Management of stage 1 endometrial carcinoma - Postoperative radiotherapy is not justified in women with medium risk disease

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Fortunately, family physicians worldwide have managed to shine enough light on the world of frontline primary care practice to glimpse the potential enhancement offered by research done in networks of practices. They have done this largely through spirited volunteerism, the help of enlightened collaborators, and raw stubbornness. The paper this week by Thomas et al reports more progress in establishing one of the critical infrastructures for family practice and primary care research: the laboratory known as the practice based research network.1 As they note, early surveillance systems in the United Kingdom and the Netherlands inspired family physicians in other countries to create during the past 40 years research networks that explored frontline clinical practice.

These networks typically adapt to the characteristics of their practices, leaders, opportunities, and health systems. Just like other human organisations, they require leadership, personnel, communication systems, expert consultation, and time to mature. The descriptions of networks in the United Kingdom, Israel, and France, and the lessons reported in the paper by Thomas et al are consistent with experience elsewhere, from New Zealand to South Africa to Canada. Indeed, there is now a substantial literature that confirms that these networks are feasible and capable of important research that can affect not just a few people but virtually everyone.2–11

What these laboratories need now is broader recognition of their viability, importance, and impact, and acceptance that they merit sustained funding as a continuing infrastructure, akin to a reusable rocket. Such a rocket can carry different payloads at different times. And, over time, just as a space station can be created, a new understanding of how people get sick, how they get well, and how they stay healthy can be discovered using the reusable practice based research network. This journey has been and can continue to be as exciting as exploring outer space or revealing the genetic and molecular mechanisms of life. There must be well trained explorers with curiosity and ambition, and they must have helpers and tools such as measuring devices, classification and coding systems, and information systems.

Management of stage 1 endometrial carcinoma

Postoperative radiotherapy is not justified in women with medium risk disease

Endometrial adenocarcinoma mainly affects postmenopausal women. The mainstay of treatment is hysterectomy with bilateral salpingo-oophorectomy. Most women are diagnosed with stage I disease, where the tumour is limited to the body of the uterus. Within this stage the differentiation grade and depth of myometrial invasion are among the most important predictors for the presence of regional (pelvic and para-aortic) lymph node metastases and recurrence.1 2

In the absence of mature results from randomised trials, debate continues on the merits of pelvic and para-aortic lymphadenectomy and postoperative radiotherapy. The practice of lymphadenectomy varies considerably.3 Several opinion leaders, mainly from the United States, state that every woman with endometrial carcinoma should undergo complete lymphadenectomy. Some gynaecologists who as a rule do complete lymphadenectomies restrict themselves to selective node sampling in certain subgroups of women. One subgroup comprises patients who are less suited to complete lymphadenectomy because of age, obesity, or frailty from complicating medical problems—and up to 70% of patients with clinically early stage uterine cancer have significant coexisting cardiac, pulmonary, vascular, or endocrine disease.4 A second subgroup comprises those with a low risk of lymph node metastases.
The probability of regional lymph node metastases is 3-5% in patients with a well to moderately differentiated, superficially invasive primary tumour confined to the uterine body.1 These women have to be identified with a variety of preoperative and intraoperative diagnostic procedures of limited accuracy.

In many centres, especially in Europe, gynaecologists do not perform lymphadenectomy when pelvic lymph nodes are not suspicious. They argue that the benefit of lymphadenectomy is unclear. Indeed, claims of its intrinsic therapeutic value have been challenged.3 If lymphadenectomy is performed for diagnostic reasons then histological findings in the nodes should affect a decision on postoperative therapy, usually radiotherapy. Yet many patients with tumour negative nodes are referred for postoperative radiotherapy.

Doubts about the effects of postoperative radiotherapy in patients with adverse prognostic factors are common.5 Dutch investigators have recently described a randomised controlled trial of 714 women with medium risk stage I endometrial carcinoma—well differentiated tumours with deep (>50%) myometrial invasion, moderately differentiated carcinoma with any invasion, or poorly differentiated tumours with superficial (<50%) myometrial invasion.5 None of the patients underwent lymphadenectomy. In the irradiated group the five year locoregional recurrence rate was 4% and the five year overall survival rate 81%. In the non-irradiated (control) group these figures were 14% and 85% respectively. Mean follow up was 52 months. Thus these figures show no survival benefit from postoperative radiotherapy. Ten (100/(14 – 4)) patients would have to be irradiated postoperatively (46 Gy) to prevent one case of locoregional recurrence. A total of 40 patients from the non-irradiated group developed a locoregional relapse but only four died from it. Because of the limited duration of observation the investigators propose waiting for more mature results from salvage therapy before reaching final conclusions. In general, locoregional recurrences in non-irradiated patients are usually treated with radiotherapy (70 Gy), with an estimated overall cure rate of 67%.6

Based on the results from their trial the Dutch investigators have proposed new guidelines for the use of postoperative radiotherapy. They state that, in the absence of survival benefit, postoperative radiotherapy is justified when the absolute risk of locoregional recurrence is >10% or >15% and the risk of uncontrolled local disease after salvage treatment is high. On the basis of multivariate analysis they have identified two subgroups. In women with either a moderately differentiated, superficially invasive tumour or age <60 years the risk of locoregional relapse is estimated to be less than 5%. These women should not need radiotherapy. In the remaining group (age ≥60 years and superficially invasive, poorly differentiated tumour or deeply invasive, well to moderately differentiated tumour) the five year locoregional relapse rate is 18% in the non-irradiated women and 5% in the irradiated women. Here, 8 (100/(18 – 5)) patients need to be treated to prevent one locoregional recurrence without survival benefit.

According to the investigators, the grounds for postoperative pelvic radiotherapy are to prevent uncontrolled local disease and the physical and psychological morbidity of the diagnosis and treatment of a locoregional relapse. One has to ask whether dying from uncontrolled disease outside the pelvis is preferable to dying from disease in the pelvis. Given the 14% locoregional relapse rate in the non-irradiated group and 4% rate in the irradiated group, we estimate that about 30% (4/14) of the locoregional relapses are not prevented by radiation. Complications of radiotherapy do occur in 25% of patients and are severe in 2%. What is the impact of these complications for psychological functioning or more broader quality of life?

The great majority of the irradiated patients would never have had a locoregional recurrence. Adjuvant radiotherapy offers no survival benefit, fails to prevent locoregional recurrence in about 30% of patients, and harms many women who would never develop such a recurrence. It seems justified to abandon postoperative radiotherapy in patients with medium risk stage I endometrial carcinoma.

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