraaortic area was included to T12.

Chism has pointed out that only 3% of all patients with uterine cervix cancer could benefit from extended field irradiation. Consequently, it is important to define the patient population more accurately if one is to show a benefit from this treatment. The decision to treat the regional lymphatics should take into account the control rate at the primary site, the relative probabilities of regional lymphatic and hematogenous metastasis, and the likelihood of controlling the lymph node metastasis without serious sequelae. In general, small aggregates of cancer cells in the regional lymphatics can be controlled.

*The complication rates reported by El Senoussi were greater because each complication was counted separately, and many patients had multiple complications.
TABLE 5. Clinical Trials of Extended Field Irradiation for Carcinoma of the Uterine Cervix

<table>
<thead>
<tr>
<th>Author</th>
<th>No. Patients</th>
<th>Stages</th>
<th>Lymphadenectomy</th>
<th>Status of Paraaortic Nodes</th>
<th>Dose</th>
<th>Survival</th>
<th>Major Complications</th>
<th>Fatal Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Silberstein</td>
<td>6</td>
<td>I–III</td>
<td>No</td>
<td>(+)</td>
<td>6,000 rads/6 wks</td>
<td>3/6</td>
<td>minimum 4 yrs</td>
<td>1/6</td>
</tr>
<tr>
<td>Averette</td>
<td>17</td>
<td>IB–IV</td>
<td>Transperitoneal</td>
<td>(+)</td>
<td>4,000–5,000 rads</td>
<td>18% NED @ 13–27 mos</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Lepanto</td>
<td>21</td>
<td>IB–IV</td>
<td>No</td>
<td>(+)</td>
<td>5,000 rads/5 wks</td>
<td>38% minimum 2 yrs</td>
<td>19%</td>
<td>5%</td>
</tr>
<tr>
<td>Rotman</td>
<td>42</td>
<td>IIB–IVA</td>
<td>No</td>
<td>(+) or (−)</td>
<td>4,500 rads/5 wks</td>
<td>71% @ 2 yrs</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Sudarsanam</td>
<td>21</td>
<td>IB–IV</td>
<td>Yes</td>
<td>(+)</td>
<td>4,000–4,320 rads/4–5 wks</td>
<td>19% @ 19–63 mos</td>
<td>1 small bowel obstruction</td>
<td></td>
</tr>
<tr>
<td>El Senoussi</td>
<td>257</td>
<td>IIB–IVA</td>
<td>Only 83 pts.</td>
<td>(−)</td>
<td>4,000–6,000 rads</td>
<td>19% unlimited follow-up</td>
<td>43%</td>
<td>11%</td>
</tr>
<tr>
<td>Hughes</td>
<td>22</td>
<td>IB–IVB</td>
<td>Node sampling</td>
<td>(−)</td>
<td>4,500–5,100 rads/5–6 wks</td>
<td>29% @ 5 yrs</td>
<td>5%</td>
<td></td>
</tr>
<tr>
<td>Ballon</td>
<td>18</td>
<td>IB–IV</td>
<td>Extraperitoneal</td>
<td>(+)</td>
<td>4,320–5,130 rads/30–60 days</td>
<td>23% NED @ 5 yrs</td>
<td>No small bowel obstruction</td>
<td></td>
</tr>
<tr>
<td>Piver</td>
<td>31</td>
<td>IB–IV</td>
<td>Biopsy or transperitoneal lymphadenectomy</td>
<td>(+)</td>
<td>4,400–6,000 rads/4.1/− 8 wks</td>
<td>10% @ 5 yrs</td>
<td>45%</td>
<td>16%</td>
</tr>
<tr>
<td>Tewfik</td>
<td>23</td>
<td>IIB–IVA</td>
<td>Transperitoneal</td>
<td>(+)</td>
<td>5,000–5,500 rads/5½–6 wks</td>
<td>23% NED minimum 45 mos</td>
<td>35%</td>
<td></td>
</tr>
<tr>
<td>Rubin</td>
<td>14</td>
<td>IB–IIA</td>
<td>Transperitoneal</td>
<td>(+)</td>
<td>4,000–5,000 rads/4–6 wks</td>
<td>50% NED</td>
<td>29%</td>
<td>7%</td>
</tr>
<tr>
<td>Berman (GOG)</td>
<td>98</td>
<td>I–IV</td>
<td>Usually transperitoneal</td>
<td>(+)</td>
<td>4,000–5,000 rads</td>
<td>25% @ 3 yrs</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Sudarsanam</td>
<td>37</td>
<td>IB–IV</td>
<td>Transperitoneal</td>
<td>(−)</td>
<td>4,000–4,320 rads/4–5 wks</td>
<td>54% @ 19–63 mos</td>
<td>11%</td>
<td>0%</td>
</tr>
</tbody>
</table>
in 80–90% of patients with a dose of 4,500 rads in 5 weeks. As the volume of cancer in the regional lymphatics increases, however, local control is more difficult to achieve with doses of this magnitude and there is a greater likelihood that occult distant metastasis already has occurred.

In summary, paraaortic nodal irradiation has not made a significant impact on patient survival in most clinical trials. In these studies the potential benefit of paraaortic irradiation has been offset by a high incidence of complications. This is not to say that extended field irradiation could not benefit a small subset of patients. The most likely way to improve the results of such studies would be 1) to better define the population of patients with curable paraaortic disease and no evidence of distant spread, and 2) to diminish the frequency of complications resulting from staging procedures and treatment.

**Whole Abdominal Irradiation**

A number of clinical trials have been performed in recent years to evaluate the effectiveness of adjunctive abdominal irradiation after cytoreductive surgery for invasive ovarian cancer. With ovarian cancer the whole abdominal cavity is at risk for metastasis and there can be spread of tumor through the regional lymphatics to the external iliac and/or paraaortic lymph nodes.

In 1969 researchers at M. D. Anderson Hospital initiated a randomized clinical trial\(^{48,49}\) comparing adjunctive whole abdominal irradiation using the moving strip technique versus chemotherapy. In this study, 186 patients with stages I–III ovarian cancer underwent a staging laparotomy and resection of as much gross cancer as possible, followed by either radiotherapy or melphalan. None of the patients had residual tumors larger than 2 cm in size. With the abdominal strip technique, the abdomen was divided into 1-inch segments, which were irradiated sequentially over a 7–8 week period. Each strip received a total dose of 2,600–2,800 rads in 8 fractions, and the whole pelvis was boosted with an additional 2,000 rads in 10 fractions.

There was no difference in 5-year survival for the two treatment arms. The actuarial 5-year survival rate was 71% for the radiation therapy group compared with 72% for the chemotherapy group. However, the radiotherapy technique was suboptimal because the diaphragm was not always irradiated and the liver was shielded. There was a difference in the type of complications observed in the two groups—11 patients (12%) in the radiation therapy group had small bowel complications develop, and 2 patients in the melphalan-treated group had blood dyscrasias develop (1—leukemia, 1—pancytopenia).

In 1971 researchers at Princess Margaret Hospital conducted a randomized trial\(^{50,51}\) for patients with stages IB–III disease who had undergone total abdominal hysterectomy and bilateral salpingo-oophorectomy for invasive ovarian carcinoma. The clinical material usually was limited to patients with residual tumor smaller than 2 cm. The patients were stratified by age and pathologic subtype and then randomized to receive 1) pelvic irradiation only (stages I–II), 2) pelvic irradiation plus chlorambucil (stages I–III), or 3) pelvic irradiation plus total abdominal irradiation using the moving strip technique (stages I–III). The pelvic dose was 4,500 rads for the first two groups and 2,250 rads (boost) for the moving strip. Unlike the M. D. Anderson technique, the domes of the diaphragm were encompassed in the treatment portals and there was no liver shielding. Furthermore, the dose to the whole abdominal portals was less (2,250 rads in 10 fractions).

The pelvic failure rates were similar for all three groups. This is not surprising because the radiotherapy dose to the pelvis was the same. However, the total failure
rate was approximately 30% less in the total abdominal irradiation group, presumably because of control of occult disease in the upper abdomen. This is reflected in a superior 5-year relapse-free survival rate for the patients treated with abdominal irradiation.

In an effort to reduce treatment time and acute toxicity, researchers at Princess Margaret Hospital performed a second randomized clinical trial in 1976. In this study, the whole abdomen was irradiated with either the moving strip technique (2,250 rads in 10 fractions) or with open fields (2,250 rads in 22 fractions). As in the previous study, the pelvis received an additional 2,250 rads in 10 fractions. The preliminary results showed no difference in patient survival between the two treatment arms. However, there were more late complications with the moving strip technique (6%—6 of 99) than with the open field technique (1.2%—2 of 172).

Further information regarding the dose—response relationship is provided by a Stanford study of 82 patients with stages I—III invasive ovarian carcinoma. A dose of 5,000—5,500 rads was delivered to the lower half of the abdomen over 4—7 weeks. Pelvic failures were observed in 3% of patients with no residual tumor after surgery, in 16% of patients with less than 2 cm residual tumor, and 45% of patients with more than 2 cm residual tumor. Not unexpectedly, local control rates in the pelvis correlated with the 10-year relapse-free survival rates (79% versus 49% versus 24%) (Table 6).

The Stanford results indicate that 5,000—5,500 rads can control occult disease or tumors less than 2 cm in size in more than 90% of patients, and the Princess Margaret Hospital results indicate 4,500 rads can control disease of this magnitude in approximately 75% of patients. Thus, ovarian carcinoma is at least as radiosensitive as epithelial carcinomas of other sites. The critical question, however, is whether subclinical disease can be controlled with doses that can be safely delivered to the whole abdomen. A dose of 2,250 rads in 10 fractions with the moving strip technique seems to be able to control occult disease in the upper abdomen in many patients, because the long-term relapse-free survival rate for patients receiving whole abdominal irradiation to this dose level was 30% greater than that for patients receiving no irradiation to the abdomen. The open field dose of 2,250 rads in 22 fractions is biologically less effective than 2,250 rads in 10 fractions, however, and it should be less likely to control abdominal disease in a significant number of patients.

References
8. Johnson RJR, Walton RJ. Sequential study on the effect of the addition of hyperbaric oxygen on the five-year survival rates of carcinoma of the cervix treated with con-
TABLE 6. Clinical Trials of Adjuvant Radiotherapy for Invasive Ovarian Cancer

<table>
<thead>
<tr>
<th>Institution</th>
<th>Stage</th>
<th>Tumor Burden</th>
<th>Randomization Groups</th>
<th>Radiotherapy Dose (rads)</th>
<th>Failures in the Pelvis</th>
<th>Total Failures</th>
<th>Complications</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDAH*</td>
<td>I–III</td>
<td>&lt; 2 cm</td>
<td>Moving strip (92 pts.)</td>
<td>2,800 abdomen + 2,000 pelvis</td>
<td>12% bowel injury</td>
<td>71% @ 5 yrs</td>
<td>1 leukemia</td>
<td>72% @ 5 yrs</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Melphalan (94 pts.)</td>
<td>—</td>
<td>1 pancytopenia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PMH†‡†</td>
<td>IB–III</td>
<td>23% no residual</td>
<td>Pelvis (31 pts.)</td>
<td>4,500 pelvis</td>
<td>20% 52%</td>
<td>27%</td>
<td>47% @ 5 yrs</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(1971–1975)</td>
<td>30% &lt; 2 cm</td>
<td>Pelvis + chlorambucil (51 pts.)</td>
<td>4,500 pelvis</td>
<td>20% 45%</td>
<td>37/1 sepsis</td>
<td>45% @ 5 yrs</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>41% uncertain</td>
<td>Moving strip (50 pts.)</td>
<td>2,250 abdomen + 2,250 pelvis</td>
<td>22% 22%</td>
<td>271 leukemia</td>
<td>78% @ 5 yrs</td>
<td></td>
</tr>
<tr>
<td>PMH‡</td>
<td>IB–III</td>
<td>56% 0 or</td>
<td>Moving strip (85 pts.)</td>
<td>2,250 abdomen + 2,250 pelvis</td>
<td>5% bowel injury</td>
<td>No difference</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>uncertain</td>
<td>Open field (81 pts.)</td>
<td>2,250 abdomen + 2,250 pelvis</td>
<td>1.2% bowel injury</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stanford‡</td>
<td>I–III</td>
<td>44% no residual</td>
<td>Not randomized</td>
<td>5,000–5,500 lower abdomen</td>
<td>No residual: 3% (1/36)</td>
<td>19% (7/36)</td>
<td></td>
<td>79% @ 10 yrs</td>
</tr>
<tr>
<td></td>
<td></td>
<td>32% &lt; 2 cm</td>
<td>II</td>
<td>&lt; 2 cm: 16% (4/26)</td>
<td>50% (13/26)</td>
<td>50% (13/26)</td>
<td></td>
<td>49% @ 10 yrs</td>
</tr>
<tr>
<td></td>
<td></td>
<td>24% &gt; 2 cm</td>
<td>II</td>
<td>&gt; 2 cm: 45% (9/20)</td>
<td>65% (13/20)</td>
<td>24% (6/25)</td>
<td></td>
<td>24% @ 10 yrs</td>
</tr>
</tbody>
</table>

* M. D. Anderson Hospital.
† Princess Margaret Hospital.
‡ BSOH—bilateral salpingo-oophorectomy and hysterectomy completed group.
§ Relapse-free survival.
∥ Complications from this article are not reported; however, there was a 14% (24/167) incidence of bowel injury requiring surgical intervention with 4,500–6,000 rads to the lower abdomen.\cite{51}
27. Wharton JT, Rutledge FN. Adjunctive surgical procedures with irradiation therapy


45. Rotman M. Personal communication.


