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TREATMENT OF EARLY CERVICAL CANCER: SURVIVAL, COMPLICATIONS AND ECONOMICAL ASPECTS

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The paper presents recent data on current methods of combined modality treatment of cervical cancer patients, comparative effectiveness of different regimes of neo-and adjuvant chemotherapy and cost-effective analysis.

Key words: cervical cancer, combined modality treatment, cost-effective analysis.

Cervical cancer is second only to breast cancer in being the most common cancer among women worldwide. Globally, cervical cancer is also the second most common cause of cancer-related mortality causing approximately 234.000 deaths annually among developing countries (sub-Saharan Africa, Central America and south-central Asia), yet only killing 40.000 women in developed nations [34]. The discrepancy in cervical carcinoma-related mortality between developing and developed countries is a direct result of poor screening (Pap testing) in low resource settings, and it is hoped that widespread vaccination against the human papillomavirus, which is associated with invasive cervical cancers, will dramatically reduce the morbidity and mortality of this highly preventable cancer [26].

Clinical and surgical staging

Staging describes the degree or severity of an individual's cancer based on the local extent of the primary tumour and/or its spread throughout the body. Gynaecologic cancers have traditionally been staged according to the FIGO system, based on clinical examination. There is now good evidence that CT scanning with intravenous contrast, office examination and biopsy are sufficient to stage a patient, while exam under anesthesia, cystoscopy and proctoscopy are reserved for those few patients in whom clinical or imaging data suggest a higher risk of involvement [15]. In evaluating the pelvic extent of disease, MRI appears to be superior to CT and clinical examination [4, 28]. Because of the superiority of PET to MRI and/or CT in detecting nodal metastasis, the United States Centers for Medicare and Medicaid Services has issued a national coverage determination paying for FDG-PET imaging for the detection of pretreatment metastases in newly diagnosed cervical cancer subsequent to conventional imaging that is negative for extrapelvic metastasis [50]. The most accurate method of detecting lymphatic metastasis is clearly surgical excision of the relevant nodal chains. This approach has two theoretical advantages over imaging assessments of the retroperitoneum. First, it is much more accurate in detecting nodal spread and only limited by the extent of the resection and the accuracy of the histological assessment of the resected lymph nodes. Second, the removal of grossly involved pelvic or aortic nodes might increase cure by rendering otherwise resistant bulky disease either on the pelvic sidewall or in the aortic area sensitive to the affects of chemotherapy and RT after bulk reducing surgery [18]. This theoretical advantage of bulk reducing surgery has been more thoroughly studied before the new era of multimodality therapy when RT was used alone but is probably still relevant today [29].

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The trend over the past decade has been to do less surgical staging with the advent of more accurate imaging modalities, such as MRI and PET. Interestingly, because the detection of otherwise occult aortic nodal metastasis through surgical staging allows extension of the pelvic radiation port to cover the periaortic area and thereby potentially improve cure rates, patients undergoing pelvic radiation alone who are thought to have negative aortic nodes by imaging should theoretically have a worse outcome than those found to have negative nodes after surgical staging [29]. This has been suggested by comparing the results of GOG trials before and after the transition from surgical staging to tomographic imaging (CT/MRI) staging. Stage III patients, in whom the risk of aortic nodal spread is highest, treated on GOG protocol 120, where surgical staging was required, had a significantly better outcome than those treated in a similar fashion (once per week cisplatin during pelvic RT) in another GOG trial (protocol 165) where surgical staging was optional and only performed on a minority of patients [20]. Importantly, this was before the widespread use of PET, but suggests the increased accuracy of surgical staging compared with CT or MRI. However, cross-study comparisons are difficult to interpret, and one must weigh the costs and operative morbidity of surgical staging in choosing the appropriate staging technique [29].

Prognostic factors

The most powerful predictor of survival among patients treated for locally advanced cervical cancer is the extent of disease expressed as FIGO stage. When disease is confined to the pelvis after surgical staging and patients are treated with once per week cisplatin and pelvic RT, the 4-year progression-free survival and overall survival rates for stage II patients are 64,2 % and 68,1 %, respectively, and 51,4 % and 55,4 % for stage III patients, respectively. The survival is much less for stage III patients when imaging rather than surgery is used to assess aortic spread with 4-year progression-free survival and overall survival being 37,7 % and 42,7 %, respectively [29]. In 1991, F.B. Stehman et al. [48] from the GOG conducted an analysis of prognostic variables from three GOG trials conducted between 1977 and 1985. Multivariate analysis showed patient age, performance status, aortic lymph node status, tumour size, and pelvic node status to be significantly associated with time to progression. When modelling for survival, all these factors, as well as clinical stage and bilateral extension within the pelvis, were also significant. These findings have been confirmed after analyzing more contemporary GOG trials where once per week cisplatin was used with pelvic RT [48]. Interestingly, in this multivariate analysis, stage, tumour grade, race, and age were all independently predictive of time to progression and overall survival in the new era of multimodality therapy (for all, $p<0,05$). Finally, the GOG has also shown that women who smoke while on therapy have a worse outcome than those that do not smoke during chemotherapy and RT [51]. Although squamous tumours and adenocarcinomas are the most frequent histological subtypes of cervical cancers, the prognostic significance of these different cell types is not clear. However, the preponderance of data suggest that they are prognostically equivalent in the era of chemoradiation therapy [44]. In contrast, neuroendocrine (small tumours) cancers have a worse prognosis stage for stage [2]. Clearly, tumours that do not respond to initial therapy have a worse outcome. One study suggested that the 5-year survival was only 32 % if persistent (in the irradiated region) abnormal FDG uptake in the cervix or lymph nodes was seen on average 3 months after therapy for locally advanced cervical cancer [12].

Treatment

The traditional treatment of invasive cervical cancer has been by surgery or radiotherapy (RT) or, in certain situations, a combination of both.

Radiotherapy/concomitant chemoradiotherapy

For more locally advanced disease, with spread beyond the uterus (stage IIB to IVA according to the FIGO staging system), RT is the primary modality of treatment [36]. Although women with bulky stage I lesions (4 cm, FIGO stage IB2) or bulky (4 cm) FIGO stage IIA lesions can be successfully treated with either neoadjuvant chemotherapy followed by either surgery or chemotherapy with RT or radical hysterectomy with pelvic and aortic lymphadenectomy followed by tailored postoperative therapy, the world standard is shifting toward including these two groups of patients into those more broadly entitled locally advanced cervical cancer, which has heretofore only included those patients with FIGO stages IIB, IIIB and IVA cancers. This is because the chance of bulky stage IB2 or bulky IIA tumors (defined as ≥4 cm in diameter) being associated with surgical and pathologic risk factors that increase the risk of recurrence is so high that chemotherapy with RT after neoadjuvant chemotherapy or after radical surgery is frequently required based on

carefully done prospective cooperative group trials [31, 38, 43, 47].

This makes the cost and morbidity prohibitive of three treatment modalities (surgery, RT, and chemotherapy) without clear evidence of therapeutic benefit compared with two treatment modalities (chemotherapy and RT). Standard primary treatment for stage IB2, IIA (4 cm), IIIB, and IVA cervical cancer without evidence of spread beyond the pelvis is chemotherapy and pelvic external-beam radiation and intracavitary brachytherapy. Those with nodal spread to the common iliac lymph nodes are treated with extended-field radiation similar to those with biopsy-proven aortic node metastasis because the risk of occult periaortic spread is so great. RT alone fails to control the progression of cervical cancer in 35 % to 90 % of women with locally advanced disease. Concurrent chemoradiation has been employed in the treatment of many cancers in an attempt to improve local control and eradicate distant metastases [29].

The standard prescription for RT used to treat bulky (stage IB2) or locally advanced cervical cancer generally considered to be FIGO stages IIA through IVA has been dictated by common practice and patterns of care studies [6, 7, 21, 33]. In contrast, the addition of concomitant chemotherapy to RT has been studied in a number of randomized prospective trials. In 1999, after publication of five trials, the National Cancer Institute (NCI) issued an alert recommending that "concomitant (cisplatin-based) chemoradiotherapy should be considered instead of radiotherapy alone in women with cervical cancer". This led to a change in the treatment for many women with cervical cancer [3]. Historically, chemotherapy given before or after radiation therapy for cervical cancer did not show improvement [41]. These five randomized phase III trials have shown an overall survival advantage for cisplatin-based therapy given concurrently with radiation therapy [16, 32, 38, 40, 49, 52], while one following trial examining this regimen demonstrated no benefit [35]. The patient populations in these studies included women with FIGO stages IB2 to IVA cervical cancer treated with primary radiation therapy, and women with FIGO stages I to IIA disease who, at the time of primary surgery, were found to have poor prognostic factors, which included the following:

– metastatic disease in pelvic lymph nodes;
– arametrial disease;
– positive surgical margins.

Although the positive trials vary somewhat in terms of the stage of disease, dose of radiation, and schedule of cisplatin and radiation, the trials demonstrate significant survival benefit for this combined approach. The risk of death from cervical cancer was decreased by 30 % to 50 % with the use of concurrent chemoradiation therapy. Based on these results, strong consideration should be given to the incorporation of concurrent cisplatin-based chemotherapy with radiation therapy in women who require radiation therapy for treatment of cervical cancer [3, 16, 32, 35, 38, 40, 41, 49, 52].

In the randomized control trials of W.A. Peters et al. [38] patients with clinical stage IA(2), IB, and IIA carcinoma of the cervix, initially treated with radical hysterectomy and pelvic lymphadenectomy, and who had positive pelvic lymph nodes and/or positive margins and/or microscopic involvement of the parametrium were eligible for the study and randomized to receive RT or RT + CT. Between 1991 and 1996, 268 patients were entered onto the study. Progression-free and overall survival are significantly improved in the patients receiving CT. The projected progression-free survivals at 4 years is 63 % with RT and 80% with RT + CT. The projected overall survival rate at 4 years is 71 % with RT and 81% with RT + CT. Grades 3 and 4 hematologic and gastrointestinal toxicity were more frequent in the RT + CT group [38].

Others two phase III trials have confirmed the superiority of cisplatin-based chemoradiation for the treatment of locally advanced cervical cancer. C.W. Whitney et al. [52] published the results of concurrent cisplatin plus FU and pelvic RT versus hydroxyurea plus pelvic RT in women with FIGO stage IIB-IVA disease who had undergone surgical staging and were found to have negative common iliac and aortocaval lymph nodes (GOG protocol 85). Among 368 eligible patients, the median follow-up time among survivors was 8,7 years. Disease progression occurred in 43 % of patients randomly assigned to cisplatin plus FU versus 53 % of patients randomly assigned to hydroxyurea. Progression-free survival was significantly better among patients treated with the combined chemotherapy regimen ($p<0,033$), with 3-year survival rates of 67 % (cisplatin and FU arm) versus 57 % (hydroxyurea). P.G. Rose et al. [40] reported the results from the three-arm GOG trial of pelvic RT plus concurrent: single-agent cisplatin versus cisplatin plus FU plus hydroxurea versus hydroxurea alone (protocol 120). All patients had FIGO stage IIB-IVA cervical cancer with

surgically confirmed negative common iliac and aortocaval lymph nodes. The median duration of follow-up was 35 months for 526 women included in the final analysis. Significant improvements in progression-free and overall survival were observed in patients randomly assigned to either cisplatin-containing arm. Effectively, the results from GOG protocol 85 and GOG protocol 120 were critical in supplanting hydroxurea as the radiosensitizer of choice.

Excluding patients with nodal involvement by CT scan, GOG protocol 123 evaluated the benefit of preoperative chemoradiation therapy (once per week cisplatin 40 mg/m^2, maximal weekly dose of 70 mg) versus RT alone in patients with locally advanced disease confined to the cervix (ie, stage IB2) [16]. All patients underwent adjuvant hysterectomy. In this landmark study, the rates of both progression-free survival ($p<0,001$) and overall survival ($p<0,008$) were significantly higher in the combined therapy group at 4 years. Patients receiving radiosensitizing chemotherapy experienced higher frequencies of grade 3 and grade 4 adverse haematological effects and adverse gastrointestinal effects.

M. Morris et al. [32] reported the results from RTOG protocol 90-01. In this study, the effects of pelvic radiation plus concurrent cisplatin and fluorouracil (FU) were compared with pelvic radiation plus extended field RT. This was the only trial to include chemotherapy during LDR brachytherapy. Eligibility requirements for this study differed from the previous GOG studies with the inclusion of patients with FIGO stage IB2-IIA tumors. The estimated 5-year survival rates were 73 % versus 58 %, respectively, for patients treated with chemoradiation therapy versus RT alone. A significant difference in disease-free survival was also seen in favourur of the chemotherapy arm. The addition of chemotherapy to RT was effective in reducing both the frequency of local recurrences and distant metastases, with the latter observation refuting those detractors who claim that the benefit conferred by radiosensitizing chemotherapy is strictly a function of increasing the relative dose intensity of the radiation that can be delivered to the pelvis. These results have been sustained in an update of RTOG protocol 90-01 with 8 years of follow-up [8].

R. Pearcey et al. [35] report a National Cancer Institute of Canada (NCIC) – sponsored the sixth randomized trial that uses cisplatin-based chemotherapy administered concurrently during radiation therapy for cervical cancer. In this trial, 253 patients treated at multiple institutions with stage IB (tumor size 5 cm) to IVA squamous cervical cancer received radiation with weekly cisplatin at a dose of 40 mg/m^2/wk or radiation therapy alone. Survival was not significantly different at 3 years (69 % vs. 66 %) or 5 years (62 % vs. 58 %) for chemotherapy and radiation or radiation alone, respectively. Rose PG et al analyzed if the results of this trial are irreconcilable with the more positive results of the five previous trials. The strengths of the Canadian study were that it was a multicenter prospective randomized trial, it used appropriate doses of chemotherapy (cisplatin 40 mg/m^2 delivered weekly), and the distribution of radiation therapy dose and schedule was similar between the two regimens. They gathered the evidence from all six trials for reduction in the risk of death with concurrent cisplatin-based chemotherapy and radiation therapy compared with their respective control groups [41]. Compared with the control group, the NCIC trial observed a 12 % lower death rate for the chemoradiation group. Note the widest 95 % confidence limit among the six trials, which does not exclude clinically important risk reductions of up to 39 %. It is important to recognize that when pooling the results from these trials, including NCIC, the reduction in the risk estimate is 36 %, which is within the NCIC 95 % confidence limit. Consequently, the NCIC trial results may simply be a product of statistical variation. Across all six studies, a decrease in pelvic recurrence is noted. Collectively, this represents a 12,4 % decrease of the pelvis being the site of first failure (odds ratio – 0,51; 95 % confidence interval, 0,42 to 0,63) [41].

In 2008, Claire Vale et al. [3] published a systematic review and meta-analysis that aimed to collect, validate, and reanalyze individual patient data from the results of 18 trials from 11 countries worldwide, including the five studies that formed the basis of the 1999 NCI alert, and include 4.818 women. On the basis of the 15 trials in the main analysis, there was clear evidence that adding chemotherapy to radiotherapy improves both overall and disease-free survival. For the group of trials in which chemoradiotherapy alone was used, there was a 6 % absolute survival benefit and an 8 % disease-free survival benefit at 5 years, with no evidence of heterogeneity. These analyses endorse the recommendations made in the NCI alert, but with far greater reliability and precision regarding the gains of chemoradiotherapy.

The benefit of chemoradiotherapy on survival and disease-free survival was supported by similar benefits on the other outcomes analyzed, although the evidence for time to metastases was less compelling. Chemoradiotherapy is thought to exert its major beneficial effects by improving local disease control. However, the benefit of chemoradiotherapy on metastases suggested previously [10] and confirmed in this meta-analysis may indicate that it also has a modest systemic effect.

This meta-analysis shows that the benefit associated with chemoradiotherapy may not depend on the use of platinum. Previous recommendations have been limited to platinum-based chemoradiotherapy, but this meta-analysis shows a significant benefit associated with nonplatinum regimens. However, as our results are not based on a direct comparison, we cannot be clear about the relative merits of platinum versus nonplatinum. The only randomized trial that has directly compared platinum (cisplatin) and non-platinum based FU chemoradiotherapy closed early, because interim analyses suggested that FU-based chemoradiotherapy was unlikely to improve progression-free survival compared with cisplatin, even if full accrual had been completed. Furthermore, because it closed early, it was underpowered to detect a difference between the two chemoradiotherapy regimens [21]. For women who are unable to tolerate cisplatin or when more easily tolerated chemotherapy is required, non-platinum based chemoradiotherapy offers an additional option. They found no evidence to suggest that the effect of chemoradiotherapy differs by any of the trial characteristics investigated. Currently, therefore, there is insufficient evidence to suggest that any one treatment type, dose, or schedule is better than any other. The effect of chemoradiotherapy seems consistent across patient subgroups, defined by age, histology, grade, or pelvic node involvement. There was, however, the suggestion of a decreasing relative effect of chemoradiotherapy on survival with increasing tumor stage, with estimated absolute survival benefits of 10 % (stage Ia to IIa), 7 % (stage IIb), and 3 % (stage III to IVa) at 5 years. Even if this trend occurred by chance, applying the overall HR (0,81) to each of the stage subgroups gives an improvement in 5-year survival for all stages, thus confirming that chemoradiotherapy benefits women with all stages of cervical cancer, although the size of the benefit may vary.

Although chemoradiotherapy increases some serious acute toxicity, particularly hematologic and GI toxicities, few of the trials in this meta-analysis measured late toxicity, and only one of the trials eligible for inclusion in this meta-analysis reported quality-of-life outcomes [23]. This highlights the need for prospective evaluations of treatment tolerability and quality of life in future trials that investigate the use of new or targeted therapies.

Because the combination of cisplatin plus FU results in added toxicity, once per week single-agent cisplatin administered at 40 mg/m^2 has emerged as the standard radiosensitizer in locally advanced cervical cancer. At present, radiosensitizing chemotherapy is recommended during that part of the treatment program when external-beam pelvic RT is administered [29].

The criteria for adjuvant radiotherapy following radical hysterectomy have changed. More recently, patients with “intermediate risk” features, based on tumour size, depth of invasion and lymphovascular invasion, also appear to derive a benefit from adjuvant radiotherapy [47]. As the percentage of patients potentially benefiting from adjuvant radiotherapy following radical hysterectomy increases, concerns over treatment-related toxicity have led some to question the need for treatment using both radical surgery and chemoradiation [11].

Neoadjuvant chemotherapy plus surgery

Neoadjuvant chemotherapy (NACT) offers the potential to reduce tumor volume, thereby facilitating primary surgery. In addition it may serve to control micro-metastatic disease and so improve survival. Two randomized studies suggested an increased survival with neoadjuvant chemotherapy followed by surgery compared with radiotherapy alone [45, 46]. In the study of J.E. Sardi et al. [45], 295 patients with Stage IIb cervical carcinoma were randomized between radiotherapy (RT) vs. surgery followed by radiotherapy (S + RT) vs. neoadjuvant chemotherapy (vincristine, bleomycin cisplatinum at 10 days interval) followed by radiotherapy (NACT + RT) vs. NACT + S + RT. The 7 years survival rates were 65 % for the chemotherapy-surgery and 48 % for the radiotherapy arm ($p<0,005$). In other study [46], 441 patients with FIGO stage IB2-III cervical cancer were randomly assigned to: 1) cisplatin-based neoadjuvant chemotherapy (NACT) (P total dose range: 240–320 mg/m^2) followed by type III–IV radical hysterectomy and systematic pelvic lymphadenectomy or 2) external radiotherapy followed by intracavitary radiation. With a median

follow-up of 53 months (surviving patients), the 5-year overall survival rates were 56,5 % vs. 44,4 % in the chemo-surgery and the radiation group, respectively (p=0,01), and for patients with stage IB2-IIB were 64,7 % vs. 46,4 % (p=0,005). For patients with stage IB2-II disease the 4-year survival rate was 65 % versus 51 %. This novel approach could therefore represent an alternative promising treatment for locally advanced cervical cancer. However, in these studies the control arm consisted of radiotherapy alone, while no data are available on the comparison with concomitant radiotherapy and chemo-radiation as standard arm.

The review of Chocrane collaboration [44] aimed to determine whether neoadjuvant chemotherapy given prior to surgery can improve outcomes in women with cervical cancer. Although overall, the results tend towards a benefit of neoadjuvant chemotherapy, the results are inconsistent both by outcome and by trial. Amongst the analyses the only statistically significant result was for PFS. The majority of recurrences and deaths from cervical cancer take place within the first three years after treatment. Therefore, they might expect the results for OS and PFS to be fairly similar, which is not the case in this review. Post-operative radiotherapy was used in all the trials and was fairly similar and balanced between treatment arms. However, there were large differences in the number of patients within the individual trials that received this post-operative treatment. Therefore, it is worth considering that this may be contributing to the variation in the individual trial results. A further consideration is that because most of the included trials have given a large proportion of patients chemotherapy, surgery and radiotherapy as primary treatment, this not only increase side effects but also reduces the chance of salvage therapy for those patients with isolated pelvic recurrences. Considering the rationale for giving chemotherapy prior to surgery, exploratory analyses were also undertaken looking at pathological response based on lymph node status and parametrial infiltration. Two recently published phase II trials [1, 24] reported that optimal tumour response is a significant prognostic factor and could be used as a surrogate outcome for survival. Based on the available data, their results suggest a significant benefit of neoadjuvant chemotherapy for decreasing adverse pathological findings. However, while in some trials this seems to lead to better local and distant control and a benefit in overall and PFS, this pattern does not hold across all trials. However, potential delays to definitive treatment or lack of access to radiotherapy, especially in the developing world, mean that there is continued interest in the use of neoadjuvant chemotherapy. If survival benefit is linked to the level of pathological response then it follows that more effective neoadjuvant chemotherapy schedules may be key to improving outcome for women with cervical cancer and the authors of the recently published phase II trial in stage IB2 to IVA patients [24] suggested that neoadjuvant chemotherapy using three cycles of paclitaxel, ifosfamide and cisplatin (TIP) at three-weekly intervals followed by surgery was a valid alternative to chemoradiation. However, the authors also reported that whilst there was a favourable pathological response when compared to paclitaxel and cisplatin (TP), the grade 3 or 4 haematological toxicity associated with this regimen was considerable, particularly with the triplet regimen (TIP 78 % vs. TP 29 %). It is also noteworthy that the women in this trial are younger (median age 45 for TIP and 42 for TP) and with better performance status than the general population of women with cervical cancer, and so this regimen may not be tolerated by older, less fit women. A number of phase II trials are looking at alternative neoadjuvant chemotherapy regimens in locally advanced cervical cancer. Carboplatin is considered to have similar effectiveness to cisplatin but with easier administration and less associated toxicity and is being evaluated in combination with paclitaxel as a dose-dense, weekly neoadjuvant regimen prior to chemoradiation. Results from this trial, recently presented at ASCO [27], show a high response rate with limited grade 3 or 4 toxicity (13 %). Also, because raised levels of epidermal growth factor receptor (EGFR) [14, 17] and vascular endothelial growth factor (VEGF) [25] are considered to be independent prognostic factors, there is also increasing interest in the use of newer biological agents that act as EGFR and VEGF inhibitors. Therefore, two further phase II trials are looking at giving either cetuximab as single-agent neoadjuvant chemotherapy prior to chemoradiation (NCT00292955) or carboplatin in combination with bevacizumab (NCT00600210). It remains to be seen whether the results of these trials will offer a feasible alternative to current neoadjuvant chemotherapy regimens in the surgical setting. Furthermore, two ongoing randomised phase III trials (EORTC 55994, NCT00193739) are currently comparing neoadjuvant chemotherapy followed by surgery with concomitant chemoradiation and the results of these trials may also be important in determining whether

neoadjuvant chemotherapy prior to surgery is a valid alternative to chemoradiation.

Cost-effective analysis

The treatment of Stage I cervical cancer is estimated to cost approximately $19 billion dollars annually in developed countries alone [9, 53]. In 2005, R.P. Rocconi et al. [39] determine the cost-effectiveness of common strategies for the management of patients with Stage IB2 squamous cell carcinoma of the cervix (CXCA). Through a decision analysis model compared three strategies: 1) radical hysterectomy with pelvic and para-aortic lymphadenectomy followed by tailored chemoradiation therapy for high-risk patients (RHYST); 2) primary chemoradiation therapy for all patients (CTRT); 3) neoadjuvant chemotherapy followed by radical hysterectomy and tailored chemoradiation therapy for high-risk patients (NAC). In model, patients in the RHYST strategy had a 5-DFS of 69 %. It remained the most cost-effective strategy over a wide range of clinical and cost estimates. In fact, RHYST maintained its cost-effective advantage over CTRT down to an efficacy of 10 %. This benefit was maintained even when the effectiveness of CTRT eclipsed 99 %. Individually, all 3 strategies are reasonable with a cost per-cure of $41.212 for RHYST, $43.197 for NAC, and $72.613 for CTRT. However, compared to the RHYST strategy, policymakers must be willing to spend approximately $500.000 per additional survivor for the NAC strategy or $2,2 million per additional survivor for the CTRT strategy. Therefore, RHYST would be favoured in settings where resources are limited. Equally important as costs and efficacy are the potential complications associated with each treatment. Higher complication rates (40 %) are experienced when patients receive both radical surgery and radiation therapy compared to primary chemoradiation alone (25 %) [16, 22, 37, 47]. Their model demonstrates that only a percentage of patients who undergo a radical hysterectomy will require postoperative chemoradiation. This subset of RHYST patients will experience the acute radiation-associated complications related to combination therapy; however, all CTRT patients will experience the radiation-associated complications from primary chemoradiation. The complication rates of each strategy (RHYST, NAC, CTRT) were similar (22 %, 25 %, 27 %, respectively). Due to the inability to establish accurate cost estimates, the costs to diagnose and treat complications were not included in the model. One might criticize the 40 % estimate used for patients who required adjuvant chemoradiation after radical hysterectomy given that the reported range of adjuvant chemoradiation in the literature varies widely from 34 % to 84 %. In a sensitivity analysis, even when 80 % of patients in surgical strategies received adjuvant chemoradiation, the RHYST strategy remained the most cost-effective strategy. RHYST maintained a significant cost-benefit of $15 M less than NAC and nearly $150 M less than CTRT. In conclusion, radical hysterectomy followed by tailored chemoradiation is an efficacious treatment modality with a favourable side effect profile for patients with Stage IB2 cervical cancer. Radical hysterectomy appears to be a cost-effective strategy to manage these patients and would be favoured in settings where resources are limited.

In 2007, E.L. Jewell et al. [13] sought to determine, using a Markov state transition model which incorporates the available literature concerning survival, cost and adverse event rates, whether primary chemoradiation (CR) or primary radical hysterectomy with tailored adjuvant therapy (RH + TA) is a more cost-effective strategy for treatment of stage IB2 cervical cancer. They conclude that RH + TA is a potentially cost effective approach to the management of patients with stage IB2 cervical cancer. The cost-effectiveness of this strategy is particularly sensitive to both estimates of 5-year survival and the cost of brachytherapy. Radical hysterectomy allows for the identification of patients with lower risk features who are spared the effects of chemoradiation. Decisions regarding the management of this disease must be informed by considerations of the likelihood of cure, the cost of the treatments and the quality of life related to treatment toxicities and complications.

J.A. Lachance et al. (2008) [19] compared two cohorts of patients treated with definitive chemoradiation including external beam radiotherapy followed by either two low-dose rate brachytherapy applications, or one low-dose rate applicator and adjuvant simple hysterectomy. The choice of treatment strategy was based on attending gynaecological oncologist's preferences. In that study, these treatment alternatives were shown to have comparable efficacy as well as comparable chronic toxicity [5]. In view of these findings, they hypothesized that cost differences between these two strategies may become an important consideration. So, they compare cost differences between the two treatment strategies in patients with stage IB2 cervical cancer. Given that all patients were initially treated

with external beam radiotherapy with chemosensitization followed by a single low-dose rate brachytherapy procedure, we focused on the costs associated with the divergent portion of the treatment, that is, definitive chemoradiation via a second low-dose rate brachytherapy application vs. an extrafascial hysterectomy. They retrieved cost data associated with hospitalization for the completion of respective treatment, including pharmacy, laboratory and pathology, radiation, and operating room services, as well as the costs of supplies and room and board. The cost of care for adjuvant hysterectomy group was greater ($8.316,70 vs. $5.508.70, p<0,0001). Specific differences included higher operating room costs ($1.520 vs. $414, p<0,0001), pharmacy costs ($675 vs. $342, p<0,0001), and laboratory/pathology costs ($597 vs. $89, p<0,0001). They conclude that definitive chemoradiation appears to be associated with lower costs for management of stage IB2 cervical cancer when compared to simple adjuvant hysterectomy. After reviewing their institutional experience, their data suggest that definitive chemoradiation is the preferred treatment strategy compared to chemoradiation plus hysterectomy, based on its lower cost and comparable efficacy and toxicity.

The incremental costs that may be associated with chemoradiation have not yet been addressed. Interest in these data may be greatest in countries with a high incidence of the disease, many of which may already have limited health care resources. The growth of managed care in the United States and its interest in research-based economic evaluations led us to perform an analysis of the economic impact of these five trials.

P.G. Rose et al. (1999) [42] compares the clinical results of cisplatin-based chemoradiation versus the control arms of radiation alone or radiation with hydroxyurea, in terms of incremental cost per year of life gained. They conducted a pharmacoeconomic analysis to determine whether the alternative cisplatin-based chemoradiation is cost effective as compared with standard therapy using radiation alone. Cost per year of life gained for cisplatin-based chemoradiation regimens varied from $2.384 to $28.770 based on published survival and from $308 to $3.712 based on estimated survival. Variations in regimen cost were largely dependent on treatment setting. Administration costs per patient for cisplatin and fluorouracil in the inpatient setting were $8.839 compared with $3.590 in the outpatient setting. The increased median survival cost per year of life gained with cisplatin-based chemoradiation (inpatient and outpatient settings) adds a substantial benefit at an acceptable cost compared with radiation therapy alone.

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