Conservative Surgery for Women with Low-Risk, Early Stage Cervical Cancer

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1. To evaluate the safety and feasibility of performing conservative surgery in women with stage IA2 or IB1 carcinoma of the cervix with favorable pathologic features

1.2 Secondary Objectives:

1. To estimate the cervix cancer recurrence rate at 2 years in women treated with conservative surgery for stage IA2 or IB1 carcinoma of the cervix with favorable pathologic features
2. To compare pelvic lymph node involvement in patients undergoing conservative surgery with historical data from matched patients treated with radical hysterectomy
3. To estimate the sensitivity of sentinel lymph node biopsy in the determination of pelvic lymph node metastases in this group of patients
4. To compare the treatment-associated morbidity in patients undergoing conservative surgery with historical data from matched patients treated with radical hysterectomy
5. To assess quality of life factors, sexual functioning, symptoms and satisfaction with healthcare decisions in this group of patients

2.0 Background

2.1 Cervical cancer:

Cervical cancer is the most common cause of death from gynecologic cancer worldwide. In developed countries with good public health infrastructure, early cytological detection of cervical cancer using the Pap smear has led to an impressive reduction of mortality. However, in less developed regions such as Central America, South East Africa and India, the incidence and mortality rates are still very high. Today, more than 80% of all cervical cancer deaths occur in developing countries. In the United States alone, it is estimated that there will be approximately 11,070 new cases and 3,870 deaths in 2008 [1].

2.2 Treatment of cervical cancer:

The standard treatment for women with early stage cervical carcinoma consists of either radical surgery or radiotherapy. Survival rates are similar between the two treatment modalities [2], and the therapy choice is based on side effect profiles, patient related factors and patient/physician preference. For women undergoing surgical management, the treatment consists of a radical hysterectomy and pelvic lymph node dissection. The traditional Wertheim type III radical hysterectomy includes removal of the uterus, upper vagina and resection of the parametrium [3]. Although radical hysterectomy results in excellent local tumor control, it is also associated with significant morbidity [2, 4-8]. Much of this morbidity is due to removal of the parametrium, which contains autonomic nerve fibers associated with bladder, bowel and sexual function.

A new surgical approach, radical trachelectomy, offers a conservative approach for women with stage IA2 or small IB1 disease who wish to retain fertility. This operation removes the cervix and parametrium, while sparing the uterine fundus. First introduced by Daniel Dargent in 1994, the laparoscopic vaginal radical trachelectomy has been widely adopted in Europe and North America. Multiple single-center retrospective and prospective studies have reported that radical

trachelectomy is feasible, safe and with seemingly equivalent disease-free and overall survival rates when compared to radical hysterectomy [9-12]. In addition, it has been shown that in 60% of radical trachelectomy specimens, there is no residual disease [10]. However, like radical hysterectomy, radical trachelectomy involves removal of the parametrium and the associated complications.

2.3 Lymphatic mapping and sentinel lymph node biopsy:
In patients with cervical cancer, lymph node involvement is a major indication for adjuvant treatment and an important predictor of long-term survival. All surgically treated patients therefore undergo a complete pelvic lymphadenectomy. However, the majority of patients with early stage disease do not have lymph node metastases and lymphatic mapping with sentinel lymph node (SLN) biopsy has been evaluated as a potential replacement for complete pelvic lymph node dissection. Levenback and colleagues [13] performed lymphatic mapping and SLN identification in cervical cancer patients undergoing laparotomy with radical hysterectomy and retroperitoneal lymph node dissection. They found SLN identification to have a sensitivity of 87.5% for histologically node-positive patients, and a 97% negative predictive value for metastatic disease in non-sentinel lymph nodes. Using similar methods adapted for laparoscopic radical hysterectomy and lymph node dissection, Pijpers *et al.* [14] reported lymphatic mapping with SLN biopsy to have a sensitivity of 92%. In a meta-analysis of 16 lymphatic mapping studies, Frumovitz *et al.* [15] reported lymphatic mapping and SLN biopsy to have an overall sensitivity of 91% and negative predictive value of 97%.

2.4 Parametrial involvement in early cervical cancer:
The utility of parametrial resection in women with early stage cervical cancer is controversial. Several studies have evaluated the incidence of parametrial involvement and the pathologic features associated with parametrial spread [16-21]. Kinney *et al* [16] evaluated 83 patients with stage IB1 squamous cell carcinoma of the cervix, with tumor size <2 cm and no lymphovascular involvement (LVSI). None of the patients in this study had parametrial involvement.

A subsequent report by Covens and colleagues [17] evaluated 842 patients with stage IA1 to IB1 cervical cancer who underwent radical hysterectomy. They noted that 33 patients (4%) had parametrial involvement. Parametrial involvement was associated with larger tumor size, LVSI, greater depth of invasion and positive pelvic lymph nodes. They performed a subset analysis on 536 patients with tumor size ≤2 cm, negative lymph nodes and <10 mm of invasion. In this subgroup of patients with favorable pathologic features, the incidence of parametrial involvement was 0.6%. At a median of follow-up of 51 months, the 2 and 5-year recurrence free survival in this subgroup was 98 and 96% respectively [17].

A recent study by Stegeman *et al.* [18] evaluated 103 premenopausal patients with stage IA1 to IB1 cervical cancer. All patients had tumors measuring <2 cm in diameter, <10 mm of invasion and negative pelvic lymph nodes. The different histologies included squamous cell (n=74, 72%), adenocarcinoma (n=25, 24%), adenosquamous (n=3, 3%) and clear cell (n=1, 1%). Only two of the103 patients (1.9%) had parametrial involvement. One patient had a 2 cm squamous cell carcinoma measuring 2 cm with 9 mm of invasion, and the second patient had squamous cell carcinoma measuring 1.2 cm with 4 mm of invasion. Of note, both of these patients had LVSI

present. The authors also performed a review of the literature and combined the data from three additional studies that met the same inclusion criteria. They found that only 5 of 799 patients (0.6%) with low-risk pathologic characteristics had parametrial involvement [18].

Wright and colleagues [19] reported on 594 patients who underwent radical hysterectomy. Parametrial involvement was noted in 64 patients (10.8%) and was associated with advanced grade, deep cervical invasion, LVSI, large tumor size and lymph node metastases. In a subgroup of 270 patients with negative lymph nodes, no LVSI and tumors <2 cm, the incidence of parametrial involvement was only 0.4%. Among these 270 patients, 2 (0.7%) recurrences were noted after a median follow-up of 59 months [19].

A recent study by Strnad *et al* [21] evaluated 158 women with stage IA2 and IB1 cervical cancer who underwent radical abdominal hysterectomy and sentinel lymph node mapping. No parametrial involvement was noted in patients with negative sentinel lymph nodes, compared with 28% of patients with positive sentinel lymph nodes.

2.5 Conservative surgery for early cervical cancer:

Rob *et al.* [22] recently reported on the feasibility and safety of performing less radical, fertility-sparing surgery in 26 women with stage IA2 or IB1 cervical carcinoma. All patients had tumors <2 cm in diameter and desired to maintain fertility. Histologic subtypes included squamous (n=21, 81%), adenocarcinoma (n=4, 15%) and adenosquamous (n=1, 4%). Twelve patients (46%) had grade 1 tumors, 9 (35%) had grade 2 tumors, and 5 (19%) had grade 3 tumors. LVSI was noted in 10 (39%) of patients.

All patients underwent laparoscopic sentinel lymph node identification with frozen section. If the frozen section was negative, a complete pelvic lymphadenectomy was performed. After a 7-day interval, a large cone or simple vaginal trachelectomy was performed in patients with negative nodes. Of the 26 patients enrolled, 4 had positive sentinel lymph nodes on frozen section, and radical hysterectomy was immediately performed. In the remaining 22 patients, all lymph nodes were negative for malignancy on final pathology [22].

The median follow-up was 49 months, with one recurrence reported. This occurred in a patient with a stage IB1 tumor with 8 mm invasion and LVSI present. The recurrence occurred in the isthmus of the uterus, 14 months after the initial surgery and the patient was treated with chemoradiation. Of the 15 women who planned pregnancy, 11 became pregnant and 7 delivered infants. Intraoperative complications occurred in two patients who had vascular injuries associated with the laparoscopic lymph node dissection. There were no complications related to the large cone of simple trachelectomy procedures. The authors concluded that large cone or simple trachelectomy with laparoscopic pelvic lymph node dissection is safe and feasible with a high pregnancy rate in women with early stage cervical cancer [22].

3.0 Rationale:

Radical hysterectomy with pelvic lymph node dissection is the current standard for the treatment of early stage cervical cancer. While this is an effective treatment, it is associated with morbidity due to removal of the parametrium, which contains autonomic nerve fibers associated with bladder, bowel and sexual function. Several retrospective studies have shown that in early stage cervical cancer with favorable pathologic characteristics, the parametrial involvement is only 0 to 0.6% [16-19].

The proposed clinical trial will evaluate the safety and feasibility of performing conservative surgery in women with stage IA2 or IB1 carcinoma of the cervix (Appendix O) with favorable pathologic features. All patients will be counseled regarding future fertility. In patients no longer desiring future fertility, a simple hysterectomy and lymphatic mapping with sentinel lymph node biopsy and/or pelvic lymph node dissection will be performed. Patients desiring future fertility will undergo a cone and lymphatic mapping with sentinel lymph node biopsy and/or pelvic lymph node dissection only. The cervix cancer recurrence rate at 2 years in these women will be determined. Pelvic lymph node involvement and treatment-associated morbidity in these patients undergoing conservative surgery will be compared with historical data from patients treated with radical hysterectomy. Quality of life factors, sexual functioning, symptoms and satisfaction with healthcare decisions in this group of patients will be assessed. In addition, the sensitivity of sentinel lymph node biopsy in the determination of pelvic lymph node metastases in this group of patients will be estimated.

4.0 Patient Eligibility

4.1 Inclusion Criteria:

1. Histologically confirmed squamous cell carcinoma of the cervix (any grade) or Histologically confirmed grade 1 or 2 adenocarcinoma of the cervix
2. FIGO stage IA2 or IB1 disease
3. Tumor diameter $\leq$2 cm on physical exam and on imaging studies
4. No lymphovascular space invasion (LVSI) present on biopsy or previous cone
5. Less than 10mm of cervical stromal invasion
6. Cone margins and endocervical curettage (ECC) specimen negative for invasive cancer, cervical intraepithelial neoplasia (CIN) CIN II, CIN III or adenocarcinoma-in-situ. (A negative margin is defined as no invasive cancer within 1.0mm of both the endocervical and ectocervical margins and no AIS or CIN II or CIN III at the inked or cauterized margin; one repeat cone and ECC permitted)
7. Patients are eligible for the study when a cone and ECC are performed prior to pre-enrollment in the study, and pathologic eligibility criteria are met. The cone and ECC must be performed within 12 weeks prior to pre-enrollment in the study. If the cone and ECC performed prior to pre-enrollment do not meet the pathologic criteria, patients may be pre-enrolled and are allowed 1 repeat cone & ECC after pre-enrollment in order to meet pathologic eligibility criteria. (see section 6.1)
8. Patients must sign an approved informed consent document
9. If patient is of childbearing potential, she must have a negative blood or urine pregnancy test within 14 days of surgical treatment on study.

10. Imaging with Positron emission tomography (PET) scan, computed tomography (CT) scan of the abdomen and pelvis, and/or magnetic resonance imaging (MRI) of the abdomen and pelvis must be performed and negative for metastatic disease within 12 weeks of enrollment.

4.2 Exclusion Criteria:

1. Clear cell, neuroendocrine, adenosquamous, serous carcinoma or other high-risk histologies
2. Grade 3 adenocarcinoma
3. FIGO stage IA1, IB2, II, III or IV disease
4. Tumors >2 cm in diameter on physical exam or imaging studies
5. Presence of LVSI
6. Greater than or equal to 10mm of cervical stromal invasion
7. Cone margins or ECC specimen positive for invasive cancer, CIN II, CIN III or adenocarcinoma-in-situ (one repeat cone permitted)
8. Neoadjuvant radiation therapy or chemotherapy for cervical cancer
9. Patients unwilling or unable to provide informed consent for the study
10. Evidence of metastatic disease on PET, CT, and/or MRI performed within 12 weeks of enrollment
11. Patients who have had a simple hysterectomy (cut through hysterectomy)

5.0 Study Design

This is a prospective, multi-institutional cohort study evaluating the outcomes of performing conservative surgery in women with stage IA2-IB1 cervical cancer with favorable pathologic characteristics. Up to 195 total patients will be enrolled to this study in order to accrue 100 evaluable patients.

6.0 Treatment Plan

The study will prospectively enroll women with stage IA2-IB1 cervical cancer with favorable pathologic characteristics.

6.1 Surgery:

For participants who undergo cervical cone and endocervical curettage (ECC), it is preferred that the cone is a cold-knife cone (CKC) but a loop electrosurgical excision procedure (LEEP) is also acceptable. Patients will be eligible if the cone and ECC is performed at one of the participating sites or by a referring physician prior to the patient being seen at one of the participating sites. All patients must have a negative cone and ECC prior to study registration. In all cases, the pathology will be centrally reviewed at MD Anderson. The results from the cone and ECC must meet the pathologic inclusion criteria. If the cone margin and/or ECC is positive for invasive cancer, adenocarcinoma-in-situ, CIN II or CIN III one repeat cone and ECC is allowed after pre-enrollment. If the repeat cone margins and ECC are negative (a negative margin is defined as no invasive cancer within 1.0mm of both the endocervical and ectocervical margins and no AIS or CIN II or CIN III at the inked or cauterized margin), and the pathologic eligibility criteria are

still met, the patient will undergo surgery as described below. If the repeat cone and or ECC margins are positive for invasive cancer, adenocarcinoma-in-situ, CIN II or CIN III, the patient will be removed from the study and treated at the discretion of her physician. Patients are eligible for the study if the first and/or repeat cone and ECC were performed prior to pre-enrollment in the study, provided the pathologic eligibility criteria are met and the most recent cone and ECC were performed within 12 weeks prior to pre-enrollment. If the cone and ECC performed prior to pre-enrollment do not meet the pathologic criteria, patients may be pre-enrolled and are allowed 1 repeat cone & ECC after pre-enrollment in order to meet pathologic eligibility criteria. If a patient underwent a cone without ECC and the cone meets pathologic criteria, the patient must undergo an ECC and must show to be negative in order to meet eligibility criteria.

The pathology from the cone and ECC must be reviewed at MD Anderson and eligibility confirmed prior to proceeding with conservative surgery. Surgery must occur within 12 weeks after the cone and ECC. All patients will be counseled regarding future fertility. If future fertility is desired or if the patient declines a hysterectomy, no further treatment will be performed. If future fertility is not desired, a simple hysterectomy with or without bilateral salpingo-oophorectomy will be performed. These procedures may be performed by laparotomy, vaginally, by laparoscopy or using the Davinci® robotic system (Sunnyvale, CA).

If suspicious lymph nodes are noted at the time of surgery, they will be removed and sent for intra-operative pathologic evaluation. If the intra-operative pathologic evaluation shows metastatic disease to the lymph nodes, the patient will be treated at the discretion of her physician.

If, in the patients undergoing simple hysterectomy, the final pathology results show residual disease in the cervix, the patients will be offered observation or further treatment with parametrectomy vs. radiotherapy based on the pathologic findings and the clinical judgment of the treating physician. If the final pathology results show malignant pelvic lymph nodes, the patient will be treated with radiation therapy +/- chemotherapy at the discretion of the treating physician.

6.2 Pathology:

All cervical cone and ECC specimens must be centrally reviewed at MD Anderson by a gynecologic pathologist to confirm the pathologic characteristics necessary for eligibility for the study. This will be done prior to the patient undergoing conservative surgery per the protocol. A negative cone margin is defined as no invasive cancer within 1.0mm of both the endocervical and ectocervical margins and no AIS or CIN II or CIN III at the inked or cauterized margin. In addition, all final pathologic specimens from the subsequent surgery (sentinel and non-sentinel lymph node specimens, as well as the hysterectomy specimen if performed) will be reviewed at MD Anderson. If there is a discrepancy between the pathologic interpretation at the participating site and, the pathologists and PIs at MD Anderson and the participating site, as well as the patient will be notified. The patient will be managed at the discretion of her treating physician. For study purposes, the MD Anderson interpretation will be used.

6.3 Follow-Up:

Patients will be seen and evaluated every 3 months after their first postoperative visit (+/- 4 weeks) with physical exam and Pap smear for two years. If any abnormalities are detected, patients will be evaluated and treated at the discretion of their physician. Patients who have lymphatic mapping with sentinel lymph node biopsy and/or pelvic lymph node dissection only must practice effective birth control for at least 6 months postoperatively. After two years, patients will be contacted yearly for 3 years by study staff to assess their status.

6.4 Data Collected:

Data collected at the time of pre-enrollment (if available) will include age at cancer diagnosis, ethnicity, menopausal status, and may or may not include, body mass index (BMI), presenting symptoms, history of sexually transmitted diseases, smoking history, and history of infertility. Pathology reports and clinical charts will be reviewed for pathologic information including tumor size, stage, grade, histology, LVSI and margin status. Surgical information including operative time, estimated blood loss, transfusion requirements in the intraoperative and immediate postoperative period, length of stay and complications will also be collected. The data will be collected at each of the participating sites. Each participating site will enter the data collected into the REDCap system.

Study data will be collected and managed using REDCap (Research Electronic Data Capture) electronic data capture tools hosted at MD Anderson. [27] REDCap (www.project-redcap.org) is a secure, web-based application with controlled access designed to support data capture for research studies, providing: 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless downloads to common statistical packages; and 4) procedures for importing data from external sources. In the case of multi-center studies REDCap uses Data Access Groups (DAGs) to ensure that personnel at each institution are blinded to the data from other institutions. REDCap (https://redcap.mdanderson.org) is hosted on a secure server by MD Anderson Cancer Center's Department of Research Information Systems & Technology Services. REDCap has undergone a Governance Risk & Compliance Assessment (05/14/14) by MD Anderson's Information Security Office and found to be compliant with HIPAA, Texas Administrative Codes 202-203, University of Texas Policy 165, federal regulations outlined in 21CFR Part 11, and UTMDACC Institutional Policy #ADM0335. Those having access to the data file include the study PI and research team personnel. All protected health information (PHI) will be removed from the data when it is exported from REDCap for analysis. All dates for a given patient will be shifted by a randomly generated number between 0 and 364, thus preserving the distance between dates. Dates for each patient will be shifted by a different randomly generated number.

6.5 Quality of Life:

All questionnaires will be available in English, Spanish, and Portuguese. Patients will be asked to complete five self-administered questionnaires. Patient may decline to complete questionnaires or certain questions if they do not feel comfortable answering. Questionnaires (SF-12, FACT-Cx, MDASI, FSFI and SWDS – see section 8.0 below) will be given at the following time points:

1. Preoperatively (within 4 weeks prior to scheduled surgery)
2. Three months following the first postoperative visit (+/- 1 month)

3. Six months following the first postoperative visit (+/- 1 month)
4. One year following the first postoperative visit (+/- 1 month)
5. Two years following the first postoperative visit (+/- 1 month)

7.0 Quality of Life Instruments

7.1 General Health-Related Quality of Life: The SF-12 (Appendix D):

This 12-item questionnaire was developed from the longer SF-36. The SF-12 estimates each of eight health domains (physical functioning, role-physical, role-emotional, mental health, bodily pain, vitality, social functioning and general health) using a tool that takes less than 2 minutes to administer. Scores are given in each domain as well as summary scores for overall physical and mental status. Empirical cross-validation studies have shown correlations between the SF-12 and SF-36 surveys ranging from 0.93 to 0.97 [23].

7.2 FACT-CX (Appendix E):

The FACT-G is the generic score to measure quality of life for patients with cancer. This instrument contains 27 questions from 4 domains: physical well-being, social/family well-being, emotional well-being, and function well-being. The FACT instruments are well regarded particularly because several disease specific subscales exist, including cervix cancer (FACT-CX). The cervix cancer subscale consists of 15 questions pertaining to patients with cervix cancer. The FACT-CX should take about 5 minutes to complete.

7.3 MD Anderson Symptom Inventory (MDASI) (Appendix F):

The MD Anderson Symptom Inventory (MDASI) is a 19-item questionnaire. The first 13 items assess patient symptoms during the prior 24 hours and should take less than 3 minutes to complete. Symptoms assessed include pain, fatigue, nausea/vomiting, anorexia, sleep symptoms, and distress. The last 6 items assess how those symptoms have interfered with the patient's general well-being, including their general activity, mood, ability to walk and perform normal work, as well as their relationships with others and enjoyment of life. The validity and reliability of the MDASI have been well-established [24].

7.4 Female Sexual Functioning Index (FSFI) (Appendix G):

Sexual functioning will be assessed using the Female Sexual Function Index (FSFI), a 19-item multiple-choice survey that takes approximately 5 minutes to complete [25]. The questionnaire measures sexual desire, arousal (both subjective and physiological), lubrication, orgasm, satisfaction, and pain. Validation studies on sexually dysfunctional and matched control women aged 21 to 70 have demonstrated excellent internal consistency (0.89 to 0.97) and 2 to 4 week test-retest reliability (0.79 to 0.88) for each subscale [25].

7.5 Satisfaction with Decision (SWD) Scale (Appendix H):

The Satisfaction with Decision scale is a six-item survey that measures the patient's satisfaction with health care decisions. The instrument has been shown to have excellent reliability and validity [26].

8.0 Statistical Considerations

8.1 Sample Size

We will enroll and evaluate a minimum of 20 and a maximum of 100 evaluable patients at a rate of approximately 4 patients per month. The anticipated accrual rate of 4 patients per month will be considered viable once at least 50% of the participating sites have opened the trial. We anticipate that approximately 40% of participants will result in a screen failure and 10% of participants will be inevaluable due to the cone specimen not meeting the pathologic inclusion criteria.

8.2 Feasibility Monitoring Rule

The immediate failure rate is defined as residual disease in the simple hysterectomy specimen. The proposed treatment strategy will be considered infeasible if the immediate failure rate is more than 3%. We will use a monitoring rule to stop the trial early if P(immediate failure rate > 3% | data from the trial) > 0.80. That is, given the outcomes from the patients who have already been evaluated, if we determine that there is more than an 80% chance that the immediate failure rate is more than 3%, we will stop the trial.

This decision rule gives the following stopping rule. We assume a beta (0.15, 4.85) prior distribution for the immediate failure rate. This prior distribution has a mean of 0.030 and a standard deviation of 0.023. We will stop the trial if

[# of pts with immediate failure / # of pts evaluated]

≥ 2/20, 3/27, 4/52, 5/77

The operating characteristics of this monitoring rule are shown in Table 1.

Table 1. Operating Characteristics of Feasibility Monitoring Rule

Residual Disease Rate	Probability of Stopping Early	Sample Size		
		P_{25}	P_{50}	P_{75}
0.01	0.036	100	100	100
0.02	0.162	100	100	100
0.03	0.332	50	100	100
0.04	0.527	25	92	100
0.05	0.697	20	47	100
0.06	0.812	20	36	76
0.07	0.895	20	24	55

8.3 Efficacy Monitoring Rule

Our efficacy outcome is the recurrence rate at 2 years, which is approximately 5% in this patient population with standard treatment. We will follow each patient for at least 24 months. We expect to have no recurrences at 2 years.

We will stop the study if there are 2 or more patients meeting our revised inclusion/exclusion criteria with recurrence by 2 years following completion of therapy. There is a 0.80 probability of observing 1 or fewer patients with recurrence before observing 82 patients without recurrence, if the probability of recurrence is 0.01. This calculation was performed using the negative binomial probability distribution.

Our original sample size was 100 patients, but during the course of the study we have modified the inclusion/exclusion criteria to exclude patients with cut-through hysterectomies (n=16 enrolled) and patients with a diagnosis of CIN 2/3 at margins with 10 mm invasion (n=1 enrolled). We currently have 72 evaluable patients enrolled according to our original inclusion/exclusion criteria. With the revised inclusion/exclusion criteria we have 72 – 16 – 1 = 55 evaluable patients enrolled. We plan to enroll 100 – 72 = 28 more evaluable patients, yielding 100 ***total*** patients and 83 ***evaluable*** patients according to our revised inclusion/exclusion criteria.

8.4 Analysis

We will perform all analyses described below for the ***total*** number of patients enrolled and eligible according to our original inclusion/exclusion criteria (n=100) and for all patients ***evaluable*** according to our revised inclusion/exclusion criteria (n=83).

Demographics

We will use descriptive statistics to summarize the demographic and clinical characteristics of the patients in this study.

Immediate Failure Rate

We will estimate the immediate failure rate with a 90% credible interval. If we have 3 immediate failures out of 100 ***total*** patients, then our 90% credible interval for the immediate failure rate will be 0.9% to 6.1%. If we have 3 immediate failures out of 83 ***evaluable*** patients, then our 90% credible interval for the immediate failure rate will be 1.0% to 7.3%. We will also report the posterior probability that the immediate failure rate is 3% or more for the ***total*** number of patients and for the ***evaluable*** patients.

Recurrence Rate

We will estimate the recurrence rate at 2 years with an exact 95% binomial confidence interval.

If we complete the study with 0/83 ***evaluable*** patients with recurrence by 2 years after surgery, an exact binomial 95% confidence interval estimate of the recurrence rate will be 0 to 4.3%. With 1/83 ***evaluable*** patients with recurrence by 2 years after surgery the confidence interval will be 0.1% to 5.9%.

If we complete the study with 100 ***total*** patients and only 3 patients with recurrence by 2 years following completion of therapy our estimate of the recurrence rate at 2 years will be 0.8% to 8.0%.

Clinical Characteristics

We will compare the lymph node involvement in the study patients with historical data from patients treated with radical hysterectomy. We will use a chi-square test to compare these 2 patient groups with respect to histology. We will use a two-sample t-test to compare patients with respect to tumor size and depth of invasion.

We will compare the treatment-associated morbidity (estimated blood loss, number of transfusions in the intraoperative and immediate postoperative period, surgery time, length of hospital stay and complications within 60 days of surgery) for the patients in this study with historical data from patients treated with radical hysterectomy. We will use a two-sample t-test to compare these 2 patient groups with respect to estimated blood loss, surgery time and length of hospital stay. We will use a chi-square test to compare these 2 patient groups with respect to number of transfusions and complications.

Quality of Life

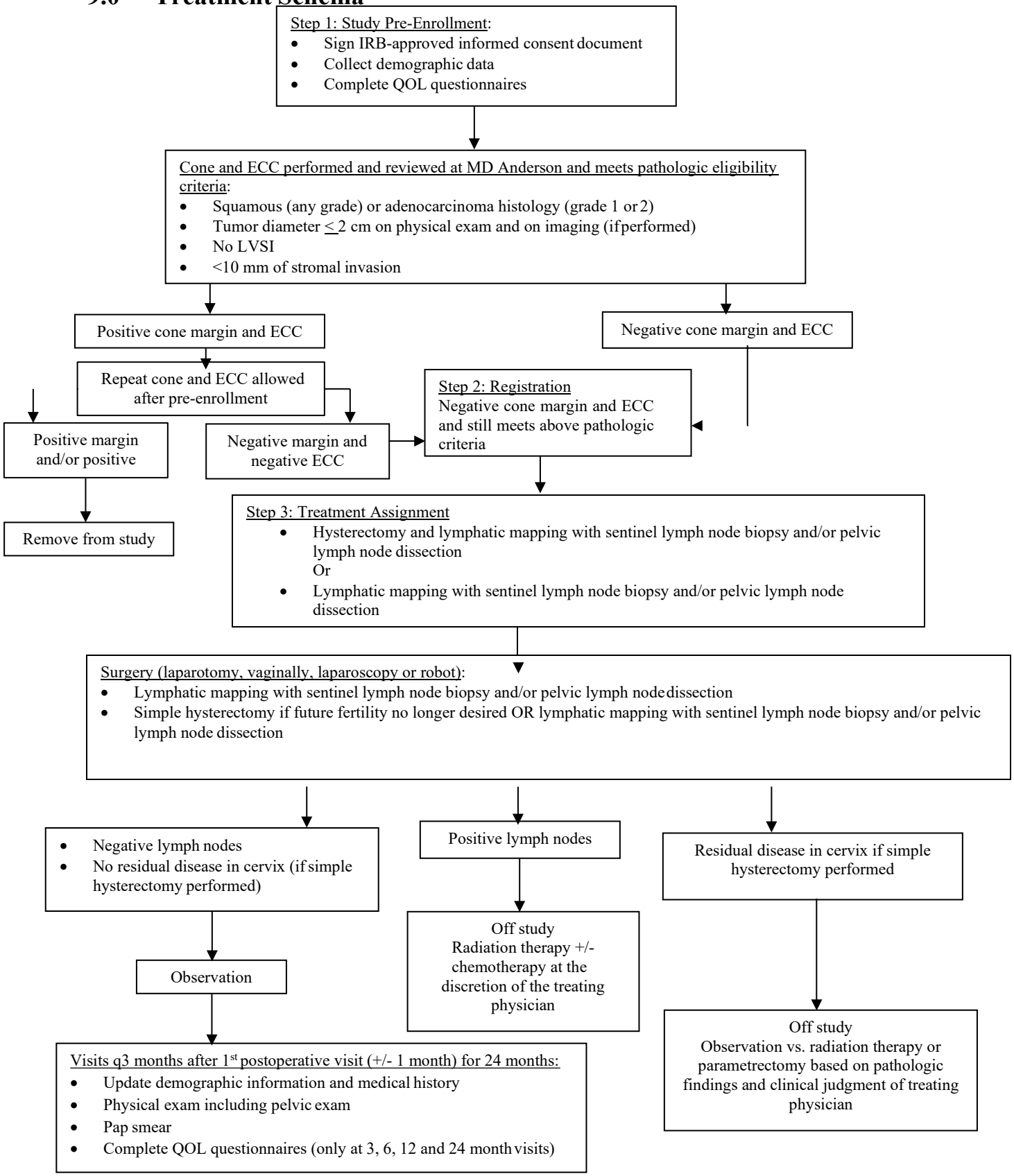
We will summarize each of the quality of life in these patients using descriptive statistics and boxplots at each evaluation time. We will summarize each of the quality of life instruments described in section 8 (SF12, FACT-CX, MDASI, FSFI, SWD) using tabulations, descriptive statistics, and boxplots at each evaluation time. We will estimate the mean score for each instrument at each evaluation time with a 95% confidence interval. We will similarly summarize the change from baseline for each instrument, and we will use mixed effects regression to model the change from baseline in the scores of each instrument over time.

As a sensitivity analysis we will conduct the analysis of change scores described above with the last available instrument score replacing missing instrument scores for those patients who drop out of the study.

Sentinel Lymph Nodes

We will classify each patient as having metastases present, micrometastases present, isolated tumor cells present, or no tumor present according to the histopathology of the sentinel lymph nodes. We will tabulate the number and percent of patients in each of these 4 categories. We will estimate the proportion of patients identified with metastases present, micrometastases present, isolated tumor cells, and tumor absent with 95% confidence intervals.

9.0 Treatment Schema



10.1 Patient Withdrawal

Patients will be advised that they may voluntarily withdraw from the study at anytime, for any reason and it will not affect their medical care. However, in such cases, appropriate effort will be made by the research team to determine the reason for voluntary withdrawal from the study and to document reason for withdrawal in the medical record, if known. The last known status of these patients will be reported with the study results and all attempts to locate patients lost to follow up will also be documented.

The following are circumstances for which a patient would be identified as not continuing her participation in the study:

- Positive Lymph Nodes after surgery
- Residual disease in cervix (if simple hysterectomy performed)
- Recurrence
- Study Completed / Terminated
- Death
- Voluntary Withdrawal
- Unable to Return
- Unwilling to Return
- Intercurrent Illness
- Move to another area
- Lost to follow-up
- Other

The investigators at all sites will notify the PI immediately if a participant is noted to have residual disease on hysterectomy specimen or if a participant develops a recurrence.

If a patient relocates to another geographic area, which requires a change of physician, reasonable attempts will be made to locate and request cooperation from that physician in order to complete follow-up. The required follow-up tests can be performed at another institution and sent to the participating site for review.

11.0 Data and Protocol Management:

Protocol and data management specifics are listed in the ConCerv Data Quality Management Plan (DQMP) and is attached as Appendix T.

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