The copyright of this thesis vests in the author. No quotation from it or information derived from it is to be published without full acknowledgement of the source. The thesis is to be used for private study or non-commercial research purposes only.

Published by the University of Cape Town (UCT) in terms of the non-exclusive license granted to UCT by the author.
“A retrospective study of patients with Stage IB2 cervical cancer treated at Groote Schuur Hospital 1993-2008”.

by

STUDENT: KELLIE ALLEYNE-MIKE
ALLKEL002

SUBMITTED TO THE UNIVERSITY OF CAPE TOWN
In partial fulfilment of the requirements for the degree

MMed Radiation Oncology

Supervisors: Leon Van Wijk, (Division of Radiation Oncology)
Alistair Hunter (Radiobiology Section),
Groote Schuur Hospital / University of Cape Town
Date of submission: 31st January 2013
DECLARATION:

I, DR. KELLIE ROZELLE ALLEYNE-MIKE, hereby declare that the work on which this minor dissertation is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university.

I empower the university to reproduce for the purpose of research either the whole or any portion of the contents in any manner whatsoever.

Signature
Signed by candidate

Date: 24\textsuperscript{th} May 2013
ACKNOWLEDGEMENTS:

My first word of thanks is to God for His wisdom and guidance. I am grateful for my family and in particular my mother, Evelyn, my grandmother, Iva Elizabeth and my brother, Kevin for their steadfast emotional support.

I would also like to extend my gratitude to Dr. Leon Van Wijk for his unparalleled patience and wealth of advice and to Dr. Alistair Hunter for his invaluable input and collaboration on this research endeavour. I would also like to especially express my appreciation to Professor Raymond Abratt and Professor Robbert Soeters for their review and insight.

A particular note of thanks for the support I received from the clerical staff who made sure that the entire data collection process flowed effortlessly. Finally, I would like to express my gratitude to my sponsor, the Government of the Republic of Trinidad and Tobago, for granting me the opportunity to participate in this programme of research.
# TABLE OF CONTENTS:

## PART A:

- Abstract and Study Protocol 6

## PART B

- Structured Literature Review 11

## PART C

- Publication-Ready Manuscript 26

## PART D- Appendices

- I: Data Capture Instrument 47
- II: Official Ethics approval letters 53
- III: Journal Guidelines for Authors 59
PART A
PART A: ABSTRACT AND STUDY PROTOCOL

ABSTRACT:

Objective: To compare the efficacy of treatment modalities in patients with stage IB2 cervical cancer treated at Groote Schuur Hospital, Cape Town, South Africa.

Materials and methods: This was a retrospective observational study of patients with stage IB2 cervical cancer treated from 1993-2008 with either primary radiation therapy (RT), with or without follow-on hysterectomy, or primary surgery (with or without adjuvant RT). Weekly cisplatin given concurrently with RT was used since 2003. Patient outcomes and grade 3-4 treatment-related toxicities were recorded.

Results: The study included 78 eligible patients for whom the 5-year overall survival rate was 70.8%. Overall 5-year survival rate by treatment modality was 88% for the 25 patients in the surgery group and 62.5% for the 53 patients in the RT group, respectively. There was a marked difference in the proportion of patients in each group receiving additional therapy: 88% of patients in the primary surgery group had adjuvant RT, while only 5.7% of patients in the primary RT group went on to have a hysterectomy. Grade 3-4 toxicity was found in 13.2% of the RT versus 4% for the surgery group (p=0.4).

Conclusion: The optimal primary treatment for stage IB2 cervical cancer remains unclear. Both types of primary treatments were found to be feasible therapeutic approaches. Primary surgery appears to have better survival outcomes at our institution. Selection bias and inadequate concurrent chemotherapy in 58% of patients receiving primary RT may account for the difference in survival.

The number of patients in the surgery group requiring “bimodal” adjuvant treatment has cost implications in our resource-constrained environment, hence primary concurrent chemoradiation is being increasingly utilized for stage IB2 cervical cancer at our institution. Evidence from a randomized controlled study is needed to determine the optimal treatment for stage IB2 cervical cancer.
Title of Project:

A retrospective study of patients with Stage 1B2 cervical cancer treated at Groote Schuur Hospital 1993-2008

Research Question:

Are there differences in outcome with patients with stage 1B2 cervical cancer treated with radical radiation/chemo-radiation versus radical surgery as primary modality for patients at Groote Schuur Hospital in Cape Town, South Africa, during the years 1993-2008?

Aim of the Study:

To establish by means of a retrospective audit the comparison between outcomes for patients with cervical cancer stage 1B2 who were treated either with surgery or with chemo-radiation as the primary modality treatment for the period 1993 till 2008.

Primary endpoint:

➢ Overall survival.

Secondary endpoints:

➢ Monitoring of Grade 3 or 4 toxicities.

Materials and Methods:

The study period is from 1993 till 2008.
Inclusion criteria for the study are:

- Patients with histologically proven squamous carcinoma, adenocarcinoma or adenosquamous carcinoma of cervix.

- Stage IB2 cancers (based on the FIGO sub-staging for stage IB cervical cancer introduced in 1988).

Exclusion criteria for the study are:

- Patients in the primary radiation (or chemo-radiation) group who have received an external beam dose to the whole pelvis of less than 45 Gray (LQED2).

- Patients in the primary surgery group who had surgery less than a radical hysterectomy and no pelvic lymphadenectomy.

- Small cell cancer of the cervix.

- Patients who have not received brachytherapy.

- Patients lost to follow-up less than one year after completion of primary treatment.

Patients will be selected from a departmental gynaecological clinical database. Data will be extracted from this database and supplemented from individual patient folders. Direct patient contact is not a requirement for this study.

Patients were assessed by a combined (multi-disciplinary) team where the initial staging assessment was done. The decision as to the primary treatment was made by the multi-disciplinary team and in making that decision, factors such as patient age, co-morbidities, performance status and extent of disease were taken into consideration.

Patients treated with surgery as their primary treatment had post-operative pathological review to determine whether the risk of microscopic residual disease warranted adjuvant treatment (radiation, chemotherapy or both). The risk factors considered were primary tumour size, depth of stromal invasion, presence of lymph node metastases, adequacy of resection lines, lympho-vascular space invasion (LVSI) and/or microscopic parametrial involvement.

Similarly, patients with primary (chemo-) radiation therapy were assessed after 2-3 months for tumour response. Patients with suspicion of residual cancer were considered for follow-on
hysterectomy as part of the primary treatment course. This ‘salvage’ surgery must be done within four months of the completion date of chemo-RT to be considered as part of the primary treatment. Evidence of disease found after this period was assessed as loco-regional recurrence (with or without distant metastases).

Surgical intervention involved radical (Wertheim’s) hysterectomy and pelvic lymph node dissection. The ovaries were preserved in premenopausal patients.

Radiation therapy involved either:

- **Primary radiation** (or concurrent chemo-radiation (CRT) with weekly cisplatin at a dose of 40mg/m², capped at 60 mg per dose). External beam radiotherapy (EBRT) doses varied over the study period but exceeded 45 Gy. Intracavitary therapy (ICT) with Iridium high dose-rate after-loading brachytherapy was incorporated in the latter half of the EBRT course.

- **Adjuvant** whole pelvic RT (or CRT with weekly cisplatin) following primary surgery, as part of the primary treatment course. In selected cases, a “reduced pelvic volume” was used, depending on the individual risk factors for recurrence. In some cases, vaginal ICT was added.

Treatment related morbidity (RTOG grades 3-4) will also be recorded and evaluated for each primary treatment group to better assess the respective “therapeutic ratio” of the two approaches.

A spreadsheet containing all the relevant data points will be generated. Treatment outcomes and toxicity scores will be grouped according to the primary therapy and compared with the log-rank test. Of additional interest would be the proportion of patients in each of the two treatment approaches who undergo “double treatment”; in other words, requiring adjuvant RT after primary surgery, or surgery after primary RT, respectively.

A discussion of the findings will be prepared in relation to the relevant literature, made available through an internet search. This literature will be referenced and acknowledged with the audit.

Apart from the primary purpose of this audit project, it is hoped that the findings will also contribute to future decision-making in the Combined RT-Gynaecology Clinic.

Dr. Kellie Alleyne-Mike

Division of Radiation Oncology

L-Block

Groote Schuur Hospital.
PART B
PART B: STRUCTURED LITERATURE REVIEW:

OBJECTIVES OF THIS LITERATURE REVIEW:

The objectives of this review are to provide the reader with the background and justification for the research, to describe the work already done in this field, and then to collate this information so as to evaluate and establish its relevance. Analysis may help to identify areas where further study is needed.

Marshall and Rossman (1999) have stated that a discussion of related literature “builds a logical framework for research and sets it within a tradition of enquiry and a context of related studies”. Research is about contributing to a knowledge base; knowing what others have done and discovered is an important first step towards formulating the research question. Whilst one has to be cautious of the extent to which one’s research simply replicates that of previous investigators, the literature review could, in the opinion of this writer, play a confirmatory role in quantitative research by strengthening an evidence base.

LITERATURE RESEARCH STRATEGY:

This literature review was conducted by utilising searches of Science Direct, EBSCO, The Cochrane Library, Google Scholar and PubMed, provided through the University of Cape Town library resources. The search strategy employed keywords related to treatment of “bulky early cervical cancer” and stage IB2 cervical cancer. Review of the relevant abstracts identified by the search was first undertaken and, subsequently, the full article publications were assessed. Articles were chosen, based on relevance to the topic and the level of evidence.

In the hierarchy of evidence generally accepted in clinical and other scientific research, meta-analyses are deemed to occupy the highest tier. However, evidence based medicine further includes information from randomised controlled trials (RCT’s) which carry relatively more weight when compared to cohort, case-control, or cross-sectional studies. Many peer-reviewed journals were sourced to allow for adequate diversity in the review of the chosen topic.
INTRODUCTION TO THE LITERATURE REVIEW FOR THIS STUDY

The treatment of cervical carcinoma is generally based on the disease stage however, there are other determinants which influence the choice of therapy such as the tumour volume and extent within a specific stage, availability of treatment modalities, therapeutic skills, patient preference, co-morbidities and the performance status of the patient. The subdivision of stage IB (macroscopic tumour confined to the cervix) into IB1 and IB2 was recommended in 1995: stage IB1 tumors are ≤4 cm in diameter, and stage IB2 tumours are >4 cm. This subdivision addresses the issue of tumour bulk within a stage IB, taking into account that patients with large stage IB tumors may have a worse prognosis and a greater tendency for lymph node metastasis (Creasman 1995).

For stage IB2, patients are treated with either primary surgery in the form of radical hysterectomy, with or without adjuvant radiotherapy, or primary radiation therapy (RT), with or without additional hysterectomy. It should be noted that for the past decade, both adjuvant and primary radiotherapy are delivered concurrently with cisplatinum-based chemotherapy. In this report, such concurrent chemo-radiation is abbreviated as CRT.

The current study explores the treatment methods and outcomes of stage IB2 cervical cancer patients managed at Groote Schuur Hospital between the years 1993-2008. Many reports have been published in the past, mostly as single institution retrospective series, exploring the management of “bulky” stage I cervical cancer. In order to interpret and discuss the results of the current study, a survey of the available literature was conducted and the pertinent areas of interest were:

a) relative effectiveness of surgery versus RT as primary treatment for stage IB2 cervical cancer;

b) definition of adverse prognostic features in post-operative series;

c) preoperative factors and biological factors assessed during treatment;

d) effectiveness of adjuvant RT (or CRT), after primary surgery;

e) retrospective studies of stage IB2 cervical cancer;

f) utilising reduced pelvic volume (RPV) adjuvant radiation in node-negative patients;

g) relative cost-effectiveness of the two primary modalities in stage IB2 cervical cancer;

h) neoadjuvant chemotherapy.
LITERATURE REVIEW:

a) Relative effectiveness of Radiation versus Surgery:

The merits of primary surgery include pathologic assessment of the extent of the disease, the preservation of ovarian and vaginal function and a shorter treatment time if used as a single modality. However, two treatment modalities are often required. Primary CRT usually does not require adjuvant treatment but the duration of the treatment course is longer and there is a risk for delayed toxicity (Ackerman 2004; Moore 2003). In our study the criteria for salvage hysterectomy following primary CRT included patients who had histological confirmation of disease recurrence within 4 months of completing RT. Thus patients presenting with relapse subsequent to this were not considered as requiring dual modality as part of their primary treatment. An early study of the efficacy of surgery versus RT in stage I cervical cancer was reported by Morley and Seski (cited by Moore, 2003). They compared 208 women receiving radical hysterectomy with 193 women treated with pelvic irradiation and brachytherapy between 1945-1975. The methodology was stated as a “modified alternating series”. The corrected survival rates at five years were 87.3% for surgery versus 91.3% for RT, with similar complication rates. Similar results were published by Volterrani and Feltre in 1983 in a retrospective study of 250 patients with stage I cervical cancer. Disease-free survival at five years was 90.9% and 89.3% for surgery versus RT, respectively. These early reports were important in adding knowledge about what constitutes best practice in early cervical cancer.

An important RCT in early cervical cancer was reported by Landoni and co-workers in 1997. Most of the 337 patients enrolled in the trial had squamous pathology. Of note, 32% of the patients had tumours greater than 4 cm in both the surgical and the RT arms. Adjuvant RT was performed in 84% of the surgical cases if the tumour was >4 cm, versus 54% for smaller tumours. Apart from the adequate sample size, a further strength of the study was a median follow-up of 84 months. The five year actuarial overall survival rate was shown to be statistically similar in both the treatment groups: 83% for surgery and 74% for RT. An equal proportion of women in both groups developed recurrence (25% and 26% in the surgical and radiotherapy arms, respectively). The authors concluded that there was no difference in outcome with regard to primary treatment modality for squamous carcinoma; however, more patients in the surgery group experienced serious treatment-related morbidity (28%, versus 12% in the RT group).

b) Histopathologic prognostic factors in post-operative cases:
Decision-making for adjuvant therapy depends on the identification of histopathological factors which denote recurrence risk.

Two Gynaecology Oncology Group (GOG) studies examined the influence of histopathological factors in surgically treated stage IB squamous carcinoma. Histological grade did not predict for nodal spread or DFI but increasing stromal invasion and, to a lesser extent, (LVSI) were predictive (Delgado et al., 1990). In another report, reviewing surgically treated patients who were node negative, a score was devised based on the presence of LVSI, the depth of stromal invasion, and tumour size. A “GOG score” of 120 or larger was associated with a 3-year DFI of around 60%, which may warrant adjuvant RT (Delgado et al., 1989).

Subsequent GOG studies examined the role of adjuvant therapy in stage IB cervical cancer, in which the following risk categories were proposed:

1) High-risk: the presence of positive nodes, parametria and/or resection lines (Peters et al., 2000).

2) Intermediate-risk:

- Presence of LVSI plus deep third cervical stromal invasion and tumour of any size.
- Presence of LVSI plus middle third stromal invasion and tumour size ≥2 cm.
- Presence of LVSI plus superficial third stromal invasion and tumour size ≥5 cm.
- No LVSI but deep or middle one-third stromal invasion and tumour size ≥4 cm (Sedlis et al., 1999).

Low-risk denotes the absence of the above factors.

The issue of “close” resection margins has not been specifically defined in GOG studies. Resection margin status after radical hysterectomy in stage IB cervical cancer was assessed by Viswanathan and co-workers (2006), who concluded that post-operative radiation therapy may decrease local recurrence in patients with “close” (> 0 but < 10 mm) para-cervical margins. Their study showed that the addition of adjuvant radiation therapy improved relapse-free survival (RFS) in all margin groupings, although the authors were cautious to recommend it where a close margin is the only risk factor.
Biewenga et al. (2009) have reviewed 12 published prognostic models which purport to predict survival and recurrence in early stage cervical cancer. These models were retrospectively applied to a group of 512 patients, and an analysis made of each model’s performance. All models underestimated the recurrence-free survival or disease specific survival. Only two were well suited for use in the population being assessed. The authors concluded that the difference in performance was due to the degree of heterogeneity in the choice of risk factors in each model, and because the individual factors were all equally weighted.

The use of established prognostic factors has proven to be valuable in aiding decision making regarding adjuvant treatment, but caution must be taken in the model chosen for a particular population.

c) Pre-operative factors and biological factors assessed during treatment.

An important prospective study was carried out by Dunst et al (2003). This study identified the haemoglobin level as a strong predictor of local response to radiation therapy (both pre-treatment levels and those during treatment). Angiogenesis was also determined by measuring the grade of vascularization which, if increased, along with poor tumour oxygenation, was found to have an adverse effect on local tumour control and survival.

Other pre-operative factors which affect the response to treatment of patients with cervical cancer have been identified by Lai et al (1999) in a retrospective series. Variables such as the tumour stage (assessed by clinical examination), depth of stromal invasion (detected using magnetic resonance imaging), tumour de-differentiation, tumour size and DNA index (evaluated by flow cytometry) were all independent predictors of outcome after multivariate analysis was done.

Apart from tumour size, none of these factors were evaluated in the present study. The influence of haemoglobin levels will be the subject of further study in our institution, since low haemoglobin levels can be managed in an effort to improve local response. The other biological factors, while valuable indicators of treatment outcome, are not yet in routine clinical usage.

d) Effectiveness of RT (or CRT) after primary surgery:
Concurrent chemo-radiation is now considered to be the standard of care for cervical cancer, as opposed to radiation therapy alone. This view is based on information derived from five RCTs (Keys et al. 1999; Whitney et al. 1999; Rose et al. 1999; Peters et al. 2000; Eifel et al. 2004). In addition, various meta-analyses have confirmed the superiority of CRT over RT alone in cervical cancer. Green et al. (2001) found an improvement in overall survival (OS) with both platinum (HR 0.70, p<0.0001) and non platinum based regimes (HR 0.81, p=0.20). Progression-free survival (PFS) was also better with chemo-radiation (HR 0.61, p < 0.0001). The authors concluded that the absolute benefit in OS was 16%, with a 12% benefit in PFS, and a reduction in risk of death of 31%. This meta-analysis also evaluated grade 3 and 4 toxicities. Haematological toxicity was the most common adverse effect documented. Gastro-intestinal tract (GIT) toxicities were more significant in the CRT treatment arm when compared to control: 9.4% versus 4.3% (p<0.0001).

In 2010, the Cochrane Group in the United Kingdom reviewed 18 randomised clinical trials of CRT in cervical cancer. The hazard ratios for each stage were assessed and they showed a 10% increase in the 5-year survival when compared to RT alone for stages IB to IIA, which has relevance for the current study.

One subgroup of early cervical cancer requiring post-operative adjuvant therapy does not appear to have been examined in the context of CRT versus RT in the setting of a RCT. The GOG study of Sedlis and co-workers (1999) randomised 277 patients with intermediate-risk factors and stage IB disease who had undergone radical hysterectomy to adjuvant radiation therapy or to no further treatment. There was a statistically significant reduction in the risk of recurrence for patients who received adjuvant radiation therapy (p=0.008) but this was accompanied by a concomitant increase in grade 3 and 4 toxicities.

The follow-up to this study, published in 2006 by Rotman and co-workers, reported a sustained improvement in progression-free survival at 12 years follow-up (p=0.009) along with a reduced recurrence risk (p=0.007). However, the authors noted that overall survival was not significantly different in the two arms after six years of follow-up (p=0.07). Death due to non-disease related causes was suggested as the rationale for this unexpected finding as only four patients in the radiation arm recurred after this period. They also suggested that the power of the study may not have been sufficient to portray the continued survival benefit. A benefit in OS was observed in patients with adenocarcinoma as opposed to squamous carcinoma. While this study has established the benefits of adjuvant RT in patients with
intermediate-risk factors, the GOG has initiated a study of adjuvant CRT versus RT in this group (NCI 2010).

Regarding adjuvant therapy in the high-risk group (positive margins, parametria, and/or pelvic lymph nodes), the study by Peters and colleagues demonstrated the benefit of CRT in this subset of patients. Patients were randomised to RT, or RT with four cycles of cisplatinum and 5-fluorouracil chemotherapy. The addition of concomitant chemotherapy improved both OS and DFI (Peters et al., 2000).

The number of concomitant chemotherapy cycles also appears to be important. Nugent and co-workers (2010) retrospectively evaluated the effect on OS and PFS of completing six cycles of weekly cisplatinum concurrent with RT. Their study of 118 patients included stages I to IV, including 34% IB2 patients. In multivariate analysis, the number of chemotherapy cycles was shown to be independently predictive of survival. The dose of cisplatinum was 40mg/m² weekly; patients receiving fewer than five cycles of chemotherapy had a reduced survival benefit when compared with those receiving 5-6 cycles, thus suboptimal cumulative dose of chemotherapy may impact negatively on survival. The full course of chemotherapy was not given in cases of poor performance status, poor compliance and severe treatment related side effects, among others.

The role of adjuvant CRT delivered with intensity modulated radiation therapy (IMRT) is being investigated as an approach to improve the therapeutic ratio. Chen and co-workers compared IMRT with conventional four field box CRT. Similar loco-regional control was demonstrated with reduced acute and chronic GIT toxicities and acute GU toxicity (Chen et al. 2008).

Thus adjuvant treatment confers a survival benefit in certain subsets of patients. Concurrent CRT is the standard although its necessity in patients with only intermediate risk factors is still a question under investigation. Newer techniques such as IMRT may improve dose intensity to target regions while reducing normal tissue toxicity.

e) Retrospective studies of stage IB2 cervical cancer:

Yessaian et al (2004) evaluated the indications for adjuvant therapy with CRT after radical hysterectomy in 58 patients with stage IB2 who had undergone radical hysterectomy. Using the aforementioned GOG histopathological criteria, they retrospectively identified groups of patients who were eligible for adjuvant CRT. It was noted that 51 of the 58 patients (88%)
should have received adjuvant treatment instead of the 36 actually treated. The authors suggest that this perhaps explains the overall survival at 62%. They also stress the importance of counseling patients with stage IB2 requesting primary surgery so that they are aware of the high probability of requiring adjuvant RT/CRT.

In another retrospective, a single-institution study, the authors report on their experience with primary chemo-radiation in 49 patients with stage IB2 cervical cancer (Goksedef and co-workers, 2009). The 3-year PFS and OS were 79% and 86% respectively. Follow-on hysterectomy was not used. The authors conclude that routine hysterectomy is not necessary after definitive primary CRT in stage IB2, since their results compare favourably with the CRT plus adjuvant hysterectomy arm of the GOG 123 study (Keys et al., 1999).

In a 2008 retrospective study by Zivanovic et al., 47 patients with IB2 were treated either with surgery (57%) or RT/CRT (43%). The 3-year OS was 72% and 55%, respectively (p=0.161). Patients with co-morbidities were more likely to be offered primary RT/CRT. Treatment-related toxicities were the highest for surgery plus adjuvant therapy when compared to either of those two modalities alone due to the fact that almost two-thirds of these patients received adjuvant treatment.

Thus, definitive treatment with either surgery or RT/CRT appear to have comparable survival in stage IB2 cervical cancer. There appears to be greater toxicity in the surgery arm possibly due to the significant proportion of patients requiring adjuvant treatment. Subsequent hysterectomy in the patients who were treated with definitive radiation therapy is not routinely required.

f) Utilizing RPV adjuvant radiation in node-negative patients:

With histological risk factors dictating a need for post-operative CRT in more than 50% of cases of stage IB2, it would be better to deliver the adjuvant CRT as safely as possible. In the node negative group, the predominant risk is of central recurrence, as opposed to node positive patients who tend to relapse loco-regionally and distally (Thomas & Dembo, 1991). Many institutions have been assessing the benefit using smaller radiation fields applied to the tumour bed only. The dimensions of the RPV at our institution are 8 x 8 x 8 cm, with the inferior border of the volume being 2 cm distal to the vaginal vault.

Hong and co-workers (2002) used this approach in 228 patients who were node negative but had the presence of at least parametrial invasion, close margins or stromal invasion. Twenty
percent consisted of bulky tumours (>4 cm). Most patients had concurrent chemotherapy and brachytherapy. The authors found that there was an increase in upper pelvic relapse which did not have a significant effect on survival. There was reduced toxicity with the use of a RPV.

Similarly, Ohara et al. (2004) attempted to reduce toxicity with the use of a RPV. However, the focus of their study was the outcome with regard to treatment toxicity. They observed a general reduction in GIT adverse effects and leucopenias but conversely an increase in bladder toxicity in patients who were in the RPV arm, as opposed to the ‘whole pelvis’ arm. While the authors believed this bladder toxicity to be a side effect of the surgical procedure (since both arms received RT to the whole bladder), it remains difficult to explain.

The potential for reduced toxicity is encouraging, though a RCT is required to validate the safety of this practice as regards recurrence patterns.

g) Relative cost-effectiveness of the two primary modalities in stage IB2 cervical cancer:

Jewell et al. (2007) did an analysis on cost-effectiveness, comparing radical hysterectomy (RHYST) with tailored adjuvant CRT versus primary CRT. The main methodology was Markov state transition modeling. Data from previous literature reviews were used to factor in expected overall survival, and treatment related toxicities. Costing schemes were obtained from Medicare data. Radical hysterectomy followed by tailored CRT was found to be the most cost-effective option. Survival superiority, the cost of managing treatment toxicity and the cost of palliative care, where necessary, was also factored in.

In a second cost-effectiveness modeling exercise, Rocconi et al. (2005) chose a hypothetical cohort of 10,000 patients and randomised them to three treatment strategies of RHYST, primary CRT, Neoadjuvant chemotherapy (NACT) (followed by radical hysterectomy and tailored CRT). In each grouping, adjuvant treatment may have been employed, based on certain radiologic or pathologic findings. Data from phase III trials were predominantly employed but, in some cases, it was necessary to utilise data from phase II studies. In a manner similar to the study by Jewell et al., risk and frequency of complications were accounted for in the analysis. RHYST (with or without adjuvant CRT) again provided the most cost-effective method of treatment. The “cost per cure” estimated for NACT and primary CRT was higher than RHYST. CRT was found to cure more patients but at a considerable cost. One of the major differences in this analysis by Rocconi et al. was that the
cost to diagnose and treat complications was not included in their estimations (unlike the study by Jewell et al.). Another limitation was that the rate of adjuvant CRT after RHYST was estimated at only 40%. The authors do, however, comment that in sensitivity analysis, when 80% of patients having primary surgery received adjuvant CRT, RHYST still remained the most cost-effective treatment.

It cannot be assumed that these study findings can be generalized to the South African situation; from a simplistic viewpoint, a bi-modality treatment (surgery plus adjuvant CRT) may or may not be more expensive than a single one (primary CRT), but it does consume more limited resources – surgical as well RT resources.

h) NACT:

Another area of interest in the management of stage IB2 cervical cancer is neoadjuvant chemotherapy. The combinations of therapy which can produce the best outcome are still being investigated. The Neoadjuvant Chemotherapy for Cervical Cancer Meta-analysis Collaboration of the Cochrane group reviewed 18 trials comparing NACT followed by RT, with RT only (at that time 93% of the known randomised evidence). Patients receiving more intense doses of cisplatinum, or receiving CT at least every fortnight, appeared to have a superior survival. Their subsequent analysis compared NACT, followed by surgery, with RT alone. Five trials, accounting for 97% of known randomised trials were compared. Again, there appeared to be greater survival benefit in the NACT arm but the authors felt that the data was not substantial enough due to the relatively small number of patients and the high degree of heterogeneity among the trials.

More recently, an updated review from the Cochrane group (Rydzewska et al., 2010) compared NACT plus surgery, to surgery only, in patients with cervical cancer. Six RCTs were reviewed, enlisting just over 1000 women. Analysis of pathological responses to NACT showed a “significant decrease in adverse pathological findings”. The PFS was significantly improved by the neoadjuvant approach (p=0.01). No benefit in OS was found, hence it remains unknown whether NACT offers an advance in the management of cervical cancer, whether for early or more advanced stages.

A final impression is that a truly comprehensive approach to the management of cervical cancer in general, and stage IB2 in particular, is required, which should involve all the following strategies:
1) Prevention: vaccination against the oncogenic strains of the HPV virus;

2) Screening: a recent article published by Everett et al. (2011) reviewed 38 trials assessing the most effective method of encouraging women to undergo cervical cancer screening. The authors concluded that ‘the incidence of cervical cancer is reduced by 93.5%, 92.5%, 90.8%, 83.6% and 64.1% if women have screening every year, every two years, every three years, every five years and every ten years’.

3) Efficacious treatment: for stage IB2, both primary surgery and radiation are feasible therapeutic options. The most effective mode, or combinations thereof, still has to be determined.

4) Minimise toxicity: the adverse effects of a particular treatment must be evaluated and the potential impact on a patient’s quality of life should be taken into account during counselling of patients regarding options of therapy. A 2009 study by Hsu et al. compared surgery and radiation therapy in early cervical cancer. They found that a different group of complications predominated in each treatment arm but that there were few differences in long term quality of life for the two groups.

5) Treatment cost: this is of particular importance in developing countries where the reality of economic constraints can often influence access to appropriate treatment. A treatment option which is economically feasible without undue compromise to patient survival is warranted.

6) Patient preference: patients must be given sufficient facts to make informed decisions. The inherent risks in any procedure such as early menopause, effects on sexual function and compromise of reproductive potential due to ovarian ablation (whether it be surgical or secondary to radiation therapy) should be imparted.

Areas for continued research include:
- Direct comparison of primary CRT versus RHYST in a randomised controlled trial would provide more definitive information to practitioners regarding the best mode of treatment for stage IB2.
- Validation of prognostic models for our treatment population which can guide the decision regarding adjuvant treatment.
- There is still ongoing research into NACT and its role in this particular stage of the disease.
- The role of IMRT and image-guided brachytherapy should be explored as RT refinements.

~ 21 ~
These will, in all probability, play a role in our future management of this disease.

REFERENCES:

Ackerman, I. 2004, "FIGO Stage IB2 cervix cancer and putting all your eggs in one basket", *Gynecologic Oncology*, vol. 94, no. 2, pp. 245-246.


Lai, C., Hong, J., Ng, K., Chang, T., Tseng, C., Chou, H. & Huang, K. 1999, Preoperative prognostic variables and the impact of postoperative adjuvant therapy on the outcomes of stage IB or II cervical carcinoma patients with or without pelvic lymph node metastases: an analysis of 891 cases, Cancer, vol 85, no. 7, pp 1537-46


PART C
A retrospective review of patients with stage 1B2 cervical cancer treated with radical radiation versus radical surgery as a primary modality.

Kellie Alleyne-Mike FC RadOnc(SA)*, Leon van Wijk FF Rad(T)SA*, Alistair Hunter PhD^

(*Division of Radiation Oncology, ^Radiobiology Section, Groote Schuur Hospital and University of Cape Town, Anzio Road, Observatory, Cape Town, South Africa).

Corresponding Author:
Dr. K. Alleyne-Mike, LE33 Clinic, Groote Schuur Hospital, Observatory, 7925, South Africa.
Tel: *27-21-404-4261
Fax: *27-21-448-5707
E-mail: kmike.tt@gmail.com
Address for Reprints: As above

Funding support or Conflict of Interest: Nothing to declare. No funding received.
A retrospective review of patients with stage 1B2 cervical cancer treated with radical radiation versus radical surgery as a primary modality


(*Division of Radiation Oncology, ^Radiobiology Section, Groote Schuur Hospital and University of Cape Town, Anzio Road, Observatory, Cape Town, South Africa)

ABSTRACT:

Objective: To review the efficacy of treatment modalities in patients with stage IB2 cervical cancer treated at Groote Schuur Hospital, Cape Town, South Africa.

Materials and methods: This was a retrospective observational study of patients with stage IB2 cervical cancer treated from 1993-2008 with either primary radiation therapy (RT), with or without follow-on hysterectomy, or primary surgery (with or without adjuvant RT). Weekly cisplatin given concurrently with RT was used since 2003. Patient outcomes and grade 3-4 treatment-related toxicities were recorded.

Results: The study included 78 eligible patients for whom the 5-year overall survival rate was 70.8%. Overall 5-year survival rate by treatment modality was 88% for the 25 patients in the surgery group and 62.5% for the 53 patients in the RT group, respectively. There was a marked difference in the proportion of patients in each group receiving additional therapy: 88% of patients in the primary surgery group had adjuvant RT, while only 5.7% of patients in the primary RT group went on to have a hysterectomy. Grade 3-4 toxicity was found in 13.2% of the RT versus 4% for the surgery group (p=0.4).

Conclusion: The optimal primary treatment for stage IB2 cervical cancer remains unclear. Both types of primary treatments were found to be feasible therapeutic approaches. Primary surgery appears to have better survival outcomes at our institution. Selection bias and inadequate concurrent chemotherapy in 58% of patients receiving primary RT may account for the difference in survival.

The number of patients in the surgery group requiring “bimodal” adjuvant treatment has cost implications in our resource-constrained environment, hence primary concurrent chemoradiation is being increasingly utilized for stage IB2 cervical cancer at our institution. Evidence from a randomized controlled study is needed to determine the optimal treatment for stage IB2 cervical cancer.

Key words: cervical cancer, stage IB2, surgery, radiotherapy.

Corresponding author: kmike.tt@gmail.com
INTRODUCTION:

In many developing countries, including South Africa, cervical cancer is one of the most common female cancers.1 Treatment for cervical cancer is relatively well defined for most stages, however, for stage IB2 there are no clear guidelines as to the best single treatment approach. Either primary surgery or radiotherapy (RT) is considered to be feasible. The merits of primary surgery include pathologic assessment of the extent of disease and preservation of ovarian and vaginal function. However, adjuvant treatment is more often required with primary surgery than with primary RT, which also carries a greater risk of delayed toxicity.2

The sub-classification of Stage IB cervical cancer recognizes that bulkier cervix-confined tumors may require different treatment approaches. The treatment of stage IB2 in our unit became biased towards primary RT because of concerns that adjuvant radiation may be frequently required if these bulky tumors were treated surgically. The consequences of such bimodal treatment include a protracted treatment course, increased costs for the patient and institution, and potentially increased treatment complications.

This retrospective observational study was undertaken to evaluate local practice and outcome of patients with stage IB2 cervical cancer treated at Groote Schuur Hospital (GSH), Cape Town, South Africa, over a 16 year period (1993-2008). Permission to perform the data collection was obtained from the hospital management and the Human Research Ethics Committee of the Faculty of Health Sciences, University of Cape Town (Ref 129/2011).

MATERIALS AND METHODS:

Study setting: All patients referred with biopsy-positive cervical cancer were assessed at a weekly multi-disciplinary team (MDT) meeting. Staging of patients included a full blood count, renal and liver function tests, gynecologic pelvi-rectal examination, chest X-ray, ultrasonography of the renal tract and cystoscopy. Sigmoidoscopy was performed only where clinically indicated. More sophisticated radiological investigations for routine metastatic screening were not performed.

Prior to the FIGO subdivision of stage IB in 1995, either one of the two therapeutic modalities of primary RT or surgery was prescribed for “bulky” IB cervical cancer, defined as tumors >4 cm in diameter.3 Patients with significant comorbidities and those with larger tumors were offered primary RT. Subsequent to 1995, there was selection pressure towards primary RT in an attempt to reduce bimodal treatment, though surgery was still offered to some patients with relatively smaller IB2 tumors.

Primary RT doses to the pelvis varied between 40-56Gy (median 49.5Gy) over the study period and involved a four field box technique which covered the tumour bed and pelvic nodal regions up to the L5/S1 intervertebral space. Intracavitary brachytherapy was administered with low dose radium sources prior to 1994, and subsequently with fractionated high dose rate iridium therapy (5.0-7.5 Gy to Point A for four sessions). The other significant change in therapy over the study period occurred in 2003, when concurrent weekly
cisplatinum with RT was introduced. The cisplatin dose was 40mg/m², with a maximum dose of 60mg per week, and a maximum of six weekly cycles. Following primary RT, patients were assessed after three months for extrafacial hysterectomy if histologic signs of tumor persistence were found.

Primary surgery involved a Piver type 2 radical hysterectomy and bilateral pelvic lymphadenectomy. Decisions about post-operative therapy were taken at the weekly MDT review. The indications for adjuvant RT included: positive pelvic lymph node(s); close (<5 mm) or involved resection lines; histological parametrical invasion; or Gynecologic Oncology Group (GOG) score of ≥ 120 (product of relative risks for various tumor sizes, depths of invasion, and presence or absence of lymphatic space invasion).⁴ The adjuvant RT portals covered the whole pelvis. Variations in the adjuvant radiation technique included: a) reduced pelvic volume (RPV) radiation in node-negative patients, since the volume at risk for recurrence was considered to be the cervical tumor bed, or b) extended field radiation in patients with multiple positive pelvic and/or para-aortic lymph nodes. The dimensions of the RPV were 8 x 8 x 8 cm, with the inferior border of the volume being 2 cm distal to the vaginal vault. Vault brachytherapy was added if the vaginal resection lines were compromised.

Patients were followed up at 3-monthly intervals for a year, thereafter at longer intervals. Investigations were prompted by clinical suspicion.

Study methodology: A list of patients with stage IB2 cervical carcinoma treated between the years 1993 and 2008 was retrieved from the Gyn-Oncology database at GSH. Patients diagnosed with Stage IB >4 cm in diameter before 1995 were assigned retrospectively to stage IB2.

Patients were grouped into the two treatment approaches of primary surgery and primary RT. Each approach could become “bimodal” if adjunctive therapy was given. Hysterectomy after RT was defined as bimodal if it was performed within four months of completing RT. Surgery beyond this period was considered to be “salvage” and was not included in the analysis.

The inclusion criteria for this study were:

- clinically staged 1B2 cervical cancer of histological subtypes: squamous, adenosquamous or adenocarcinoma variety;
- in the primary radiation group, an external beam dose to the whole pelvis of at least 40 Gy, plus brachytherapy;
- in the primary surgery group, a completed radical hysterectomy and pelvic lymphadenectomy (complete or partial nodal dissection);
- follow-up for at least one year after completion of primary treatment;
• absence of concurrent malignancies (except non-melanoma skin cancers) or previous pelvic irradiation

Data collected included patient demographics, treatment modalities applied, response to treatment, and disease status on follow-up. Treatment-related morbidities experienced 90 days or more after the completion of the treatment were considered to be late toxicities and graded according to the Radiation Therapy Oncology Group (RTOG) toxicity scores. Only grade 3 and 4 toxicities for gastrointestinal tract (GIT), bladder, and bone were documented. Follow-up was truncated at five years. Patients were censored at last follow-up or at time of death.

Statistical calculations were made using Prism Graph pad (version 5.00; Graphpad software®, San Diego, Cal) and Epi Info (version 7; CDC, Atlanta, USA). Overall survival (OS) was defined as the time from treatment initiation until last follow-up or death. The 5-year OS rate was estimated using the Kaplan-Meier method, and the log rank test was performed to compare groups. The means of two groups were compared with the student t-test for continuous data, and with the chi-squared test for categorical variables.

RESULTS:

A total of 98 patients with stage IB2 were identified for the selected 16 year period from 1993 to 2008. Of these, 78 patients met the inclusion criteria. Twenty patients were excluded (Figure 1).

The median follow-up period was 59 months (6-60 months). The basic characteristics of the study population are shown in Table 1. Figure 1 demonstrates that 25 of the 78 patients (32.1%) underwent primary surgery and, of these, 22 (88%) went on to have adjuvant RT. Ten patients received RT to the whole pelvis and one received extended field RT. In 11 node-negative patients, a RPV was irradiated. Figure 2 illustrates the indications for adjuvant therapy.

In the primary surgical group, 3 patients of the 25 patients (12%) relapsed (Table 2). Of the two loco-regional relapses (8%), one patient with an adenocarcinoma received adjuvant RT with a RPV and relapsed with an ovarian metastasis 21 months later. This metastasis was outside the irradiation volume.

The 5-year OS rate of the primary surgery group was 88%, which was significantly better than the 62.5% for primary RT (p = 0.03 - Figure 3A).

The primary RT group comprised 53 patients (67.9%), of whom only three underwent additional treatment with hysterectomy (5.7%). Of the 53 patients in this group, 58% had 0-3 cycles of concurrent weekly cisplatinum. The remainder received 4-6 cycles, with comparable survival to the primary surgery group (Figure 3B). Thirteen (24.5%) of the primary RT patients experienced a recurrence, 6 of whom had a component of loco-regional infield failure (11.3%-Table 2).
Late treatment toxicity of RTOG grade 3-4 severity was seen in 4% of patients in the primary surgery group and 13.2% in the primary RT group, but this difference was not significant (p=0.4). None of the grade 3 or 4 complications occurred in the RPV adjuvant group.

**Table 3** illustrates univariate analysis of 5 year OS.

DISCUSSION:

This study records the treatment methods and outcomes of 78 patients with stage IB2 cervical cancer at GSH between 1993 and 2008. Patients were included if they presented with the common histological varieties, had completed curative treatment and had at least one year of follow-up.

This study shows that 88% of the surgical cohort received post-operative RT, and although the number of patients was relatively small, there was no apparent increase in complications over primary RT. There was also an indication of better survival in the surgical group (Figure 3B). It is necessary to examine further the relative merits of each treatment.

Previous unrandomized studies have shown that surgery and RT yield similar outcomes in stage IB cancer, with 5-year survival between 80-90% for both modalities. A landmark study was reported in 1997 by Landoni and colleagues, in which 343 patients with stage IB-IIA cervical carcinoma were randomized between radical hysterectomy versus radiation therapy. After a median follow-up of 87 months, the 5-year OS and disease free rates were similar in both groups (for all patients, the OS was 83% and disease free interval was 74%). However, significantly greater treatment related morbidity was noted in the surgery arm compared with the RT arm, irrespective of cervical diameter.

Of relevance for the current study is that Landoni et al. found that approximately a third of the patients in each arm had cervical diameter > 4 cm. Post-operative radiotherapy was delivered in 84% of such patients, in contrast to 54% of patients with smaller tumors. In the subsets of patients with cervical diameter > 4 cm, pelvic relapse was significantly higher in the RT group than in the high-risk surgical + RT group (70% versus 53% of relapses). These authors recommended that primary surgery should be reserved for those patients less likely to need adjuvant treatment.

Whether adjuvant treatment is required in surgically treated IB2 cervical cancer depends on the selection of histological factors known to predict for pelvic relapse. The GOG has established the following risk categories from its earlier studies:

- **High**: positive nodes, parametria and/or resection lines;
- **Intermediate**: negative lymphovascular space invasion (LVSI), ≥ two-thirds depth of cervical stromal invasion (CSI) and tumor > 4cm; or positive LVSI, deep CSI and tumor of any size; or positive LVSI, middle third CSI and tumor > 2cm; or superficial third CSI and tumor > 5cm;
- **Low**: absence of these factors.
In 2008, Zivanovic and co-workers\textsuperscript{11} reported on the treatment patterns of 47 patients with stage IB2 cervical cancer at their institution: 57\% underwent primary surgery and 43\% had RT. Overall, 52\% of the primary surgery cases received adjuvant RT, while only 10\% of the RT group underwent adjuvant simple hysterectomy (88\% versus 5.7\%, respectively, in the current study). In that study, the 3-year overall survival rates were 72\% and 55\% for primary surgery versus RT, respectively (p=0.161). Complication rates were comparable. Significantly more patients selected for RT had poorer anaesthetic risk factors and larger tumor size (median 6.1 cm, versus 5.1 cm for surgery). The authors conclude that while both modalities are feasible strategies for Stage IB2, the low rate of adjuvant radiation may be due to the presence of suspected nodal involvement on pre-operative imaging favouring selection towards RT.

A primary surgical approach was described in 2004 by Yessaian and colleagues\textsuperscript{12}. Adjuvant RT was administered in 62\% of 58 patients with stage IB2 cervical cancer. The 5-year OS was 62\%. According to the current GOG risk criteria, 88\% of their patients should have received adjuvant RT. These risk criteria were also applied retrospectively to a cohort of 72 Stage IB2 patients by Havrilesky et al.\textsuperscript{13} “Tailored” adjuvant RT was applied only to 31\% of patients: in 0\%, 12\% and 94\% of the low, intermediate, and high-risk groups, respectively. The current GOG criteria predict that 92\% of all their patients should have received adjuvant RT. Five-year OS were 100\% (low-risk), 80\% (intermediate-risk) and 47\% (high-risk). These authors warn that if the GOG criteria are to be followed, patients offered primary surgery need to understand that there is a significant chance of requiring adjuvant RT.

Kamelle and co-workers retrospectively identified 86 patients with stage IB2 who had undergone radical surgery.\textsuperscript{14} Overall, 52\% of their patients received adjuvant radiation: all the high-risk patients, none of the low-risk group, and only 31\% of the intermediate-risk group. In the latter, there was no significant difference in disease-free interval (DFI) whether adjuvant therapy was given or not. Notably, those intermediate-risk patients without LVSI had a DFI of 97\%. The authors suggest that the traditional GOG criteria may exaggerate risk in the intermediate group, particularly in those with negative LVSI, who could be treated with surgery alone. However, the median follow-up in this study was only 25 months.

Monk and Koh\textsuperscript{15} have stressed that if the established GOG risk criteria are adhered to, 90\% of patients with stage IB2 lesions treated with radical surgery may require adjuvant chemoradiation. Concurrent chemo-radiation has become standard practice in seemingly all stages of cervical cancer\textsuperscript{16}, thought it has never been directly compared with RT alone within the context of a randomized study in the GOG intermediate-risk group. To address this issue, such a trial is currently being conducted.\textsuperscript{17}

In the node negative group, the predominant risk is for central recurrence; in contrast, node positive patients tend to relapse regionally or distally.\textsuperscript{18} Hong and co-workers\textsuperscript{19} retrospectively analyzed responses of patients with histologically proven node negative cervical cancer stages I to IIA, who had received either whole pelvic RT, or RT to a RPV. Adjuvant radiation with a RPV reduced the incidence and severity of small bowel complications without compromising survival. Similar approaches have been reported\textsuperscript{20},
though the safety and effectiveness of RPV versus traditional adjuvant RT have not been subjected to comparison in the setting of a RCT. In the current study, a RPV was administered to half the patients receiving adjuvant RT. None of these patients exhibited treatment complications. However, while such an approach theoretically reduces the risk of toxicity, the costs of dual therapy remain unchanged.

Concerning post-operative risk stratification from prognostic models, a recent study was reported by Biewenga and colleagues (2011)\(^\text{21}\). Altogether 11 clinical and histological factors were examined in 710 patients who had surgery for early cervical cancer. A score chart was derived by multivariate Cox regression modelling and other statistical tools. While the main purpose of such a model would be to select and stratify patients for RCTs, this new tool could be applied to our stage IB2 patients in the future to reduce the numbers requiring adjuvant RT. Caution is needed, however, since this model has not been externally validated and the effect on survival of reducing indications for adjuvant therapy is unknown.

Primary surgery plus adjuvant chemo-radiation appears intuitively more expensive than primary RT alone, though a direct cost-effectiveness comparison has never been done at our institution. Jewell and co-workers\(^\text{22}\) have estimated the relative cost-effectiveness of the two treatment approaches in stage IB2. Primary surgery plus tailored adjuvant RT was more expensive than primary RT ($27 800 versus $21 400) but depended strongly on the level of recommendation for adjuvant therapy. While it may not be accurate to generalize between institutions, this economic modelling confirms that bimodality treatment is more costly.

In the present study, there was no significant difference in grade 3-4 late treatment related toxicities observed between the primary RT and surgery groups (crude rate 13.2% versus 4%, \(p=0.4\)). There was, however, a poorer 5-year OS for the primary RT group of 62.5%, versus 88% for the surgical group (\(p=0.03\)). Various confounding factors could account for the worse outcome in the RT cohort. The larger median tumor size of 5.5 cm (versus 5.0 cm for the primary surgery group, Table 1) and worse survival of larger tumors on univariate analysis (\(p=0.01\), Table 3), indicate a selection bias. The number of chemotherapy cycles given concurrently with radiation was also shown to have a significant impact on survival (Figure 3B), an observation which was also described by Nugent et al.\(^\text{23}\). The 58% of patients receiving 0-3 weekly cycles in our small series showed inferior survival to the remainder who received 4-6 cycles.

Few patients undergoing primary RT require bimodal therapy. Routine hysterectomy after RT is unnecessary.\(^\text{24}\) Nijhuis et al\(^\text{25}\) have found that a gynecologic examination under anaesthesia was able to identify patients who had residual disease post-RT and who would be eligible for follow-on hysterectomy, so that only those likely to benefit are identified. Only 5.7% of the patients in our primary RT group underwent extrafacial hysterectomy for tumour persistence.

Since the best therapy for stage IB2 is currently unknown, potential improvements in our management could include performing MRI pre-operatively to optimize the selection of patients for surgery, and PET-CT to detect metastatic disease, or residual cancer post-RT. Local practice will, however, be subject to skills and resource availability.
CONCLUSION:

There are many limitations inherent to observational studies conducted retrospectively at a single institution, including selection bias, small patient numbers and deficiencies in individual patient data quality. Nevertheless, the current study suggests that both primary surgery and primary RT are feasible modalities in the management of stage IB2 cervical cancer at GSH. The observed trend of poorer survival outcome with primary RT may have resulted from the influences of treatment selection as well as both unmeasured and known covariates, such as tumor size and the number of chemotherapy cycles.

In the surgical group, the use of tailored post-operative RT was well tolerated and safe, although ongoing concern about cost requires that the threshold for adjuvant RT be reviewed. In our resource-constrained environment, primary RT (with adequate concomitant cisplatin-based chemotherapy) is increasingly being utilised to avoid bimodal therapy.

This retrospective study, while confirming feasibility of the available modalities, does not inform the optimal approach for stage IB2 cervical cancer. A randomized controlled study of the two treatment modalities is required. Ideally a third arm of neo-adjuvant chemotherapy followed by surgery or RT should be included in such a study, along with measurement of cost-effectiveness and quality of life in each arm.
TABLES AND FIGURES:

**FIGURE 1:** A flow distribution of the number of patients treated, the proportions requiring adjuvant treatment and the numbers of relapses and treatment related toxicities.

---

Cervical carcinoma
Stage 1B2 (total, n = 98)

Eligible patients n = 78

- Primary Surgery (n= 25) 32.1%
  - Adjuvant Radiation?
    - Yes (n=22) 88%
      - Relapse n= 3/22
    - No (n=3) 12%
      - Relapse n= 0/3

- Primary radiation / Chemoradiation (n=53) 67.9%
  - Adjuvant Surgery?
    - Yes (n=3) 5.7%
      - Relapse n=1/3
    - No (n=50) 94.3%
      - Relapse n=12/50

EXCLUSIONS: (n = 20)
- unusual pathology (3)
- lost to follow-up (2)
- incomplete treatment (10)
- records not available (5)

TREATMENT TOXICITY IN:
- 1/25 (4%)
- 7/53 (13.2%)
TABLE 1: Demographics and association between treatment modalities.

<table>
<thead>
<tr>
<th>VARIABLE</th>
<th>ALL PATIENTS</th>
<th>PRIMARY SURGERY</th>
<th>PRIMARY RT</th>
<th>P VALUE</th>
</tr>
</thead>
<tbody>
<tr>
<td>N (%)</td>
<td>78 (100%)</td>
<td>25 (32.1%)</td>
<td>53 (67.9%)</td>
<td></td>
</tr>
<tr>
<td>Race:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>29 (37.2%)</td>
<td>11 (44%)</td>
<td>18 (34.0%)</td>
<td></td>
</tr>
<tr>
<td>Coloured</td>
<td>44 (56.4%)</td>
<td>12 (48%)</td>
<td>32 (60.4%)</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>5 (6.4%)</td>
<td>2 (8%)</td>
<td>3 (5.7%)</td>
<td></td>
</tr>
<tr>
<td>Age:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>45.6</td>
<td>47.1 (SD 10.43)</td>
<td>44.8 (SD 10.69)</td>
<td>0.36&lt;sup&gt;t&lt;/sup&gt;</td>
</tr>
<tr>
<td>Histology:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Squamous</td>
<td>65 (83.3%)</td>
<td>18 (72%)</td>
<td>47 (88.7%)</td>
<td></td>
</tr>
<tr>
<td>Non squamous</td>
<td>13 (16.7%)</td>
<td>7 (28%)</td>
<td>6 (11.3%)</td>
<td></td>
</tr>
<tr>
<td>Tumor size (cm):</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>4.1-11.0</td>
<td>4.1-6.0</td>
<td>4.1-11.0</td>
<td></td>
</tr>
<tr>
<td>Median (Med)</td>
<td>5.0</td>
<td>5.0</td>
<td>5.5</td>
<td></td>
</tr>
<tr>
<td>Median (&gt;4 - &lt;5)</td>
<td>25 (32.1%)</td>
<td>12 (48%)</td>
<td>13 (24.5%)</td>
<td>0.04&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Median (≥ 5)</td>
<td>53 (67.9%)</td>
<td>13 (52%)</td>
<td>40 (75.5%)</td>
<td></td>
</tr>
</tbody>
</table>

<sup>c</sup>- P values were obtained using the chi-squared test

<sup>t</sup>- P values were obtained using the t test

~ 37 ~
FIGURE 2: The distribution of post-operative indications for RT in the primary surgical group.

^ Close margins: 17 patients
^ Positive margins: 3 patients
^ GOG score (see Methods section)
**TABLE 2**: Rates of toxicity, disease progression and death

<table>
<thead>
<tr>
<th></th>
<th>% Primary RT (n=53)</th>
<th>% Primary Surgery (n=25)</th>
<th>% of TOTAL (n=78)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Recurrence:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Loco-regional</td>
<td>24.5</td>
<td>12.0</td>
<td>20.5</td>
</tr>
<tr>
<td>Distant</td>
<td>9.4</td>
<td>8.0</td>
<td>9.0</td>
</tr>
<tr>
<td>Both local and distant</td>
<td>13.2</td>
<td>8.0</td>
<td>9.0</td>
</tr>
<tr>
<td><strong>Progression</strong></td>
<td>1.9</td>
<td>4.0</td>
<td>1.3</td>
</tr>
<tr>
<td>Partial response</td>
<td>5.7</td>
<td>-</td>
<td>3.8</td>
</tr>
<tr>
<td><strong>Vital status:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alive disease free</td>
<td>62.3</td>
<td>84.0</td>
<td>69.2</td>
</tr>
<tr>
<td>Alive with disease</td>
<td>1.9</td>
<td>1.9</td>
<td>2.6</td>
</tr>
<tr>
<td>Death: from disease</td>
<td>30.2</td>
<td>8.0</td>
<td>23.1</td>
</tr>
<tr>
<td>Death: related to treatment</td>
<td>1.9</td>
<td>4.0</td>
<td>1.3</td>
</tr>
<tr>
<td>Death: other cause</td>
<td>3.8</td>
<td>4.0</td>
<td>3.8</td>
</tr>
<tr>
<td><strong>Toxicity:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>3.8*</td>
<td>4.0</td>
<td>4.9</td>
</tr>
<tr>
<td>Bladder</td>
<td>9.4*</td>
<td>-</td>
<td>6.4</td>
</tr>
<tr>
<td>Bone</td>
<td>1.9</td>
<td>-</td>
<td>1.3</td>
</tr>
</tbody>
</table>

*One patient had 2 areas of toxicity.
FIGURE 3: Kaplan Meier curves illustrating overall survival trends in the different groups.

A

B

TABLE 3: Univariate analysis of 5-year overall survival.

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>5-YEAR OVERALL SURVIVAL</th>
<th>P VALUE</th>
<th>HAZARD RATIO</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ALL GROUPS</strong></td>
<td>78</td>
<td>70.8%</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>AGE AT DIAGNOSIS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 45</td>
<td>38</td>
<td>70.5%(53.0-82.5%)</td>
<td>0.75</td>
<td>1.14 (0.49 - 2.66)</td>
</tr>
<tr>
<td>≥ 45</td>
<td>40</td>
<td>71.0%(53.5-82.9%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>TUMOR DIAMETER</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(CM)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>median &lt;(5cm)</td>
<td>25</td>
<td>90.8%(23.1-97.6%)</td>
<td>0.01</td>
<td>0.33 (0.14 - 0.81)</td>
</tr>
<tr>
<td>median ≥ (5cm)</td>
<td>53</td>
<td>62.4%(47.9-73.9%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>HISTOLOGY</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Squamous</td>
<td>65</td>
<td>68.1% (54.9-78.1%)</td>
<td>0.28</td>
<td>1.83 (0.61 - 5.47)</td>
</tr>
<tr>
<td>Non Squamous</td>
<td>13</td>
<td>83.9% (49.4%-95.7%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>TREATMENT MODALITY</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary Surgery</td>
<td>25</td>
<td>88.0%</td>
<td>a 0.03</td>
<td>0.38 (0.16 - 0.93)</td>
</tr>
<tr>
<td>Primary RT (overall)</td>
<td>53</td>
<td>62.5%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of chemo cycles:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary RT (0-3 cycles)</td>
<td>22</td>
<td>39.4%</td>
<td>b 0.0007</td>
<td></td>
</tr>
<tr>
<td>Primary RT (4-6 cycles)</td>
<td>31</td>
<td>79.3%</td>
<td>c 0.45</td>
<td></td>
</tr>
</tbody>
</table>

P value was obtained using the Log-rank test.

a- Primary Surgery vs Primary RT (overall)

b- Primary Surgery vs Primary RT (0-3 cycles of concurrent cisplatin)

c- Primary Surgery vs Primary RT (4-6 cycles of concurrent cisplatin)
REFERENCES:


PART D
## APPENDICES:

### I: DATA CAPTURE INSTRUMENT:

<table>
<thead>
<tr>
<th>Name</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Surname</td>
<td></td>
</tr>
<tr>
<td>Hosp.No</td>
<td></td>
</tr>
<tr>
<td>RT No.</td>
<td></td>
</tr>
<tr>
<td>Age at Diagnosis</td>
<td></td>
</tr>
<tr>
<td>Race</td>
<td>Black(B)</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Date of Registration</td>
<td></td>
</tr>
<tr>
<td>Date of treatment commencement</td>
<td></td>
</tr>
</tbody>
</table>

**Histology:**

<table>
<thead>
<tr>
<th>Squamous</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Adenocarcinoma</td>
<td></td>
</tr>
<tr>
<td>Adenosquamous</td>
<td></td>
</tr>
<tr>
<td>RVD status</td>
<td>Yes</td>
</tr>
<tr>
<td>------------</td>
<td>-----</td>
</tr>
<tr>
<td>CD4</td>
<td>Pre-tmt</td>
</tr>
</tbody>
</table>

Treatment Sequencing:

- Surgery: S
- EBRT (External Beam RT): E
- BRT (Brachytherapy): B
- Chemo: C

Individual Patient Treatment:

Tumor size:

Initial Surgical arm:

- S only
- S + E
- S + E + B

Initial post-surgical factors: (where applicable)

<table>
<thead>
<tr>
<th>Tumor (widest diam/cm)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Depth of stromal invasion (mm)</td>
<td></td>
</tr>
<tr>
<td>-------------------------------</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Presence of LN Metastases</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Adequacy of resection margins (mm)</th>
<th>Positive</th>
<th>&lt; 5</th>
<th>&gt; 5</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Lymphovasc invas.</th>
<th>pos</th>
<th>neg</th>
<th>unknown</th>
</tr>
</thead>
</table>

Radiation arm (where applicable):

| E + B | E + B + C | E + B + S | E + B + C + S |

External Beam RT:

<table>
<thead>
<tr>
<th>given with chemo</th>
<th>1</th>
</tr>
</thead>
<tbody>
<tr>
<td>given without chemo</td>
<td>2</td>
</tr>
</tbody>
</table>

Salvage surgery path (where applicable):

<table>
<thead>
<tr>
<th>Tumor (widest diam/cm)</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Depth of stromal invasion (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adequacy of resection margins (mm)</td>
</tr>
<tr>
<td>----------------------------------</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Lymphovasc invas.</th>
<th>pos</th>
<th>neg</th>
<th>unknown</th>
</tr>
</thead>
</table>

Primary Course completed:

- **YES**
- **NO**

Response to primary treatment:

<table>
<thead>
<tr>
<th>CR</th>
<th>Complete response</th>
</tr>
</thead>
<tbody>
<tr>
<td>PR</td>
<td>Partial response</td>
</tr>
<tr>
<td>NR</td>
<td>No response</td>
</tr>
<tr>
<td>PD</td>
<td>Progressive disease</td>
</tr>
<tr>
<td>NE</td>
<td>Not evaluable</td>
</tr>
</tbody>
</table>

Treatment related toxicities:

<table>
<thead>
<tr>
<th>GIT</th>
<th>Bladder</th>
<th>Bone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 4</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Relapse:

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Type of relapse:

<table>
<thead>
<tr>
<th>Loco-Regional</th>
<th>L</th>
<th>central</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>pelvic side wall</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Distant</th>
<th>D</th>
<th></th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Both</th>
<th>L + D</th>
<th></th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Not Applicable</th>
<th>N</th>
<th></th>
</tr>
</thead>
</table>

### Treatment or recurrence/relapse:

<table>
<thead>
<tr>
<th>S (surgery)</th>
<th></th>
<th></th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>C (chemo)</th>
<th></th>
<th></th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>E (external beam radiation therapy)</th>
<th></th>
<th></th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>TLC (supportive care/symptom control)</th>
<th></th>
<th></th>
</tr>
</thead>
</table>

### Current Patient Status:

<table>
<thead>
<tr>
<th>Alive disease free</th>
<th></th>
<th></th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Alive with disease</th>
<th></th>
<th></th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Lost to follow-up</th>
<th></th>
<th></th>
</tr>
</thead>
</table>
Deceased | Disease (D-dis) |
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Treatment (D-Tr)</td>
</tr>
<tr>
<td></td>
<td>Other (D-Oth)</td>
</tr>
</tbody>
</table>

OS (overall survival):

Other info relevant to case:

Incomplete treatment is described as falling under one or more of the following categories:

1) External Beam RT of < 40Gy ID2

2) External beam treatment protracted by 3 weeks or more

3) Brachytherapy not given (in primary CRT patients)

4) Brachytherapy less than prescribed fraction no.

5) No attempt at pelvic lymph node dissection

6) Less than radical hysterectomy

~ 51 ~
II: OFFICIAL ETHICS APPROVAL LETTERS:

UNIVERSITY OF CAPE TOWN

Faculty of Health Sciences
Human Research Ethics Committee
Room E52-24 Groote Schuur Hospital Old Main Building
Observatory 7925
Telephone [021] 406 6626 • Facsimile [021] 406 6411
e-mail: shurettathomas@uct.ac.za

14 March 2011

HREC REF: 129/2011

Dr K Alleyne-Mike
Radiation Oncology
LE34

Dear Dr Alleyne-Mike,

PROJECT TITLE: A RETROSPECTIVE REVIEW OF THE DIFFERENCES IN OUTCOME WITH PATIENTS WITH STAGE II/III cervical cancer treated with radiation versus radical surgery as a primary modality.

Thank you for submitting your study to the Faculty of Health Sciences Human Research Ethics Committee for review.

It is a pleasure to inform you that the Ethics Committee has formally approved the above-mentioned study.

Approval is granted for one year till the 30 March 2012.

Please submit an annual progress report (FHS016) if the research continues beyond the expiry date. Please submit a brief summary of findings if you complete the study within the approval period so that we can close our file.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please quote the HREC REF in all your correspondence.

Yours sincerely,

Signed by candidate

A/PROF MARC BLOCKMAN
CHAIRPERSON, FHS HUMAN ETHICS
Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB00001938

S Thomas
31\textsuperscript{st} January 2012

HREC REF: 12/0 / 2011

Prof. Blockman
Chairperson, HSF
Human Ethics
Groote Schuur Hospital
Observatory
7925

Dear Prof. Blockman,

• Re: Audit project:

"A retrospective review of the differences in outcome with patients with stage IB2 cervical cancer treated with radiation versus radical surgery as a primary modality."

I hereby wish to apply for permission to extend my period of review. I have previously been granted approval (May 2011) to extend my study period from 1997-2008. I would now like to request approval to collect data for the periods 1993 till 2008.

As before it will involve an audit of radiotherapy folders only; patients will not be contacted; hence confidentiality is not an issue. I will also like to advise of a change in wording of the audit project to:

"A Retrospective Study Of Patients with Stage IB2 Cervical Cancer treated at Groote Schuur Hospital between 1993-2008"

I will grateful to receive your approval of the amendment of the above mentioned study. Please let me know if any other documentation is required.

Thank you in advance.

Sincerely

Signed by candidate

Dr. K.R. Alleyn-Silke (Registrar, Dept Radiation Oncology)
### Annual Progress Report

<table>
<thead>
<tr>
<th>Date</th>
<th>7th February 2012</th>
</tr>
</thead>
<tbody>
<tr>
<td>HREC REF Number</td>
<td>19/2011</td>
</tr>
<tr>
<td>Protocol number (if applicable) &amp; Protocol title</td>
<td>A retrospective study of patients with stage IB2 cervical cancer treated at Groote Schuur Hospital 1993-2008</td>
</tr>
<tr>
<td>Principal Investigator</td>
<td>DR. KELLIE ALLEGHE-MIKE</td>
</tr>
<tr>
<td>Department / Office</td>
<td>Radiation Oncology</td>
</tr>
<tr>
<td>Internal Mail Address</td>
<td><a href="mailto:kmike.ite@gmail.com">kmike.ite@gmail.com</a></td>
</tr>
</tbody>
</table>

### List of documentation

- Amended Protocol

---

**RESEARCH ETHICS COMMITTEE**

2012 -02- 1 0

HEALTH SCIENCES FACULTY
UNIVERSITY OF CAPE TOWN

---

**HREC office use only (FWA00001637; IRB00001938)**

- **Approved**
  - This serves as notification of annual approval, including all documentation described above.
- **Not approved**
  - See attached comments.

**Type of review**

- □ Expedited
- □ Full committee

**Expiration date**

15 February 2013

**Signature**

Signed by candidate

Date
Amendment Form

<table>
<thead>
<tr>
<th>Date</th>
<th>7th February 2012</th>
</tr>
</thead>
<tbody>
<tr>
<td>HREC REF Number</td>
<td>1292011</td>
</tr>
<tr>
<td>Protocol number (if applicable) &amp; Protocol title</td>
<td>N/A</td>
</tr>
<tr>
<td>Principal Investigator</td>
<td>Dr. Aleyne-Mize</td>
</tr>
<tr>
<td>Department / Office / Internal Mail Address</td>
<td>Radiation Oncology</td>
</tr>
</tbody>
</table>

List of Proposed Amendments with Revised Version Numbers and Dates

- Title change
- Study period change (see attached appendix)

RESEARCH ETHICS COMMITTEE
2012-02-10
HEALTH SCIENCES FACULTY
UNIVERSITY OF CAPE TOWN

HREC office use only (FWA00001637; IRB00001938)

- Approved
- Type of review: Expedited
- Full committee

This serves as notification that all changes and documentation described above are approved.

Signature

Chaired by the HREC
Signed by candidate
2/3/12
Dr. B. Patel  
Chief Medical Superintendent  
Clinical Directorate  
G45, OMB  
Groote Schuur Hospital  
Observatory  
7925  

Dear Dr Patel,

- Re: Audit project: "A retrospective review of the differences in outcome with patients with stage 1b2 cervical cancer treated with radiation versus radical surgery as a primary modality"

I hereby wish to apply for permission to perform an audit study, of the above title, in the Radiation Oncology Department of this hospital. It is a requirement of the MMed degree/College exam (FRC Rad Onc.)

It will involve an audit of radiotherapy folders only; patients will not be contacted, hence confidentiality is not an issue.

Our Departmental Research Committee has approved the study, as well as the Research Ethics Committee (REC Ref No: 129/2011). I have included a copy of my study proposal for your perusal.

I shall therefore be grateful to receive your approval, as the member of the Clinical Directorate responsible for research projects at Groote Schuur Hospital, to proceed with this study. Please let me know if any other documentation is required.

Thanking you in anticipation.

Sincerely

[Signature]

Dr. K. R. Alleyne-Mike  (Registrar, Dept Radiation Oncology)

LE 33 Clinic
Dr. K. R. Alleyne-Mike  
Department of Radiation Oncology  
L-Block  

E-mail: kmike_it@yahoo.com

Dear Alleyne-Mike:

RESEARCH:  
1. Extension of Research  
2. Rewording of Research to “A Retrospective Study Of Patients With Stage 182 Cervical Cancer Treated At Groote Schuur Hospital Between 1993-2008”

Your recent letter to the hospital refers.  
You are hereby granted permission to extend and change the focus of your research.

Please note the following:

- a) Your research may not interfere with normal patient care  
- b) Hospital staff may not be asked to assist with the research.  
- c) No hospital consumables and stationary may be used.  
- d) No patient folders may be removed from the premises or be inaccessible.  
- e) Please introduce yourself to the person in charge of an area before commencing.  
- f) Please discuss the study with the Head of Radiation Oncology before commencing.

I would like to wish you every success with the project.

Yours sincerely

Signed by candidate

DR BHAVNA PATEL  
SENIOR MANAGER: MEDICAL SERVICES  
Date: 6th February 2012
III: GUIDELINES TO AUTHORS (INTERNATIONAL JOURNAL OF GYNAECOLOGIC CANCER)

Scope
*International Journal of Gynecological Cancer*, the official journal of the International Gynecologic Cancer Society and the European Society of Gynaecological Oncology, is the primary educational and informational publication for topics relevant to detection, prevention, diagnosis, and treatment of gynecologic malignancies. IJGC emphasizes a multidisciplinary approach, and includes original research (clinical trials and translational or basic research), reviews, and opinion pieces. The audience consists of gynecologists, medical oncologists, radiation oncologists, radiologists, pathologists, and research scientists with a special interest in gynecological oncology.

Ethical/Legal Considerations
A submitted manuscript must be an original contribution not previously published (except as an abstract or a preliminary report), must not be under consideration for publication elsewhere, and, if accepted, must not be published elsewhere in similar form, in any language, without the consent of Lippincott Williams & Wilkins. Each person listed as an author is expected to have participated in the study to a significant extent. Although the editors and referees make every effort to ensure the validity of published manuscripts, the final responsibility rests with the authors, not with the Journal, its editors, or the publisher.

All manuscripts must be submitted on-line through the journal’s Web site at [http://igc.edmgr.com](http://igc.edmgr.com). See submission instructions under “On-line manuscript submission.”

*Patient anonymity and informed consent:* It is the author’s responsibility to ensure that a patient’s anonymity be carefully protected and to verify that any experimental investigation with human subjects reported in the manuscript was performed with informed consent and following all the guidelines for experimental investigation with human subjects required by the institution(s) with which all the authors are affiliated. Authors should mask patients’ eyes and remove patients’ names from figures unless they obtain written consent from the patients and submit written consent with the manuscript.

*Copyright:* All authors must sign a copy of the Journal’s “Authorship Responsibility, Financial Disclosure, and Copyright Transfer” form and submit it at the time of manuscript submission.

*Compliance with NIH and Other Research Funding Agency Accessibility Requirements:* A number of research funding agencies now require or request authors to submit the post-print (the article after peer review and acceptance but not the final published article) to a repository that is accessible online by all without charge. As a service to our authors, LWW will identify to the National Library of Medicine (NLM) articles that require deposit and will transmit the post-print of an article based on research funded in whole or in part by the National Institutes
of Health, Wellcome Trust, Howard Hughes Medical Institute, or other funding agencies to PubMed Central. The Copyright Transfer Agreement provides the mechanism.

Permissions:

For permission and/or rights to use content for which the copyright holder is LWW or the society, please go to the journal's website and after clicking on the relevant article, click on the "Request Permissions" link under the "Article Tools" box that appears on the right side of the page. Alternatively, send an e-mail to customercare@copyright.com.

For Translation Rights & Licensing queries, contact Silvia Serra, Translations Rights, Licensing & Permissions Manager, Wolters Kluwer Health (Medical Research) Ltd, 250 Waterloo Road, London SE1 8RD, UK. Phone: +44 (0) 207 981 0600. E-mail: silvia.serra@wolterskluwer.com

For Special Projects and Reprints (U.S./Canada), contact Alan Moore, Director of Sales, Lippincott Williams & Wilkins, Two Commerce Square, 2001 Market Street, Philadelphia, PA 19103. Phone: 215-521-8638. E-mail: alan.moore@wolterskluwer.com

For Special Projects and Reprints (non-U.S./Canada), contact Silvia Serra, Translations Rights, Licensing & Permissions Manager, Wolters Kluwer Health (Medical Research) Ltd, 250 Waterloo Road, London SE1 8RD, UK. Phone: +44 (0) 207 981 0600. E-mail: silvia.serra@wolterskluwer.com

Manuscript Submission

On-line manuscript submission: All manuscripts must be submitted on-line through the Web site at http://igc.edmgr.com.

First-time users: Please click the Register button from the main menu and enter the requested information. On successful registration, you will be sent an e-mail indicating your user name and password. Print a copy of this information for future reference. Note: If you have received an e-mail from us with an assigned user ID and password, or if you are a repeat user, do not register again. Just log in. Once you have an assigned ID and password, you do not have to re-register, even if your status changes (that is, author, reviewer, or editor).

Authors: Please click the log-in button from the menu at the top of the page and log in to the system as an Author. Submit your manuscript according to the author instructions. You will be able to track the progress of your manuscript through the system.
Preparation of Manuscript
Manuscripts that do not adhere to the following instructions will be returned to the corresponding author for technical revision before undergoing peer review.

Manuscripts should be no longer than 3000 words (not including the abstract and references).

*Title page*: The title page must be submitted as a separate file. Include on the title page (a) complete manuscript title; (b) authors’ full names, highest academic degrees, and affiliations; (c) name and address for correspondence, including fax number, telephone number, and e-mail address; (d) address for reprints if different from that of corresponding author; and (e) all sources of support, including pharmaceutical and industry support, that require acknowledgment.

The title page must also include disclosure of funding received for this work from any of the following organizations: National Institutes of Health (NIH); Wellcome Trust; Howard Hughes Medical Institute (HHMI); and other(s).

*Structured Abstracts*: Limit the abstract to 300 words. Do not cite references in the abstract. Limit the use of abbreviations and acronyms. Use the following headings: Objective, Methods/materials, Results, and Conclusions. List three to five key words. Examples of key words: clear cell, cisplatin, ovarian carcinoma, ultrasound.

*Text*: Organize the manuscript into four main headings: Introduction, Materials and Methods, Results, and Discussion. Define abbreviations at first mention in text and in each table and figure. If a brand name is cited, supply the manufacturer's name and address (city and state/country).

*Abbreviations*: For a list of standard abbreviations, consult the Council of Biology Editors Style Guide (available from the Council of Science Editors, 9650 Rockville Pike, Bethesda, MD 20814, www.councilscienceeditors.org) or other standard sources. Write out the full term for each abbreviation at its first use unless it is a standard unit of measure.

*References*: The authors are responsible for the accuracy of the references. Key the references (double-spaced) at the end of the manuscript. Cite the references in text in the order of appearance. Cite unpublished data—such as papers submitted but not yet accepted for publication and personal communications, including e-mail communications—in parentheses in the text. If there are more than three authors, name only the first three authors and then use et al. Refer to the List of Journals Indexed in Index Medicus for abbreviations of journal names, or access the list at http://www.nlm.nih.gov/tsd/serials/lij.html. There should be no more than 25 references. If there are more than 25, please limit the published references to 25 and insert the following sentence: “For the complete list of references, please contact [author’s email address].

~ 60 ~
Sample references are given below:

**Journal article**

**Book chapter**

**Entire book**

**Software**

**Online journals**

**Database**

**World Wide Web**

**Figures:** There should be no more than 6 graphics, including figures and tables.

Digital art should be created/scanned and saved and submitted as either a TIFF (tagged image file format), an EPS (encapsulated postscript) file. PPT (Power Point) files will also be accepted. **Electronic photographs**—radiographs, CT scans, and so on—and **scanned images must have a resolution of at least 300 dpi.** **Line art must have a resolution of at least 1200 dpi (dots per inch).** If fonts are used in the artwork, they must be converted to paths or outlines or they must be embedded in the files. **Color images must be created/scanned and saved and submitted as CMYK files.** If you do not have the capability to create CMYK files, please disregard this step. Indicate in your cover letter
that you are unable to produce CMYK files. Cite figures consecutively in the text, and number them in the order in which they are discussed.

**Detailed Figure Instructions:** For a step by step guide for submitting Digital Art please visit [www.LWWonline.com](http://www.LWWonline.com). Click “For Authors” and click “Artwork” and “5 Steps for Creating Digital Artwork” in the menu to the right.

**Figure legends:** Include legends for all figures. They should be brief and specific, and they should appear on a separate manuscript page after the references. Use scale markers in the image for electron micrographs, and indicate the type of stain used.

**Color figures:** The journal accepts for publication color figures that will enhance an article. Authors who submit color figures will receive an estimate of the cost for color reproduction. If they decide not to pay for color reproduction, they can request that the figures be converted to black and white at no charge.

**Tables:** There should be no more than 6 graphics, including figures and tables.

Create tables using the table creating and editing feature of your word processing software (eg, Word, WordPerfect). Do not use Excel or comparable spreadsheet programs. Group all tables in a separate file. Cite tables consecutively in the text, and number them in that order. Each table should appear on a separate sheet and should include the table title, appropriate column heads, and explanatory legends (including definitions of any abbreviations used). Do not embed tables within the body of the manuscript. They should be self-explanatory and should supplement, rather than duplicate, the material in the text.

**Style:** Pattern manuscript style after the *American Medical Association Manual of Style* (9th edition). *Stedman’s Medical Dictionary* (27th edition) and *Merriam Webster’s Collegiate Dictionary* (10th edition) should be used as standard references. Refer to drugs and therapeutic agents by their accepted generic or chemical names, and do not abbreviate them. Use code numbers only when a generic name is not yet available. In that case, the chemical name and a figure giving the chemical structure of the drug is required. Copyright or trade names of drugs should be capitalized and placed in parentheses after the name of the drug. Names and locations (city and state in USA; city and country outside USA) of manufacturers of drugs, supplies, or equipment cited in a manuscript are required to comply with trademark law and should be provided in parentheses. Units of measure should be expressed in the metric system, and temperatures should be expressed in degrees Celsius. Conventional units should be written as SI units as appropriate.
Sections

**Original Articles:** Our intent is to publish high quality research as it relates to clinical trials, outcome analyses, translational research, cost utility analyses, etc.

**Review Articles:** Our intent is to include high quality review articles, of 2500 words and up to 20 references, which will address a topic of major interest in the field of gynecologic oncology.

**Brief Reports:** Articles having a maximum of 1500 words and an abstract with a highly focused message and minimum of methodological detail, and maximum of 15 references. Include "Brief Report: " in the title.

**Surgeon’s Corner:** Intended to describe a specific issue of surgical technique that is rather new or modified. This section is limited to 1000 words and up to 5 references and will be peer reviewed.

**Letters to the Editor:** The Editorial Board reserves the right to decline publishing insulting or inflammatory comments in letters to the editor. Letters should be a short and concise communication commenting on a recently published article in the Journal or commenting on a controversial current issue of concern to the readership. A Letter to the Editor is not a site for publication of original results. The letter should have no more than 3 authors and contain no more than 5 references, including a reference to the article in question. A statement of potential sources of conflict of interest must accompany the letter and may be published along with the letter.

Multimedia files

**Supplemental Digital Content**

**Supplemental Digital Content (SDC):** Authors may submit SDC via Editorial Manager to LWW journals that enhance their article’s text to be considered for online posting. SDC may include standard media such as text documents, graphs, audio, video, etc. On the Attach Files page of the submission process, please select Supplemental Audio, Video, or Data for your uploaded file as the Submission Item. If an article with SDC is accepted, our production staff will create a URL with the SDC file. The URL will be placed in the call-out within the article. SDC files are not copy-edited by LWW staff, they will be presented digitally as submitted. For a list of all available file types and detailed instructions, please visit [http://links.lww.com/A142](http://links.lww.com/A142).
SDC Call-outs

Supplemental Digital Content must be cited consecutively in the text of the submitted manuscript. Citations should include the type of material submitted (Audio, Figure, Table, etc.), be clearly labeled as “Supplemental Digital Content,” include the sequential list number, and provide a description of the supplemental content. All descriptive text should be included in the call-out as it will not appear elsewhere in the article.

Example:

We performed many tests on the degrees of flexibility in the elbow (see Video, Supplemental Digital Content 1, which demonstrates elbow flexibility) and found our results inconclusive.

List of Supplemental Digital Content

A listing of Supplemental Digital Content must be submitted at the end of the manuscript file. Include the SDC number and file type of the Supplemental Digital Content. This text will be removed by our production staff and not be published.

Example:

Supplemental Digital Content 1. wmv

SDC File Requirements

All acceptable file types are permissible up to 10 MBs. For audio or video files greater than 10 MBs, authors should first query the journal office for approval. For a list of all available file types and detailed instructions, please visit http://links.lww.com/A142.

After Acceptance

Page proofs and corrections: Corresponding authors will receive electronic page proofs to check the copyedited and typeset article before publication. Portable document format (PDF) files of the typeset pages and support documents (eg, reprint order form) will be sent to the corresponding author by e-mail. Complete instructions will be provided with the e-mail for downloading and printing the files and for faxing the corrected page proofs to the publisher. Those authors without an e-mail address will receive traditional page proofs. It is the author’s responsibility to ensure that there are no errors in the proofs. Changes that have been made to conform to journal style will stand if they do not alter the authors’ meaning. Only the most critical changes to the accuracy of the content will be made. Changes that are stylistic or are a reworking of previously accepted material will be disallowed. The publisher reserves the right to deny any changes that do not affect the accuracy of the content. Authors may be charged for alterations to the proofs beyond those required to correct errors or to answer
queries. Proofs must be checked carefully and corrections faxed within 24 to 48 hours of receipt, as requested in the cover letter accompanying the page proofs.

Reprints: Authors will receive a reprint order form and a price list with the page proofs. Reprint requests should be faxed to the publisher with the corrected proofs, if possible. Reprints are normally shipped 6 to 8 weeks after publication of the issue in which the item appears. Contact the Reprint Department, Lippincott Williams & Wilkins, 351 W. Camden Street, Baltimore, MD 21201; Fax: 410-528-4434; E-mail: reprints@wolterskluwer.com with any questions.

Publisher's contact: Fax corrected page proofs, reprint order form, and any other related materials to Journal Production Editor, International Journal of Gynecological Cancer, 351 W. Camden Street, Baltimore, MD 21201-2436; 410-528-4266 (fax).