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Neoadjuvant Chemotherapy in the Treatment of Cervical Cancer

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1. Introduction

The treatment of cervical cancer has seen great advances since the first radical hysterectomy was performed by Ernst Wertheim in 1898. Breakthroughs in surgical techniques, including total laparoscopic approaches, sentinel lymph node mapping, and fertility-sparing procedures have dramatically reduced the morbidity of definitive treatment, while preserving oncologic outcomes. Increasingly conservative approaches are being proposed, based on individual patient and tumour characteristics.

Cervical cancer was previously thought to be chemo-resistant, and therefore chemotherapy was used only for recurrent or metastatic disease. However, after responses were noted to platinum-based regimens (Friedlander et al., 1983, 1984), interest in the use of chemotherapy was reignited, particularly in the neoadjuvant setting. Whether prior to surgery or radiotherapy, the use of neoadjuvant chemotherapy in cervical cancer has been actively studied, in multiple settings and diverse patient populations, showing promise with acceptable toxicity profiles.

In this chapter, the use of neoadjuvant chemotherapy in the treatment of cervical cancer will be reviewed. The rationale will be explored followed by the evidence for its effectiveness prior to surgery, radiotherapy, and fertility-sparing procedures. An approach to patient selection will be provided, and chemotherapeutic regimens will be compared, concluding with areas of ongoing and future research.

2. Rationale for neoadjuvant chemotherapy in cervical cancer

One of the motivations behind neoadjuvant chemotherapy in the treatment of cervical cancer was to reduce tumour size in order to facilitate surgical resection. This was an objective, primarily in low resource countries, where cervical cancer is one of the most common causes of female cancer mortality (World Health Organization, 2011) and access to radiotherapy for patients with locally advanced tumours is limited. Tumour size reduction would not only simplify surgical procedures, but also potentially transform inoperable tumours to resectable. In conjunction with the reduction of lymph node metastases, neoadjuvant chemotherapy prior to surgery may decrease the need for postoperative radiotherapy or chemo-radiotherapy, minimizing long-term treatment-related complications, particularly in sexually active women. Prior to surgery, the blood supply to the tumour is uncompromised, allowing improved drug delivery and distribution. Local control might also be improved with early control of micrometastases.

In the setting of pelvic recurrence, the anticipated morbidity of salvage surgery after neoadjuvant chemotherapy followed by surgery would seemingly be less than that following failed radiotherapy, introducing an additional benefit to the avoidance of primary radiotherapy.

Applications prior to radiotherapy have also been envisioned, including the reduction in tumour size and distortion of pelvic anatomy to facilitate radiotherapy. The effectiveness of radiotherapy might also be improved through decreased tumour cell hypoxia and subsequently improved radiosensitivity with platinum-based agents. The administration of chemotherapy prior to radiotherapy, rather than concurrently, could decrease the radiotherapy-induced toxicity. Although attractive in theory, the benefit of chemotherapy prior to radiotherapy has not been established, particularly in the era of concurrent chemo-radiotherapy (National Cancer Institute, 1999).

Some studies have shown that the response to neoadjuvant chemotherapy may serve as an important prognostic factor, guiding the direction of subsequent therapy. Whether the response to neoadjuvant chemotherapy simply identifies a subset of patients who are destined to fare better than non-responders has been questioned. However, as a group, those receiving neoadjuvant chemotherapy have in some studies demonstrated improved progression-free and overall survival. These studies will be reviewed, highlighting study designs, treatment protocols, statistical analyses, author conclusions, and unanswered questions.

Finally, neoadjuvant chemotherapy may optimize a patient's pathologic risk factors, introducing the option of fertility-sparing treatment to a patient who would otherwise not be a candidate. In this setting, neoadjuvant chemotherapy offers benefits other than an equivalent oncologic outcome.

3. Neoadjuvant chemotherapy prior to surgery versus surgery alone

3.1 Rationale

While radical surgery or radiotherapy have been shown to be equally effective in the treatment of early stage cervical cancer (stage IB1), with equivalent disease-free and overall survival (Landoni et al., 1997), patients with locally advanced disease (FIGO IB2 – IVA) are typically treated with radical radiotherapy, including external beam and intracavitary treatments. However, neoadjuvant chemotherapy may transform previously inoperable tumours to those that are resectable. This may be desirable in patients who wish to avoid radiotherapy, or for whom radiotherapy is not available. The former patients may include young women seeking to maintain ovarian and sexual function, patients having previously received pelvic radiotherapy for other diagnoses, or patients needing to avoid the toxicities of radiotherapy due to comorbid diseases such as inflammatory bowel disease or connective tissue disorders with significant vasculitis.

Neoadjuvant chemotherapy may also be administered prior to radical surgery to improve progression-free or overall survival. By minimizing pathologic factors that contribute to poor prognosis and disease recurrence, chemotherapy prior to surgery may not only render previously inoperable tumours operable, but also decrease the risk of recurrence for patients having operable tumours with high risk features. If survival benefit is associated with improved pathological response, and improved pathological response is possible with neoadjuvant chemotherapy prior to surgery, it is possible that with optimized chemotherapy regimens, neoadjuvant chemotherapy could lead to a survival advantage in select patients with high risk features.

3.2 Tumour size reduction

The first question to be addressed is whether there is evidence to support the use of neoadjuvant chemotherapy in the reduction of tumour size. Sardi *et al.* (Sardi et al., 1986) first described a cohort of 8 patients treated with vincristine, bleomycin, and cisplatin (VBP) every 21 days, similar to the conventional protocol of Friedlander (Friedlander et al., 1984), with the substitution of vincristine for vinblastine. While reduction in tumour volumes overall was 48%, only 62.5% of patients displayed a central response, and only 28.5% responded in the parametria. A modified protocol was therefore administered to a cohort of 25 patients. This "Quick VBP" protocol was intensified, given every 10 days, which yielded a 92% central response rate, and 94.6% parametrial response, with an average regression in tumour volume of 73.5% overall. While the conventional cohort had a larger average pre-treatment tumour volume (78.4 cm^3 versus 55.7 cm^3), when stratified by stage, the "Quick VBP" protocol produced an 82% reduction in stage IIIB disease, compared to 50.1% using the conventional protocol.

Sardi *et al.* (Sardi et al., 1993) later conducted a randomized trial of radical surgery plus adjuvant radiotherapy with or without neoadjuvant chemotherapy in patients with bulky stage IB2 disease. Of the 74 patients randomized to receive neoadjuvant chemotherapy, delivered via the "Quick VBP" protocol (vincristine, bleomycin and cisplatin every 10 days for 3 cycles), 92% of patients responded (40.5% complete response, 51.4% partial response). The average change in tumour size was from 63 cm^3 to 31 cm^3. Significant reductions in tumour size to less than 25% of original volume were noted in those receiving VBP (55% in the VBP arm versus 7% in the control arm, $p < 0.00001$). Similarly, the number of patients with final tumour size less than 2 cm was significantly greater in those receiving VBP (62% versus 4% in the control arm, $p < 0.0001$), despite similar mean tumour volume between groups at randomization. This cisplatin-containing protocol of neoadjuvant chemotherapy showed efficacy in reducing tumour volume to <25% in roughly half of patients with bulky stage IB2 disease.

Given these results, it seemed promising that neoadjuvant chemotherapy may be used to reduce tumour size in order to facilitate primary surgery.

3.3 Reduction in poor prognostic factors

As suggested by Benedetti-Panici *et al.*, (Benedetti-Panici et al., 2002) one category of patients who may derive the greatest benefit from neoadjuvant chemotherapy are those with bulky stage IB2 disease. These patients are at risk for subclinical parametrial infiltration, lymph node metastases, and vascular space invasion, all of which are poor prognostic factors and for which adjuvant radiotherapy is commonly offered. Sardi *et al.* (Sardi et al., 1993) randomized 146 patients to receive radical surgery followed by adjuvant radiotherapy plus or minus neoadjuvant chemotherapy using the "Quick VBP" protocol (every 10 days for 3 cycles). All but three patients randomized to neoadjuvant chemotherapy and all but six patients randomized to control underwent radical hysterectomy. A significant reduction in tumour volume ($p < 0.0001$), incidence of vascular space invasion (15% vs. 57%, $p<0.00001$), parametrial infiltration (3% vs. 22%, $p<0.00001$), and lymph node metastases (7% vs. 31%, $p < 0.0005$) was found in patients having received neoadjuvant chemotherapy versus control, respectively. In 9% (7/74) of "Quick VBP" patients there was no evidence of residual disease on surgical specimen.

3.4 Improvement in progression-free and overall survival

While surrogate markers of treatment effectiveness might suggest neoadjuvant chemotherapy is of benefit, what is of greatest interest to patients and clinicians is whether neoadjuvant chemotherapy confers a survival advantage. The following studies, presented individually and later analyzed collectively, sought to compare patients receiving neoadjuvant chemotherapy prior to surgery versus surgery alone.

3.4.1 Neoadjuvant chemotherapy, surgery and radiotherapy in stage IB squamous carcinoma of the cervix

Sardi *et al.* (Sardi et al., 1997) performed a randomized controlled trial of patients with stage IB disease (>2 cm), comparing radical hysterectomy and whole pelvis adjuvant radiotherapy with or without neoadjuvant chemotherapy (cisplatin, vincristine, and bleomycin) (Table 1). All patients underwent a staging laparotomy. If the tumour was found to be resectable, a radical hysterectomy, with para-aortic lymphadenectomy, was performed, followed by whole pelvis radiotherapy (50 Gy). Conversely, if the cancer was found to be unresectable, patients received 50-60 Gy to the whole pelvis followed by 25-35 Gy of intracavitary treatment.

Two hundred and five patients were randomized, 102 to neoadjuvant chemotherapy and 103 to the control arm. For all patients, improved overall survival was noted in those receiving neoadjuvant chemotherapy compared to controls (81% vs. 66% at 8 years, $p = 0.05$).

While pathologic risk factors such as lymph node metastases (19% vs. 2%, $p = 0.04$) and vascular space invasion (38% vs. 2%, $p = 0.007$) were significantly improved in patients with stage IB1 disease receiving neoadjuvant chemotherapy, there was no difference in overall survival at 8 years in this subgroup (82% with neoadjuvant chemotherapy versus 77% control). Patients with stage IB2 disease, however, demonstrated improved overall survival following neoadjuvant chemotherapy (80% versus 61% at 9 years, $p < 0.01$). This benefit was driven by an increased rate of operability (100% (61/61) versus 86% (48/56), $p < 0.01$) and possibly an improvement in pathologic risk factors in those receiving neoadjuvant chemotherapy compared to controls. Of all patients with resectable tumours, greater survival was noted in those who had received neoadjuvant chemotherapy (81% vs. 69% at 7 years, $p = 0.05$).

The incidence of high-risk pathologic features was similar between controls and patients who did not respond to neoadjuvant chemotherapy. In those who responded, however, there were significantly fewer with lymph node metastases (6% vs. 40%, $p < 0.0001$), vascular space invasion (10% vs. 60%, $p = 0.009$) and parametrial involvement (2% vs. 34%, $p = 0.001$). Neoadjuvant chemotherapy appeared beneficial in decreasing the incidence of pelvic recurrences for those patients with stage IB2 disease (23% vs. 6%, $p < 0.01$). However, rates of distant metastases were the same for stage IB patients overall.

The authors concluded that in patients with stage IB1 disease there was no difference in operability or survival, and minimal difference in pathologic features, suggesting limited benefit of neoadjuvant chemotherapy in this patient population. However, patients with stage IB2 disease had a significant increase in operability, and survival.

While offering an alternative to radical radiotherapy in patients with stage IB2 disease, all patients in this study underwent adjuvant radiotherapy. Therefore, those receiving neoadjuvant chemotherapy underwent triple modality treatment in order to derive benefit. How their survival would compare to the current standard treatment of chemo-radiotherapy is also unclear. There were methodological issues in this study; violation of intention-to-treat analysis took place, with the exclusion of 3 control and 2 neoadjuvant

chemotherapy patients who did not complete treatment. Multiple interim analyses were performed, ultimately leading to early closure of the study, and finally there was no pre-stated sample-size calculation.

3.4.2 Neoadjuvant chemotherapy and surgery in bulky stage IB carcinoma of the cervix

Protocol GOG #141 (Eddy et al., 2007) was a multicentre randomized trial of radical hysterectomy and pelvic/para-aortic lymphadenectomy with or without neoadjuvant chemotherapy (vincristine and cisplatin) for patients with "bulky" stage IB2 disease (Table 1). Primary endpoints were overall and progression-free survival as well as tumour operability. Patients received adjuvant radiotherapy in the presence of surgical or pathological risk factors. Unfortunately, due to slow accrual, this study was closed prematurely after randomizing 288 patients (145 to neoadjuvant chemotherapy, 143 to control), only 70% of the calculated sample size. There was no difference between treatment groups in recurrence rates, death rates, operability, and proportion receiving adjuvant radiotherapy. The authors concluded that neoadjuvant chemotherapy did not offer any additional objective benefit to patients undergoing neoadjuvant chemotherapy prior to surgical management of stage IB cervical cancer. However, the study was underpowered to make any definitive conclusions.

3.4.3 Neoadjuvant chemotherapy and surgery in stage IB2 – IIB carcinoma of the cervix

One proposed explanation for the lack of survival benefit from neoadjuvant chemotherapy prior to definitive treatment of locally advanced cervical cancer is the delay in treatment for chemotherapy non-responders, resulting in the development of chemo-resistant cell populations or cross-resistance to radiotherapy. Chen *et al.* (Chen et al., 2008) attempted to evaluate whether high-dose, short-term neoadjuvant chemotherapy prior to surgery (Table 1) could improve response and survival rates. Patients with stage IB2 – IIB disease were randomized to undergo surgical management with or without neoadjuvant chemotherapy (cisplatin, mitomycin C, and 5-fluorouracil). Post-operative pelvic radiotherapy was used for patients with lymph node metastases, parametrial or vaginal involvement, lymph vascular space invasion, and/or ovarian metastases.

Overall, almost 70% of patients had either a complete or partial response to chemotherapy. Pathologic findings were significantly reduced, with decreased pelvic lymph node metastases (25.0% vs. 42.9%, $p = 0.02$) and parametrial involvement (25.0% vs. 41.4%, $p = 0.04$). In chemotherapy "responders" versus "non-responders", significant reductions were noted in pelvic lymph node metastases (16.0% vs. 45.5%, $p = 0.008$) and parametrial involvement (16.0% vs. 45.5%, p = 0.008). Four of the 6 patients with a complete response had no residual tumour in the final pathologic specimen.

There was no difference in recurrence between treatment arms. However, those who responded to chemotherapy had fewer recurrences compared to non-responders (16.3% vs. 47.4%, $p = 0.01$). Using the method of Kaplan and Meier, there was a significant difference in the 4-year overall survival between treatment arms (71.0% with neoadjuvant chemotherapy versus 58.0% with control, $p = 0.04$). To control for confounders, Cox proportional hazards regression modeling was used. In this analysis, tumour size, lymph node metastases, and FIGO stage were significant independent predictors of prognosis, while treatment type was not.

Study	Eligibility	Intervention Arms	Resectability	Overall Survival	Follow-up
Sardi 1997 (Argentina) N = 205	SCC 1B1 (>2 cm) 1B2	n = 103 1B1 (n = 47); 1B2 (n = 56) Staging Laparotomy or Radical Hysterectomy + PALND + Whole Pelvis Radiotherapy (50 Gy)	1B1 100% 1B2 86%	1B1: 77% (8 y) 1B2: 61% (9 y)	67 months
		n = 102 1B1 (n = 41); 1B2 (n = 61) Cisplatin 50 mg/m² Vincristine 1mg/m² Bleomycin 25 mg/m² (D 1-3) Every 10 days x 3 cycles	1B1 100% 1B2 100%	1B1: 82% (8 y) 1B2: 80% (9 y)	
Benedetti-Panici 2002 (Italy) N = 409	SCC IB2- III	n = 210 Cisplatin ≥240 mg/m² (total dose) (± Bleomycin, Vincristine, Ifosfamide) Over 6 – 8 weeks Radical Hysterectomy	78%	5 y OS: 56.5% IB2-IIB 64.7%	79 months
		n = 199 EBRT 45-50 Gy + Intracavitary 20-30 Gy.		5 y OS: 44.4% IB2-IIB: 46.4%	
Napolitano 2003 (Italy) N = 192	SCC IB- IIIB	n = 106 Cisplatin 50 mg/m² Vincristine 1mg/m² Bleomycin 25 mg/m² (D 1,3) 3 cycles every 3 weeks Radical Hysterectomy, PLND	100%	5 y OS IB-IIA: 78.6% IIB: 68.7%	--
		n = 86 Radical Hysterectomy, PLND (Stage I-IIB) EBRT 50-60 Gy, Intracavitary 30 Gy (Stage IIIA-B)	81%	5 y OS IB-IIA: 73.2% IIB: 64.3%	
Cai 2006 (China) N = 106	SCC Stage IB	n = 52 Cisplatin 75 mg/m² 5-FU 24 mg/kg/d (D 1-5) 2 cycles every 3 weeks Radical Hysterectomy + PLND	100%	5 y OS: 84.6% 1B1: 85.7% 1B2: 84.2%	62 months
		n = 54 Radical Hysterectomy + PLND		5 y OS: 75.9% 1B1: 75% 1B2: 76.7%	

Study	Eligibility	Intervention Arms	Resectability	Overall Survival	Follow-up
Eddy 2007 (USA) N = 288	Stage 1B2	n = 145 Cisplatin 50 mg/m² Vincristine 1 mg/m² 3 cycles every 10 days Radical Hysterectomy, P+PALND	78%	3 y OS: 67.7% 5 y OS: 63.3%	62 months
		n = 143 Radical Hysterectomy, P+PALND	79%	3 y OS: 69.3% 5 y OS: 60.7%	
Chen 2008 (China) N = 142	Stage IB2-IIB	n =72 Cisplatin 100 mg/m² Mitomicin C 4 mg/m² IM (D1-5) 5-Fluorouracil 24 mg/kg/day (D1-5) 2-3 cycles every 2 weeks Radical Hysterectomy + PLND	100%	4 y OS: 71%	48 months
		n = 70 Radical Hysterectomy + PLND	100%	4 y OS: 58%	

N – number of patients enrolled; SCC- squamous cell carcinoma; n – number of patients in treatment arm; P+PALND – pelvic and para-aortic lymph node dissection; D – cycle day; OS - overall survival

Table 1. Randomized Controlled Trials of Neoadjuvant Chemotherapy Prior to Surgery versus Surgery Alone

When regression modeling stratified the neoadjuvant treatment group into responders and non-responders, response to chemotherapy became an independent prognostic factor for survival ($p = 0.005$), and chemotherapy-responders had significantly improved tumour-free survival compared to non-responders ($p < 0.0001$).

The authors concluded that response to treatment was significantly associated with tumour-free survival, recurrence, and served as an independent prognostic factor, suggesting that in this research protocol, neoadjuvant chemotherapy did not translate into a recurrence or disease-free survival benefit overall, but rather, identified a subgroup of patients with improved prognosis. Those with poor response would have had minimal delay to definitive treatment, given the high-dose and abbreviated treatment in the trial protocol.

This study did not report results of overall survival, and no difference could be found in disease-free survival in the unstratified analysis. Whether this was due to insufficient sample-size or a lack of true effect cannot be determined. Intention-to-treat analysis was violated with the exclusion of two post-surgical patients who underwent no further treatment, and 1 patient was excluded from the survival analysis due to death from other causes. With 1/3 of patients requiring adjuvant radiotherapy, and a lack of overall survival benefit, the merits of neoadjuvant chemotherapy, despite surrogate markers of effect, such as decreased lymph node metastases and parametrial involvement, is questionable.

3.4.4 Neoadjuvant chemotherapy and surgery in stage IB – IIIB cervical carcinoma

A randomized study of neoadjuvant chemotherapy using cisplatin, vincristine and bleomycin (Table 1) reported by Napolitano *et al.* (Napolitano et al., 2003) looked at patients with stage IB – IIIB squamous cell carcinoma. All patients in the neoadjuvant chemotherapy arm underwent radical surgery, while control patients with stage IB – IIB disease underwent radical surgery, and patients with stage IIIA – IIIB disease underwent radiotherapy. Adjuvant radiotherapy was administered to all resectable patients with parametrial infiltration, lymph node metastases or positive surgical margins. Random allocation was planned such that 55% of patients received neoadjuvant chemotherapy.

While a difference in 5-year disease-free survival for those with stage IB – IIA disease was found (77% vs. 64%, $p = 0.05$), there was no difference in overall survival for either stage IB – IIA or stage IIB – IIIB patients. Not only was a sample size calculation lacking, but intention-to-treat analysis of progression-free survival was violated when 20 patients were excluded from the analysis (4 patients with stage III disease unresponsive to chemotherapy and 16 control patients).

3.4.5 Neoadjuvant chemotherapy and surgery in stage IB cervical carcinoma

Cai *et al*. (Cai et al., 2006) presented a randomized controlled trial of patients with stage IB squamous cell and adenocarcinoma of the cervix, receiving neoadjuvant chemotherapy (cisplatin/5-fluorouracil) followed by surgery versus surgery alone. Patients received adjuvant radiotherapy for high-risk features such as deep cervical invasion, parametrial invasion, or lymph node metastases. Primary outcomes were 5-year overall survival, and secondary outcomes included progression-free survival and disease recurrence. Patients receiving neoadjuvant chemotherapy had an improved 5-year disease-free survival (83% vs. 74%, $p = 0.04$) and overall survival (85% vs. 76%, $p = 0.01$).

Although these results might suggest a survival advantage with neoadjuvant chemotherapy, 62% of patients receiving neoadjuvant chemotherapy (vs. 54% of controls) also received adjuvant radiotherapy. Whether the survival advantage seen was related to the chemotherapy, or the combined modality treatment of chemotherapy followed by radiotherapy, is not clear.

As in many similar studies, a sample size calculation was not explicitly stated, and intention-to-treat analysis was violated (1 patient with protocol violation was excluded from the analysis), the latter compromising the validity of the study results.

3.4.6 Neoadjuvant chemotherapy and surgery in patients with locally advanced squamous cell carcinoma of the cervix

If a consistent benefit were to exist with the use of neoadjuvant chemotherapy in select patients with locally advanced cervical cancer, the choice of chemotherapeutic protocol would be challenging, given the variety and number of protocols used.

Buda *et al.* (Buda et al., 2005) sought to determine whether a 3 drug regimen (paclitaxel/ ifosfamide/cisplatin [TIP]) conferred benefit over a 2 drug protocol (ifosfamide/cisplatin [IP]) and whether pathologic response to treatment was associated with survival. This randomized, phase II trial of patients with FIGO stage IB2 – IVA disease, examined neoadjuvant chemotherapy prior to radical surgery. Patients who achieved an optimal response (either complete resolution of tumour, or tumour less than 3 mm on final specimen) received 2 additional courses of chemotherapy after surgery with the same agents used in the neoadjuvant treatment. Those found to be inoperable due to progression of

disease despite chemotherapy were offered radical radiotherapy, and those with lymph node metastases, parametrial involvement, tumour "cut-through" or suboptimal response underwent adjuvant radiotherapy or chemo-radiotherapy.

Cisplatin and ifosfamide were chosen due to their proven benefit in the neoadjuvant and salvage settings. Paclitaxel was added to the experimental arm as favourable results had also been noted with its use. The purpose of the study was to determine the optimal chemotherapeutic regimen for a future planned randomized clinical trial of neoadjuvant chemotherapy prior to surgery, versus chemo-radiotherapy.

While optimal pathologic response rates were greater in patients receiving TIP (48% vs. 23%, $p = 0.0004$), there was no significant difference in treatment failure rate or hazard of death. Rates of grade 3 and 4 neutropenia, anemia and thrombocytopenia were greater with TIP treatment ($p = 0.02$). Treatment delays and dose reductions were necessary in 35% of patients receiving TIP versus 18% receiving IP. There were 4 treatment related deaths, 1 receiving TIP and 3 receiving IP, the majority of which were in women greater than 70 years with pre-existing renal disease, suggesting the need for careful patient selection. Response to chemotherapy predicted prognosis, with average death rates higher in the group not achieving optimal response (HR 5.88, 95% CI 2.5 – 13.84, $p < 0.0001$).

The authors concluded that the TIP regiment was associated with a greater response than the IP regimen. This did not translate into a survival benefit. However the study was only powered for treatment response, not overall and disease-free survival.

To determine the incremental benefit of ifosfamide to the TIP protocol, the same Italian Collaborative Group performed a randomized phase II study comparing TIP to paclitaxel/cisplatin (TP) prior to radical surgery (Lissoni et al., 2009). Women with inoperable tumours underwent radical radiotherapy, while women with lymph node metastases, parametrial invasion, positive margins, or suboptimal response underwent either external beam radiotherapy or chemo-radiotherapy. Those with either a complete or partial response underwent 2 additional courses of chemotherapy after surgery with the same chemotherapeutic agents as their neoadjuvant treatment.

An optimal pathologic response was achieved in 25% of patients receiving TP compared to 43% receiving TIP ($p = 0.03$). This was driven primarily by the response of patients with stage IB2 disease (53% vs. 24% responding to TIP vs. TP, respectively). The authors felt that the TP regimen demonstrated less efficacy than expected, while the TIP regimen, showing superior response rates, was associated with considerable toxicity. Grade 3-4 leukopenia and neutropenia were significantly more frequent in those receiving ifosfamide (78% vs. 29%, $p < 0.0001$). However only 2 of 49 patients who achieved an optimal response to chemotherapy required adjuvant radiotherapy.

There was no difference in progression-free or overall survival, although this study was not powered to address these outcomes.

While the authors present the option of neoadjuvant chemotherapy as a valid alternative to chemo-radiotherapy, the toxicity of treatment must be considered. Furthermore, while adequate sample size was achieved, the study population in this trial was much younger than the general population with cervical cancer, with better performance status, limiting the external validity and generalizability of these results. Lastly, until such time as a randomized comparison of neoadjuvant chemotherapy followed by surgery versus concomitant chemo-radiotherapy is performed, conclusions regarding the use of neoadjuvant chemotherapy and surgery as a legitimate alternative to radiotherapy cannot be justified.

3.5 Criticisms of data

The majority of published trials comparing neoadjuvant chemotherapy prior to surgery versus surgery alone are small studies, most of which are inconclusive. Conflicting results have been found, with some studies showing significant improvement in survival (Sardi et al., 1997) and others showing significant detriment (Tattersall et al., 1995). Tierney *et al.* (Tierney et al., 1999) therefore sought to compile the results of published reports in a systematic review and meta-analysis, in order to increase the statistical power to detect a difference in survival should one exist. Using published summary data from trial reports, this meta-analysis was found to be of limited benefit, since only a subset of trials had yet been published, and some failed to include sufficient survival data to be used in the analysis. Therefore, no firm conclusions could be made.

3.6 Systematic review and meta-analysis

A decade passed and the question was revisited. Does neoadjuvant chemotherapy prior to surgery in women with operable tumours confer a survival advantage over surgery alone? A systematic review and meta-analysis, performed by Rydzewska *et al.* (Rydzewska et al., 2010) was published in the Cochrane library, examining the role of neoadjuvant chemotherapy in women with early or locally advanced cervical cancer. The primary outcome was overall survival. Secondary outcomes were progression-free survival, local and distant recurrence rates, rates of resection, and surgical morbidity. Six trials were included, with a total of 1072 women with FIGO stage IB – IIIB disease, using trial report data (Table 1). All trials used cisplatin-based chemotherapy. While data on overall survival, progression-free survival, resection rates, pathologic response, and recurrence were not available for all trial participants, the authors found that neoadjuvant chemotherapy prior to surgery resulted in an improved progression-free survival (HR = 0.76, 95% CI 0.62 – 0.94, p = 0.01). These results were similar when random effects modeling was applied (to control for study heterogeneity) (HR = 0.73, 95% CI 0.56 – 0.96, p = 0.03). However, there was no difference in overall survival (HR = 0.85, 95% CI 0.67 - 1.07, p = 0.17) (with minimal heterogeneity).

Studies showed great variation in local and distant recurrences, and rates of tumour resectability. Significantly increased rates of radical resection following neoadjuvant chemotherapy were seen in two trials (Napolitano et al., 2003; Sardi et al., 1997), while no difference was seen in three others (Cai et al., 2006; Chen et al., 2008; Eddy et al., 2007). However, statistical modeling to combine study results showed no overall benefit to neoadjuvant chemotherapy in radical resection rates, local or distant recurrences.

Meanwhile, measures of pathologic response demonstrated a significant decrease in adverse pathologic findings in patients undergoing neoadjuvant chemotherapy. There were fewer patients with lymph node metastases (OR = 0.54, 95% CI 0.39 – 0.73, p < 0.0001) and parametrial invasion (OR = 0.58, 95% CI 0.41 – 0.82, p = 0.002). Significant heterogeneity between studies was again noted, making pooled comparisons of studies inappropriate. However, when statistical adjustment was performed, using random effects modeling, the differences in pathologic response remained significant. While in some trials the improvement in pathologic response was associated with improved local and distant control and overall and progression-free survival, this was not a uniform observation across studies. Survival according to neoadjuvant chemotherapy was unaffected by total cisplatin dose, chemotherapy cycle length, or cervical cancer stage (FIGO IB versus FIGO II – IIIB). Surgical morbidity was not increased in patients undergoing neoadjuvant chemotherapy.

In 1 of the studies included in this meta-analysis (Sardi et al., 1997), all patients received post-operative adjuvant radiotherapy, regardless of risk factors. In 4 others, (Cai et al., 2006; Chen et al., 2008; Eddy et al., 2007; Napolitano et al., 2003), between 36% and 61% of patients received adjuvant radiotherapy due to risk factors identified at the time of surgery. If the objective of neoadjuvant chemotherapy prior to surgery is to decrease the need for adjuvant radiotherapy, this goal has not been achieved.

Rydzewska *et al*. highlight the discrepancy between overall survival and progression-free survival, indicating that overall survival and progression-free survival would be expected to be similar, given that most recurrences and deaths from cervical cancer take place within the first 3 years. However, bias may have been introduced, as 1 study did not present results for overall survival (Chen et al., 2008) and 1 study excluded patients with unfavourable prognoses (those not responding to chemotherapy) from the analysis of progression-free survival, but not overall survival (Napolitano et al., 2003). Therefore, given the available evidence, there is no survival benefit to neoadjuvant chemotherapy prior to surgery in patients with operable tumours, and the noted benefit in progression-free survival should be interpreted with caution.

3.7 Conclusions

Following review of the available evidence, there does not appear to be a consistent benefit in overall survival to neoadjuvant chemotherapy prior to surgery versus surgery alone. Studies suggesting an improvement in survival utilized adjuvant radiotherapy in the majority of patients, obscuring the impact of neoadjuvant chemotherapy. While different rates of pathologic response may be noted, these do not translate into a survival advantage.

4. Neoadjuvant chemotherapy prior to radiotherapy versus radiotherapy alone

4.1 Rationale

The use of neoadjuvant chemotherapy prior to radiotherapy was introduced in order to attempt improved survival in patients with locally advanced cervical cancer. While treatment consisted mainly of radical radiotherapy, cure rates were still low due to local and distant recurrences. The objective of neoadjuvant chemotherapy, therefore, was to eradicate subclinical or clinical distant metastases and to improve the local disease control by achieving a reduction in tumour size. Large tumour masses often cause anatomic distortion, affecting the placement of vaginal and cervical radiation sources. Therefore, a decrease in tumour size prior to radiotherapy might also facilitate the accurate delivery of radiation.

Theoretical benefits to neoadjuvant chemotherapy prior to radiotherapy include increased radiosensitivity and decreased hypoxic cell fractions with tumour size reduction (Eddy, 1996; Souhami et al., 1991), improved drug delivery and distribution to the tissues prior to radiation vasculitis (Eddy, 1996; Tokuhashi et al., 1997), and possible radiation potentiation using platinum-based regimens.

4.2 Objectives

The objective of this review is to determine whether neoadjuvant chemotherapy prior to radiotherapy improves response rates, disease-free and overall survival with acceptable toxicity profiles. The following collection of studies (Table 2) addresses the impact of neoadjuvant chemotherapy followed by radical radiotherapy versus radiotherapy alone.

Author	Stage	Neoadjuvant Chemotherapy	Radiation	Comparison	Response	Overall Survival	Median Follow-up
Souhami 1991 N = 91	SCC IIIB	Bleomycin 15U q12h (D1-4) Vincristine 1mg/m^2 Mitomycin 10mg/m^2 Cisplatin 50mg/m^2 Every 3 weeks x 3 cycles	EBRT 50 Gy Intra-cavitary 40 Gy	CT + RT	CR 47% PR 25%	23%	>34 months
				RT	CR 32% PR 27% (p = NS)	39% (p = 0.02)	
Tattersall 1992 N = 71	IIB – IVA	Cisplatin 50mg/m^2 Vinblastine 4mg/m^2 Bleomycin 15mg (D1,8,15) Every 3 weeks x 3 cycles	EBRT 40-55 Gy	CT + RT	CR 65% PR 29%	141 weeks[1]	37 months
				RT	CR 73% PR 16%	167 weeks	
Chiara 1994 N = 61	SCC + ASQ IIB – III	Cisplatin 60mg/m^2 Every 15 days 2 cycles before RT 4 cycles after RT	EBRT 60 Gy Intra-cavitary 40 Gy	CT + RT + CT	CR 42% PR 36%	72%	36 months
				RT	CR 41% PR 41%	83% (p = NS)	
Kumar 1994 N = 184	SCC IIB – IVA	Bleomycin 15mg Ifosfamide 1g/m^2 (D1-5) Cisplatin 50mg/m^2 Every 3 weeks x 2 cycles	EBRT 50 Gy Intraca-vitary 30 Gy	CT + RT	CR 4% PR 68%	38%	30 months
				RT	CR 69%	43% (p = NS)	22 months
Tattersall 1995 N = 260	IIB – IVA	Cisplatin 60mg/m^2 Epirubicin 110mg/m^2 Every 3 weeks x 3 cycles	EBRT 30-35 Gy Intra-cavitary 30-35 Gy	CT + RT	CR 43% PR 29%	--	16 months
				RT	CR 65% PR 27%	-- (p = 0.02)	
Sundfor 1996 N = 94	SCC IIIB – IVA	Cisplatin 100mg/m^2 5-FU 1000mg/m^2 (D 1-5) Every 3 weeks x 3 cycles	EBRT 65 Gy	CT + RT	CR 56% PR 24%	26 months	46 months
				RT	CR 61% PR 20%	22 months (p = NS)	45 months
Leborgne 1997 N = 96	IB – IVA	Cisplatin 50mg/m^2 Bleomycin 25mg/m^2 (D1-3) Vincristine 1mg/m^2 Every 10 days x 3 cycles	EBRT 20-60 Gy Intra-cavitary 30 Gy	CT + RT	CR12% PR 50%[2]	--	43 months
				RT	--	--	
Sardi 1998 N = 144	SCC IIB	Vincristine 1mg/m^2 Bleomycin 25mg/m^2 (D1-3) Cisplatin 50mg/m^2 Every 10 days x 3 cycles	EBRT 50 Gy Intra-cavitary 35-40 Gy	CT + RT	72%[2]	54%	84 months
				RT	--	48% (p = NS)	

Author	Stage	Neoadjuvant Chemotherapy	Radiation	Compa-rison	Response	Overall Survival	Median Follow-up
Herod 2000 N = 172	IB – IVA	Bleomycin 30mg Ifosfamide 5g/m^2 Cisplatin 50mg/m^2 Every 4 weeks x 2-3 cycles	According to Institution Policy	CT + RT	CR 53% PR 16%	3 years[1]	108 months
				RT	CR 37% PR 22%	2 years	
Tabata 2003 N = 61	SCC IIIB – IVA	Bleomycin 5mg/body (D1-7) Vincristine 0.7mg/m^2 (D7) Mitomycin 7mg/m^2 (D7) Cisplatin 10mg/m^2 (D1-7) Every 4 weeks x 3 cycles	EBRT 50 Gy Intra-cavitary 40 Gy	CT+RT	CR 53% PR 31%	43%	--
				RT	CR 35% PR 41%	52% (p = NS)	

[1]Median Survival; [2]Response to Chemotherapy; SCC - Squamous Cell Carcinoma; ASQ - Adenosquamous; EBRT - External Beam Radiotherapy; CT – Chemotherapy; RT – Radiotherapy; CR - Complete Response; PR - Partial Response

Table 2. Neoadjuvant Chemotherapy Prior to Radiotherapy versus Radiotherapy Alone

4.3 Data

There are over 20 randomized clinical trials exploring the role of neoadjuvant chemotherapy prior to radical radiotherapy. The trials differ in chemotherapeutic regimens, dosing schedules, inclusion criteria and control arms. However, while generally underpowered, all studies fail to detect a benefit of neoadjuvant chemotherapy prior to radiotherapy versus radiotherapy alone. In the era of concurrent chemo-radiotherapy, the concept of neoadjuvant chemotherapy prior to radiotherapy has seen reduced momentum. Some might argue that the correct dose, drug, or indication has yet to be identified or defined. Perhaps the approach of neoadjuvant chemotherapy prior to radiotherapy may warrant revisiting if new chemotherapeutic agents are introduced. In the meantime, the literature suggests no benefit, and indeed, perhaps harm, when chemotherapy precedes primary radiotherapy.

Souhami *et al.* (Souhami et al., 1991) was one of the first to publish a randomized, controlled trial, comparing patients receiving radiotherapy with or without neoadjuvant bleomycin, vincristine, mitomycin and cisplatin (BOMP). A complete response was seen following chemotherapy in 25% of patients. Following the completion of radiotherapy, there was no difference in response between treatment groups. Of the 91 patients with Stage IIIB disease, the 5-year survival was significantly superior in those receiving radiotherapy alone (39% versus 23%, p = 0.02). The mortality was driven predominantly by excess toxicity to chemotherapy, as there was no difference in locoregional or distant failures. The mortality due to chemotherapy was 10%. This trial was closed early due to the identified survival advantage in the control group.

Tattersall *et al.* (Tattersall et al., 1992) randomized 71 patients with stage IIB – IVA disease to radiation with or without neoadjuvant chemotherapy delivered as 3 cycles of cisplatin,

vinblastine, and bleomycin. At a median follow-up of 3.1 years there was no significant difference in overall survival. There were no excess complications of pelvic radiotherapy following neoadjuvant chemotherapy, suggesting that neoadjuvant chemotherapy prior to radiotherapy can be tolerated, however 7 of 34 patients randomized to neoadjuvant chemotherapy did not receive all 3 cycles. In both treatment arms the complete or partial response rate to radiotherapy was 89 – 94%, suggesting that the delay to receiving radiotherapy due to chemotherapy did not reduce the prospects of local disease control from pelvic radiotherapy. This study was underpowered, with a calculated sample size of 180 participants per arm. The trial was terminated early due to poor patient accrual and included 32 stage IIB, 3 stage IIIA, 29 stage IIIB, and 7 stage IVA patients, limiting the generalizability of results to patients with more advanced stage disease.

Kumar *et al.* (Kumar et al., 1994) randomized 184 patients with squamous cell carcinoma of the cervix, Stage IIB – IVA, to receive 2 cycles of bleomycin, ifosfamide, and cisplatin followed by radiotherapy (n = 94), versus radiotherapy alone (n = 90). At a median follow-up of 30 months and 22 months, respectively, there was no difference in overall or disease-free survival. When stratified by stage, there remained no difference in disease-free survival. This study was limited by sample size, with no pre-specified sample size calculation. Furthermore, the dose of cisplatin, at 50 mg/m^2 every 3 weeks, for 2 rather than 3 cycles, may have been insufficient to effect a response, as only 4.5% had a complete response to chemotherapy.

Chiara *et al.* (Chiara et al., 1994) randomized 61 patients with stage IIB – III disease to neoadjuvant and adjuvant cisplatin chemotherapy plus radiotherapy versus radiotherapy alone. The former group received 2 cycles of cisplatin prior to radiotherapy, followed by 4 cycles following radiotherapy. While chemotherapy did not worsen the morbidity of radiotherapy, follow-up at 3 years revealed no difference in recurrence, overall or progression-free survival. The study was limited by sub-therapeutic radiotherapy, with maximum total doses between 55 and 60 Gy, as well as a lack of pre-specified sample-size.

Tattersall *et al.* (Tattersall et al., 1995) then randomized 260 patients with stage IIB – IVA disease to neoadjuvant chemotherapy with 3 cycles of cisplatin and epirubicin plus radiation, versus radiation alone. While tolerance to the combined treatment was acceptable, and 63% of patients responded to chemotherapy alone, there was a significantly higher pelvic failure rate ($p < 0.003$) and lower disease-free survival ($p = 0.02$) at 3 years in those who received neoadjuvant chemotherapy.

Sundfor *et al.* (Sundfor et al., 1996) randomized 94 patients with Stage IIIB – IVA disease to 3 cycles of cisplatin and fluorouracil plus radiotherapy versus radiotherapy alone. At a median follow-up of 44 months there was no difference in survival, time to recurrence, local control, and metastases. There was suggestion of cross-resistance between chemotherapy and radiotherapy, as those who did not respond to chemotherapy were less likely to be cured by radiotherapy. This study planned for 150 patients per treatment arm, and was therefore underpowered.

Leborgne *et al.* (Leborgne et al., 1997) randomized 97 patients with bulky Stage IB – IVA disease to radiotherapy with or without 3 cycles of vincristine, bleomycin and cisplatin ("Quick VBP"). At 43 months follow-up there was no difference in locoregional control or disease-free survival. This study was also underpowered, planning for 75 patients per arm. Dose intensity was suboptimal in both groups. Compliance with chemotherapy was only 85%, and patients on chemotherapy received a lower dose of radiotherapy to the

parametria compared to controls. Lesion downsizing and clinical down-staging did not translate into a prolongation of disease-free survival. The study was stopped prematurely due to unequal response between the two arms, although no interim analysis was planned in the original protocol.

Sardi *et al.* (Sardi et al., 1998) performed a randomized trial of 295 stage IIB patients, divided between four arms. Patients either received radiotherapy alone (n = 73), surgery plus adjuvant radiotherapy (n = 75), neoadjuvant chemotherapy ("Quick VBP") plus radiotherapy (n = 71), neoadjuvant chemotherapy plus surgery and adjuvant radiotherapy (n = 76). At 7 years there was no difference in survival between treatment arms with the exception of tumours larger than 5 cm, where survival was improved with chemotherapy (66% vs. 36%, $p < 0.05$). Response to chemotherapy predicted survival.

Herod *et al.* (Herod et al., 2000) looked at the use of neoadjuvant chemotherapy followed by radiotherapy versus radiotherapy alone using bleomycin, ifosfamide, and cisplatin (BIP) in patients with stage IIB – IVA disease. This randomized multicentre trial of patients with inoperable cervical cancer found no difference in complete or partial response (59% with radiotherapy versus 69% with neoadjuvant chemotherapy followed by radiotherapy) or overall survival. In this study individual centres were permitted to choose their radiation protocol, approved by the Radiotherapy Steering Group prior to patient study entry. This trial was closed early due to poor patient accrual as media interest resulted in the demand, by patients and clinicians, for the new treatment off study. Despite the relatively well-tolerated BIP protocol, which contributed to rapid symptom relief in many patients (pain, bleeding and discharge), the power to detect a clinically significant difference of 15% in overall survival was only 50% given the study size.

Finally, one of the most recent studies comparing neoadjuvant chemotherapy prior to radiotherapy versus radiotherapy alone is that of Tabata *et al.* (Tabata et al., 2003). The choice of chemotherapeutic agents was based on reports of clinical efficacy of bleomycin, vincristine, mitomycin and cisplatin (BOMP). The overall response rate was 84% in those receiving neoadjuvant chemotherapy and radiotherapy compared to a 76% response to radiotherapy alone. Again, there was no difference in 5-year survival.

4.4 Systematic review and meta-analysis

Given the importance of the persistent question, whether neoadjuvant chemotherapy prior to surgery or radiotherapy has the potential to increase overall and disease-free survival, an updated systematic review and meta-analysis, using individual patient data, was performed to re-analyze the available trial data. The advantages of individual patient data over the use of published reports in a meta-analysis include: more sensitive time-to-event data, the ability to include non-published trials, the examination of different effects between treatment subgroups, and the use of updated follow-up. This was initiated and coordinated by the Medical Research Council (UK) Clinical Trials Unit and carried out by the Neoadjuvant Chemotherapy for Cervical Cancer Meta-analysis Collaboration (Tierney, et al., 2009) and published in 2009 in the Cochrane library. Trials opening after January 1975 and closing before September 2000 were included, examining the effects of neoadjuvant chemotherapy for patients with locally advanced cervical cancer (FIGO stage IB – IVA). Two outcomes were explored: 1) the effects of neoadjuvant chemotherapy prior to local treatment versus local treatment alone, and 2) neoadjuvant chemotherapy followed by surgery (with or without adjuvant radiotherapy) versus radiotherapy alone.

Trials comparing neoadjuvant chemotherapy prior to local treatment versus local treatment alone (the majority of which examined radiotherapy as the local treatment of choice), were included. Individual data on 2074 patients, from 18 trials, was obtained. This represented 92% of patients eligible from randomized trials performed between 1975 and 2000.

The majority of patients receiving neoadjuvant chemotherapy were administered cisplatin-containing regimens, with varying doses, dosing schedules, and drug combinations. Radiation treatments also varied by external beam and intracavitary dosing, and total dose received (55 – 80 Gy).

The median age of patients in this analysis was 48 years (range of median age across trials was 40-59 years) with good performance status. Patients were included with moderate or poorly differentiated stage II – III tumours of squamous cell histology, the greatest proportion made up of stage III disease (44%). The median follow-up overall was 5.7 years (range of median follow-up across trials was 1.5 – 9.0 years).

A major limitation of this meta-analysis was the significant level of heterogeneity between studies for all outcomes measured. The authors acknowledge that to combine the outcomes, given the significant differences noted between studies, would be inappropriate. However, when studies were grouped according to chemotherapy cycle length (greater or less than 14 days) or dose intensity (greater or less than 25 mg/m^2 per week), a large proportion of the heterogeneity was explained.

The authors found that cycles lasting longer than 14 days had a pooled Hazard Ratio of 1.25 (p = 0.005), suggesting a 25% increase in the risk of death in those receiving neoadjuvant chemotherapy, and an absolute reduction in 5-year survival of 8% (from 45% to 37%). Those with cycles lasting less than 14 days had a pooled Hazard Ratio of 0.83 (p = 0.05), suggesting a 17% decrease in the risk of death, and an absolute improvement in 5-year overall survival of 7% (from 45% to 52%). Heterogeneity was still present between studies with cycle length less than 14 days. When a small trial with an extreme Hazard Ratio (3.37) was excluded, the pooled Hazard Ratio became 0.76 (p = 0.005) with minimal heterogeneity.

When grouped according to cisplatin dose intensity, some of the heterogeneity between study results was explained. Those trials using cisplatin doses less than 25 mg/m^2 per week had a pooled Hazard Ratio of 1.35 (p = 0.002), suggesting a 35% increase in the risk of death and an 11% absolute reduction in 5-year survival (from 45% to 34%). Those trials using cisplatin doses greater than 25 mg/m^2 per week had a pooled Hazard Ratio of 0.91 (p = 0.2), suggesting a potential decrease of 9% in the risk of death, and a 3% absolute improvement in 5-year overall survival (from 45% to 48%). This analysis, however, was limited by the considerable heterogeneity, particularly amoung the trials with high dose intensity, making pooled analyses somewhat inappropriate.

These results are of interest, however, as they suggest that neoadjuvant chemotherapy may be beneficial if applied with adequate chemotherapy dose at optimal treatment intervals.

4.5 Criticisms of data

While some studies display improvement in disease-free or overall survival, other studies have shown detriment. The majority of trials are compromised by inadequate sample sizes as well as suboptimal use of both chemotherapy as well as radiotherapy. Given the variety of treatment protocols, interpretation of the data is difficult, as the most efficient and least toxic regimen of neoadjuvant chemotherapy is difficult to identify. The greatest limitation, however, is the lack of clinical trials comparing neoadjuvant chemotherapy to radiation

protocols that incorporate concurrent chemo-radiotherapy. Until a benefit can be demonstrated, above and beyond the survival advantage of chemo-radiotherapy, the use of neoadjuvant chemotherapy prior to radiotherapy cannot be considered an alternative.

4.6 Conclusions

As studied thus far, there is no convincing evidence that neoadjuvant chemotherapy improves survival. The randomized studies are limited by inadequate numbers to allow definitive conclusions, and many employ sub-optimal chemotherapy or radiation protocols. While surrogate markers, such as pathologic response and decreased tumour size may be promising, neoadjuvant chemotherapy prior to radiotherapy is not supported in the literature, and at present should only be considered in the setting of clinical trials where comparisons are made with the current standard treatment using concurrent chemo-radiation protocols.

5. Neoadjuvant chemotherapy prior to surgery versus radical radiotherapy

5.1 Rationale

The current standard of care in the treatment of bulky and locally advanced cervical cancer (stage IB2 – IIIB) is concurrent chemo-radiotherapy (Keys et al., 1999; Morris et al., 1999; Peters et al., 2000; Rose et al., 1999; Whitney et al., 1999). In the midst of ongoing trials investigating neoadjuvant chemotherapy prior to surgery or radiotherapy in the treatment of locally advanced cervical cancer, a National Cancer Institute Alert stated that "strong consideration should be given to the incorporation of chemotherapy with radiotherapy in women who require radiotherapy for the treatment of cervical cancer (National Cancer Institute, 1999). In a systematic review and meta-analysis of clinical trials, a 29% reduction in the risk of death, and overall survival benefit of 12% at 5-years was suggested by the results.
Randomized studies of neoadjuvant chemotherapy prior to radiotherapy versus radiotherapy alone, and neoadjuvant chemotherapy prior to surgery versus surgery alone were not able to reveal a consistent survival advantage. Whether neoadjuvant chemotherapy would allow patients to avoid radical radiotherapy is addressed in the following studies comparing neoadjuvant chemotherapy prior to surgery versus radiotherapy alone.

5.2 Data

Benedetti-Panici *et al.* (Benedetti-Panici et al., 2002**)** randomized 409 patients with stage IB2 – III squamous cell carcinoma to receive either neoadjuvant cisplatin-containing chemotherapy plus radical hysterectomy (with pelvic lymph node dissection) or standard radiotherapy. Of the 210 patients randomized to receive neoadjuvant chemotherapy and surgery, 164 underwent surgery, and 109 had negative lymph nodes and surgical resection margins. Therefore, 52% (109/210) of patients, who would otherwise have received radical radiotherapy, were treated with neoadjuvant chemotherapy and radical surgery only. Interestingly, there were 22 patients who demonstrated no residual tumour on final pathology, suggesting that in some patients, sufficient treatment may be with neoadjuvant chemotherapy alone.
Although 78% (164/210) of patients were made operable with neoadjuvant chemotherapy, the remaining 22% (46/210) received primary radiotherapy, and 34% (55/164) of those

undergoing surgery required adjuvant treatment. Neoadjuvant chemotherapy therefore did not avoid radiotherapy in 48% (101/210) of patients. Not included in this figure are those patients who, despite negative lymph nodes and surgical margins, might be considered for adjuvant radiotherapy based on other high-risk features. The added morbidity of treatment with combined chemotherapy, radical surgery, and adjuvant radiotherapy may outweigh the perceived benefits to a select subset of patients.

When compared to primary radiotherapy, however, Benedetti-Panici *et al.* found a survival benefit to neoadjuvant chemotherapy followed by surgery (Benedetti-Panici et al., 2002). When analyzed according to intention-to-treat principles, overall survival and progression-free survival were superior in those receiving neoadjuvant chemotherapy (overall survival 56.5% vs. 44.4%, respectively, $p = 0.01$; progression-free survival 55.4% vs. 41.3%, respectively, $p = 0.02$). While encouraging, this survival advantage was not uniformly distributed. When analyzed by stage, the significant benefit was seen mainly in patients with stage IB2 – IIB disease, and on subgroup analysis, in those with stage IB2 – IIA disease only. There was no significant survival advantage in patients treated for stage III disease. Radical surgery was possible in 85.5% of stage IB2 – IIB patients, compared to 55% with stage III disease ($p = 0.0001$) and there was a higher incidence of persistent disease in the lymph nodes and parametria in patients with stage III disease compared to stage IB2 – IIB (50% vs. 37%).

The median dose of radiotherapy received by control patients was only 70 Gy, and intracavitary treatment was not possible in 28% of patients. The generally accepted dose of radiotherapy is 85-90 Gy to Point A. Whether a difference in survival would persist if neoadjuvant chemotherapy plus surgery were compared to controls receiving a standard dose of primary radiotherapy or primary chemo-radiotherapy is unclear.

5.3 Systematic review and meta-analysis

Five randomized trials, including the work of Benedetti-Panici *et al* (Benedetti-Panici et al. 2002) were included in the systematic review and meta-analysis performed by the Neoadjuvant Chemotherapy for Cervical Cancer Meta-Analysis Collaboration. In this portion of the analysis, neoadjuvant chemotherapy prior to surgery versus radiotherapy alone was examined, and individual patient data was used (Tierney et al., 2009). A total of 872 patients, representing 97% of patients from known randomized trials were included. Patients received either cisplatin-containing neoadjuvant chemotherapy followed by surgery, or external beam radiotherapy (45-60 Gy) with subsequent intracavitary treatments (25-40 Gy).

The median age of study participants was 49 years (range 42 – 58 between trials), with good performance status. The majority had moderate to poorly differentiated tumours, stage IB – III, with squamous cell histology. Median follow-up was 5 years (range 3.9 to 9 years). The primary endpoint of the analysis was survival.

In 3 trials (Sardi et al., 1996; Sardi et al., 1998; Benedetti-Panici et al., 2002) patients receiving neoadjuvant chemotherapy followed by surgery demonstrated improved survival compared to those receiving radiotherapy alone. When all 5 trials were combined together, the direction of effect remained significant, with a Hazard Ratio of 0.65 ($p = 0.0004$) suggesting a 35% reduction in the risk of death and a 14% absolute improvement in survival at 5 years (from 50% to 64%). There was some heterogeneity between trial results.

In 2 of the trials included in the meta-analysis, greater than 90% of patients randomized to neoadjuvant chemotherapy also received adjuvant radiotherapy, and in 2 trials, 28% and

32% of neoadjuvant chemotherapy patients received adjuvant radiotherapy. The comparison being made, therefore, can be considered as triple modality treatment versus radiotherapy alone for many patients studied.

5.4 Conclusions

In the handful of studies exploring neoadjuvant chemotherapy prior to surgery versus radiotherapy alone, it is suggested that some patients may benefit from neoadjuvant chemotherapy followed by surgical resection. However, if the objective is to avoid primary or adjuvant radiotherapy, this goal is not easily achieved, and many patients may be subjected to triple modality treatment with the associated toxicity. Furthermore, since control arms were administered suboptimal doses of radiation, the survival advantage seen with neoadjuvant chemotherapy may not be replicated if compared to standard doses of radiation or radiation with concurrent chemotherapy.

6. Neoadjuvant chemotherapy prior to fertility-sparing surgery

6.1 Background

Radical hysterectomy with pelvic lymphadenectomy is currently considered the standard of care in the treatment of young women with stage 1B1 cervical cancer.

However, recently, greater emphasis is being placed on quality of life as well as minimization of long-term morbidity for those who survive cancer treatment. Cancer-related infertility has significant psychosocial impact on those who undergo treatment for gynecologic malignancies, including increasing rates of depression, stress and sexual dysfunction (Carter et al., 2005). Where possible, it is of foremost importance for gynecologic oncologists to minimize such effects, improving not only oncologic outcomes, but also the emotional well-being of their patients. A prominent concern of young women undergoing treatment for cervical cancer is the preservation of childbearing function in the post-treatment period.

The possibility of maintaining high cure rates while preserving the reproductive organs has been an area of active research over the past 10 years. Due to improvements in cervical screening, more women have been identified with early stage disease for whom fertility-sparing treatments can be considered. These advances also come at a time when greater proportions of newly diagnosed cases of cervical cancer are in nulliparous women (as many have postponed childbearing). The option of preservation of fertility is of great concern to a majority of such patients.

Options for the surgical management of early-stage cervical cancer include cervical conization or radical trachelectomy, the latter of which may be performed via a trans-abdominal or trans-vaginal approach.

Radical vaginal trachelectomy, first described by Dargent in 1994, involves removal of the cervix, the parametria, and part of the vaginal cuff, while preserving the uterine fundus, ovaries and fallopian tubes. This procedure, in combination with a laparoscopic pelvic lymphadenectomy, is the most common and accepted fertility- sparing procedure for early-stage cervical cancer. When compared to historic cohorts, this procedure has a comparably recurrence (4% - 5%) and mortality (2.5% - 3%) (Dursun et al., 2007; Plante et al., 2004; Plante, 2008). However, the removal of the cervix and paracervical tissue has been associated with cervical insufficiency, with a two-fold increase in second-trimester losses

compared to the general population, and a 30% incidence of preterm delivery (Beiner & Covens, 2007; Boss et al., 2005; Plante, 2008). Due to the placement of a permanent cervical cerclage at the time of trachelectomy, cesarean section is required to achieve delivery.

An alternative to radical vaginal trachelectomy is the radical abdominal trachelectomy, performed either open or laparoscopically (Abu-Rustum et al., 2008; Cibula et al., 2005; Geisler et al., 2008). While oncologic outcomes have yet to be compared, the abdominal approach may extend the inclusion criteria for patients interested in fertility sparing to those with larger primary cervical lesions (up to 4 cm in diameter). Patient selection is still restricted to those without evidence of metastatic disease (Del Priore et al., 2004; Ungar et al., 2005).

The most recent consideration is whether a radical trachelectomy is required for all invasive cervical cancers, or whether more conservative treatments might be offered, such as cone biopsy or simple trachelectomy. Recent publications have shown promising results, suggesting that such an approach may be acceptable for individually selected "low-risk" patients (Covens et al., 2002; Rob et al., 2008; Smith et al., 2010)..

6.2 Rationale

The eligibility criteria for fertility-sparing surgery typically requires lesions less than 2 cm in diameter, and less than 2/3rsd cervical stromal invasion, based on clinico-pathologic studies among patients with stage IA1- 1B1 disease (Covens et al., 2002). As such, it is not uncommon for women to be denied the option of fertility-preserving surgery in preference for radical radiotherapy.

The objective of neoadjuvant chemotherapy in patients seeking fertility preservation is primarily a reduction in the tumour size in order to facilitate resection. With complete or partial response to chemotherapy, tumours measuring 3 – 4 cm in diameter may become operable. Cure rates would be expected to be similar to those receiving primary radiotherapy, as the use of adjuvant radiotherapy for high risk pathologic findings would tend to negate any difference.

6.3 Neoadjuvant chemotherapy prior to fertility-preserving surgery

The use of neoadjuvant chemotherapy to reduce tumour size and potentially "sterilize" micrometastases in the paracervical tissues and pelvic lymph nodes has been investigated in several randomized controlled trials. If successful, a woman with a previously inoperable tumour may become a surgical candidate. Unfortunately studies were inconclusive, either due to methodological flaws or limitations in patient accrual and sample size (Benedetti-Panici et al., 2002; Cai et al., 2006; Chen et al., 2008; Eddy et al., 2007; Napolitano et al., 2003; Sardi et al., 2007).

A review of the literature describing neoadjuvant chemotherapy prior to fertility-preserving surgery reveals only a handful of publications, all of which are case-series. The largest series, by Maneo *et al.* (Maneo et al., 2008), explored the role of neoadjuvant chemotherapy followed by cold knife conization and pelvic lymphadenectomy. The single-centre study enrolled 51 nulliparous patients with Stage IB1 cervical cancer. Patients were deemed eligible if they were younger than 40 years of age, with tumor size less than 3 cm and had no lymphovascular space involvement. Neoadjuvant chemotherapy consisted of three cycles of cisplatin 75 mg/m^2, paclitaxel 175 mg/m^2 and ifosfamide 5 g/m^2 (substituted by epirubicin 80 mg/m^2 in cases of adenocarcinoma) every 3 weeks. Thirty patients (59%) decided against

the planned conservative therapy and 1 patient refused conservative surgery following completion of chemotherapy. Among 20 patients receiving the treatment protocol, all but 4 showed a clinical response to chemotherapy and eventually underwent a cold knife conization. The 4 women who were ineligible for conservative surgical treatment underwent radical hysterectomy, and 2 received adjuvant radiotherapy due to positive lymph node metastases. After the completion of neoadjuvant chemotherapy all 16 remaining patients demonstrated a complete clinical remission or minimal persistence of disease. There were no severe chemotherapy-associated toxicities, and only 1 patient was unable to tolerate all 3 cycles due to the development of hepatic toxicity. There were no perioperative complications, and only 1 patient developed cervical stenosis. Among patients who completed the planned protocol there were no recurrences after a median follow-up of 69 months. There were 10 pregnancies among 6 of 9 patients attempting to conceive, resulting in one spontaneous miscarriage and 9 term deliveries.

The authors concluded that neoadjuvant chemotherapy followed by cold knife conization and pelvic lymphadenectomy should be used with caution, with careful patient selection and inclusion only of motivated women with a strong desire for future childbearing, recognizing the limitations of a small sample size in the assessment of oncologic outcomes.

Plante *et al.*, from Canada, reported a single-institution's experience using neoadjuvant chemotherapy followed by vaginal radical trachelectomy (Plante et al., 2006). Three patients had stage IB1 cervical lesions with tumour size ranging from 3 to 4 cm. Neoadjuvant chemotherapy consisted of 3 cycles every 3 weeks of paclitaxel 175 mg/m^2 on day 1, cisplatin 75 mg/m^2 on day 2 and ifosfamide 5 g/m^2 over 24 hours with mesna 5 g/m^2 on day 2 and 3 g/m^2 on day 3 with continuous hydration. One patient developed febrile neutropenia following the first cycle of chemotherapy. Reduction of tumor size was reported in 2 patients. Over a period of 2 months all patients underwent successful laparoscopic sentinel lymph node dissection followed by pelvic lymphadenectomy and vaginal radical trachelectomy with no perioperative complications. Postsurgical pathological examination revealed no residual disease and focal carcinoma in-situ in 2 and 1 patient, respectively. None of the patients had parametrial or lymph node involvement. At the time of report, all patients were alive without evidence of disease.

A single case report from China (Liu et al., 2008) described a 24 year old nulliparous woman with a 2 cm cervical lesion encroaching the left vaginal fornix. It was a poorly differentiated squamous cell carcinoma without evidence of lympho-vascular space invasion. She was treated with one cycle of bleomycin 15 mg/m^2 on day 1 and 2, and cisplatin 70 mg/m^2 on day 1. She underwent a trans-peritoneal lymphadenectomy 10 days later followed by radical abdominal trachelectomy. The final pathology demonstrated only focal residual disease (5.5 mm by 3 mm). The patient recovered well and 2 years later delivered at 35 weeks gestation via cesarean section.

Robova *et al.*, from the Czech Republic, described their group's experience with 5 patients under the age of 40 with Stage IB1 cervical cancers greater than 2 cm in diameter with less than 2/3rsd stromal invasion (Robova et al., 2008). All patients received 3 cycles of neoadjuvant chemotherapy every 10 days consisting of cisplatin 75 mg/m^2 and ifosfamide 2 g/m^2 (substituted by doxorubicin 35 mg/m^2 in cases of adenocarcinoma). Patients underwent laparoscopic sentinel lymph node dissection followed by simple trachelectomy. Tumours ranged in size from 20 by 15 mm to 44 by 36 mm. There were 3 cases of squamous cell carcinoma, and 2 cases of adenocarcinoma. All cases had lympho-vascular space

involvement. Final pathology revealed no residual tumor in 2 patients, microscopic residual tumor in 2 patients, and a 13 by 6 mm residual tumor in 1 patient. At the time of publication, all patients were reported alive with 2 full term pregnancies achieved in 2 patients, conceived 5 and 8 months following completion of treatment.

6.4 Conclusions

Fertility preservation with successful obstetrical outcomes is possible following neoadjuvant chemotherapy and fertility-sparing surgery. At present, however, the management of locally advanced cervical cancer in women wishing to preserve fertility is supported by only 25 published cases.

The most commonly used chemotherapeutic regimens are combinations of platinum, paclitaxel and ifosfamide given in 3 cycles. This combination has been the most widely studied in the neoadjuvant setting for patients with cervical cancer undergoing further radical surgery (Benedetti-Panici et al., 2002; Cai et al., 2006; Chen et al., 2008; Eddy et al., 2007; Napolitano et al., 2003; Sardi et al., 2007). However, alkylating agents such as ifosfamide and cisplatin can be detrimental to ovarian follicles, and less gonadotoxic regimens should be evaluated in the future (Plante et al., 2006).

In the absence of long-term follow-up and greater patient numbers, conclusions regarding safety, efficacy and reproductive outcomes are only speculative. This approach should therefore be considered to be experimental, performed only in carefully selected patients, in centers with high levels of expertise.

7. Ongoing research

While neoadjuvant chemotherapy in the treatment of cervical cancer has shown limited benefit in the majority of patients for whom radical surgery or chemo-radiotherapy is available, there are questions regarding its utility that remain unanswered. Neoadjuvant chemotherapy followed by surgery has not been compared to chemo-radiotherapy, for instance, nor has neoadjuvant chemotherapy prior to chemo-radiotherapy been examined.

There are currently two ongoing randomized phase III trials exploring neoadjuvant chemotherapy followed by surgery versus chemo-radiotherapy. These include EORTC Protocol 55994 and NCT00193739. Eligibility for the former study includes FIGO stage IB2, IIA > 4 cm and IIB disease. Activated in March of 2002, this study is currently open, with a targeted sample size of 686 patients. While limited by unstandardized neoadjuvant chemotherapy protocols, these results may help to determine whether neoadjuvant chemotherapy prior to surgery is a useful alternative to chemo-radiotherapy. Given the different levels of response seen with varying chemotherapeutic regimens (Buda et al., 2005; Lissoni et al., 2009), the use of a generic platinum-based protocol, and allowing centres to select their protocol, may again lead to inconclusive results. The latter study, activated in September 2003, with a targeted sample size of 730 patients, was scheduled to close in September 2010. Eligibility includes FIGO stage IB2 – IIB squamous cell carcinoma, and the study will compare 3 cycles of paclitaxel-carboplatin neoadjuvant chemotherapy followed by surgery versus concomitant chemo-radiotherapy.

Phase II studies include the NCRI Gynaecological Cancer Clinical Studies Group investigation "CxII" of weekly neoadjuvant carboplatin/paclitaxel followed by radical chemo-radiotherapy. Including patients with FIGO stage IB2 – IVA disease, this study was

closed in November of 2008 and is currently in follow-up. As carboplatin-based regimens are expected to display similar effectiveness to cisplatin, but with easier administration and less toxicity, results of response rate and feasibility are intended to identify a regimen to be used in a subsequent phase III trial. Results presented at ASCO 2009 (McCormack et al., 2009) suggested high response rates with limited grade 3 and 4 toxicity.

8. Conclusions

The primary objectives of neoadjuvant chemotherapy in the treatment of cervical cancer include improvement in tumour characteristics to allow avoidance of radiotherapy, prolonged disease-free and overall survival, and facilitation of fertility-sparing surgery.

While some evidence supports the use of neoadjuvant chemotherapy in patients with early stage disease to permit surgical resection, improving pathologic risk factors and operability, a large proportion of patients ultimately require adjuvant radiotherapy, negating the benefit of neoadjuvant chemotherapy, and subjecting patients to triple modality treatments. Control patients received suboptimal doses of radiotherapy, however, making any comparison of treatment invalid and uninterpretable. How neoadjuvant chemotherapy followed by surgery in early stage disease compares to radiotherapy with concurrent chemotherapy has not been studied, and therefore, given the demonstrated survival advantage of primary chemo-radiotherapy, the use of neoadjuvant chemotherapy followed by surgery cannot be recommended as a superior or even equivalent option at this time.

Upon review of the available evidence, there has been no consistently proven benefit in overall survival to neoadjuvant chemotherapy prior to surgery (versus surgery alone) or radiotherapy (versus radiotherapy alone). Most randomized studies include inadequate patient numbers to support conclusions. The effect of neoadjuvant chemotherapy is then obscured by the addition of adjuvant radiotherapy.

Fertility preservation with successful obstetrical outcomes following neoadjuvant chemotherapy and fertility-sparing surgery has been possible. Women who would otherwise be treated with radiotherapy may be made operable. While promising, this approach is supported only by case series, and should therefore still be considered experimental.

In summary, neoadjuvant chemotherapy in the treatment of cervical cancer has limited applicability. Any use of such therapy should be in the setting of appropriately powered clinical trials, with comparisons made to the current standard of treatment using optimal chemo-radiation protocols.

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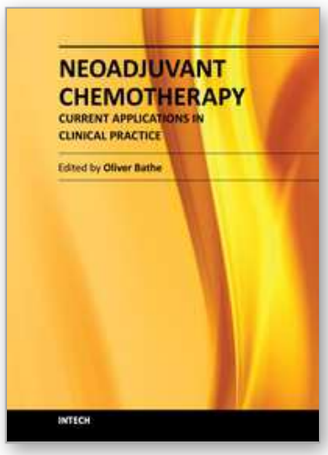

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The most significant advances in cancer therapy in recent years have involved the development of systemic therapeutics. With improvements in response rates in solid tumors, opportunities have arisen to enhance the effectiveness of surgery. Administration of systemic therapy prior to surgery - neoadjuvant chemotherapy - represents one approach by which clinicians have successfully reduced the extent of surgery and, in some instances, positively impacted on clinical outcomes. This collection of works by expert clinicians from a variety of disciplines represents an exploration of the current knowledge of the role of neoadjuvant chemotherapy in diverse tumor types.

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