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Project Title: An evaluation of factors impacting the survival of Manitoba women with ovarian cancer treated with neoadjuvant chemotherapy.

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Summary (250 words max single spaced):

Prior analyses by the Manitoba Ovarian Cancer Outcomes study group identified that late-stage ovarian cancer patients receiving neoadjuvant chemotherapy had poorer survival than patients receiving adjuvant chemotherapy. This is consistent with other observational studies identifying neoadjuvant survival being worse compared to adjuvant survival. Additional investigations into potential causes behind poorer neoadjuvant survival in Manitoba between the years 2004-2010 were conducted. In this thesis project, possible predictors of neoadjuvant treatment were examined. Furthermore, a series of clinical questions were generated to investigate the effects of treatment-related factors on neoadjuvant patient survival, such as residual tumour post-surgery, chemotherapy-induced toxicities, chemotherapy dose reduction, delay in chemotherapy treatment, and the number of cycles of chemotherapy. It was determined that predictors of neoadjuvant treatment included older age, unclassified epithelial tumour histotype, and a short time period (0-50 days) from suspicion to diagnosis of malignancy. Variables that did not substantially affect neoadjuvant patient survival included chemotherapy dose reduction, chemotherapy dose interruption, chemotherapy toxicities, and absence of residual tumour post surgery. However, neoadjuvant patients were more likely to require more than one line of chemotherapy, which might contribute to their increased risk of death. It appears that neoadjuvant patients likely present with greater disease severity compared to adjuvant patients. This may lead to clinical selection bias, whereby sicker patients are appropriately treated with neoadjuvant chemotherapy. This study demonstrated that poor survival in the neoadjuvant patient population is due to greater disease severity upon presentation, unfavourable tumour histotype, and later disease stage resulting in treatment with neoadjuvant chemotherapy.

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Introduction and Background

Over the past 40 years, survival rates for women with epithelial ovarian cancer have not drastically changed, with the 5 year survival rate remaining approximately 35%, despite the introduction of advanced surgical techniques and chemotherapy[1,2,3]. Epithelial ovarian cancers comprise the most frequent form of ovarian cancer and have the highest mortality rate. The majority of epithelial ovarian cancers consist of five distinct histological subtypes: high and low grade serous, clear cell, endometrioid and mucinous[4]. Ovarian cancers are typically treated by surgically debulking all disease in combination with chemotherapy[1]. Surgical cytoreduction followed by primary chemotherapy with a carboplatin-paclitaxel regimen is considered the gold standard for the management of ovarian cancer[5]. This is known as adjuvant therapy. Specifically, the National Comprehensive Cancer Network (NCCN) 2015 guidelines suggest that the primary treatment of epithelial ovarian cancer should consist of cytoreductive surgery for patients with disease stages II, III and IV. This is then followed by primary chemotherapy/adjuvant therapy using the following regimen: paclitaxel 175 mg/m^2 IV over 3 hours followed by carboplatin AUC (dose of carboplatin for desired exposure) 5–6 IV over 1 hour, which is repeated every 3 weeks for 6 cycles. By contrast, patients with bulky stage III/IV disease who are poor surgical candidates due to high-risk comorbidity conditions or disease factors should be considered for neoadjuvant chemotherapy treatment. Generally, when surgically unresectable disease is suspected in stage II-IV patients, neoadjuvant therapy entails 3 cycles of chemotherapy, followed by tumour resection surgery, and ending with postoperative chemotherapy for a total of 6-8 cycles of chemotherapy[6]. In the event of disease relapse after primary treatment, other therapeutic approaches should be considered depending on the individual patient's situation. These may include clinical trials, supportive care, combination platinum-based chemotherapy or other recurrence therapies, such as chemotherapy agents for platinum sensitive and platinum resistant disease, hormonal, targeted or radiation therapy[6].

A 2011 report by the International Cancer Benchmarking Partnership (ICBP) indicated that the 5-year relative survival of epithelial ovarian cancer patients in Manitoba was as low as 28% over the 2005-2007 time period, while in other Canadian health jurisdictions it ranged from 38.2% to 41.9%[7]. This prompted the members of the Manitoba Ovarian Cancer Outcomes (MOCO) study group to investigate the treatment of ovarian cancer in Manitoba, in order to determine what, if anything, was affecting the survival of Manitoba ovarian cancer patients. It was identified that late stage ovarian cancer patients receiving neoadjuvant chemotherapy (drug treatment prior to surgery) had poorer survival than patients receiving adjuvant therapy [hazard ratio (HR)=1.633, p=0.0037] (unpublished results). This is in agreement with two prior observational studies (retrospective chart reviews) indicating poorer survival for neoadjuvant patients[8,9]. However, Vergote *et al.* demonstrated in a randomized controlled trial that neoadjuvant chemotherapy followed by interval debulking is equivalent to primary debulking followed by chemotherapy for late stage disease (stages IIIc and IV)[10]. Because the initial MOCO study indicated that neoadjuvant chemotherapy showed increased risk of death, subsequent investigations were focused on determining potential causes of poorer neoadjuvant survival in comparison to adjuvant survival. For the purposes of this thesis project, possible predictors of neoadjuvant chemotherapy were examined. In addition, a series of clinical questions were generated for investigation, encompassing the effects of treatment related factors on patient survival, such as residual tumour post-surgery, chemotherapy toxicities, chemotherapy dose reduction, delay in chemotherapy treatment and when controlling for the number of cycles of chemotherapy. Within these general clinical questions, we also generated specific hypothesis, including: (1) that neoadjuvant patients experience an increased incidence of chemotherapy toxicities; (2) that toxicities experienced by neoadjuvant patients might be associated with poorer survival; and (3) that neoadjuvant patient survival may be worse than

adjuvant survival due to increased incidence of dose reduction and treatment interruption.

The aim of this project was to investigate these factors that may potentially affect the survival of neoadjuvant ovarian cancer patients in Manitoba.

Materials and Methods

Ethical Approval
Institutional research ethics board approval (HREB H2012:145) was obtained prior to initiating these studies.

Data sources
Invasive ovarian cancer cases diagnosed between January 1, 2004 and December 31, 2010 were identified through the Manitoba Cancer Registry using the following ICD-O-3 codes: C48.1-C48.8, C56, and C57 (peritoneum, ovary, fallopian tube, uterine ligaments, and other and unspecified female genital organs). In this document, the term 'diagnosis' refers to confirmation by diagnostic imaging, CA125 level, histology after surgery or cytology. The morphologies of sex cord and germ cell were excluded. Data extracted from the Registry included record type (chart or report only), histology codes, grade, age at diagnosis, AJCC staging, postal code at diagnosis, treatment information, and death date. Postal codes were used to identify residence at diagnosis and were also converted into income quintiles (stratified into urban and rural; Winnipeg and Brandon were considered urban). Data extracted from charts included physician encounters prior to and after diagnosis, diagnostic procedures, residual tumor, chemotherapy drugs administered and dates of administration, chemotherapy dose information, and dates of toxicities. Physician notes from encounters included symptom information, which identified when ovarian cancer could first be suspected. The type of physician at each encounter was also identified. Type I and II ovarian cancers were determined using grade and histology information[11].

Administrative data from Manitoba Health (Physician Claims and Hospital abstracts data) were also included. Physician notes from encounters included symptom information, which identified when ovarian cancer could first be suspected. The administrative data was used to confirm the physician encounter date for the physician encounter where ovarian cancer was suspected. The administrative data was also used to create a measure of co-morbidity using the Johns Hopkins ACG System (version 11.0).

Analyses
This patient cohort almost exclusively consisted of patients whose standard chemotherapy administration interval was 28 days. Exposure to a line of chemotherapy was considered as the time between the first cycle of that line and the last cycle plus 35 days. When referring to 'cycles' of neoadjuvant or adjuvant chemotherapy, this denoted the total number of cycles of chemotherapy within one line, which included all chemotherapy cycles occurring before and after surgery. Dose reduction was defined as a reduction of more than 20% in dose of a chemotherapy drug from the first cycle of its use. A 7-day treatment interruption was defined as more than 35 days between two cycles (or 77 days if surgery occurred between two cycles), and a 14-day treatment interruption was defined as more than 42 days between two cycles (or 84 days if surgery occurred between two cycles).

Analyses were performed on late-stage (III, IV and unknown) ovarian cancer cases that had chart information available. Descriptive statistics for the cohort were calculated. Logistic regression was used to predict whether patients received adjuvant or neo-adjuvant

chemotherapy. Cumulative incidence of toxicities, dose reduction, and treatment interruption were calculated using the Kaplan-Meier method. Neo-adjuvant patients were censored on date of surgery to avoid underestimating events in the cumulative incidence analyses, due to their non-continuous use of chemotherapy. Overall survival post-diagnosis was analyzed using time-varying Cox regression models. The predictors of gynecological oncologist encounter, treatment, toxicities, dose reduction, treatment interruption, and chemotherapy cycles were time-varying, to account for their changing status post-diagnosis. Other predictors included age at diagnosis, AJCC stage, histotype, time from suspicion to diagnosis, suspicion of ovarian cancer first occurring in the emergency room, income, residence at diagnosis (Winnipeg, outside of Winnipeg), year of diagnosis, and comorbidities. A competing risk model was used to predict second line chemotherapy with death as a competing risk. The start of follow up time was the end of first line chemotherapy. December 31, 2015 was considered the end-of-study date. Survival was measured as either a death recorded prior to, or on, the end-of-study date, or the individual was censored at the last physician encounter or end-of-study date. 4.86% of residual tumour data was missing and 38.6% of tumour size data was missing. Both missing residual tumour data and tumour size data were assumed to be missing at random. The mice package in R was used to produce 20 imputations for residual tumour and 50 imputations for tumor size. Imputations were verified by comparing the distributions of observed and imputed data conditional on propensity score. Residual tumor was analyzed by splitting the surgery categories into 0 cm, < 1 cm, and ≥ 1 cm.

Analyses were conducted using R version 3.2.3. The rms package was used for logistic and Cox regression models. The survival package was used for cumulative incidence estimates. The risk Regression package was used for competing risk analyses. Restricted cubic splines were used for continuous predictors that violated the assumption of linearity. Predicted values from restricted cubic splines adjusted for other covariates at their mean were plotted. The proportional hazard assumption was evaluated using Schoenfeld residuals. Other diagnostics were performed using residual and influence plots. Likelihood ratio testing was used for multivariable model building. Multivariable analyses were adjusted for other variables included in the model, and thus corrected for those variables.

Results

During the first year of study in the BSc Med program, I participated in the creation of the Manitoba Ovarian Cancer Patient database for the MOCO group (hereafter referred to as the MOCO database). 687 ovarian cancer patients were identified in the Registry of CancerCare Manitoba. 86 patients who were not seen in CancerCare Manitoba were excluded from the database because they lacked chart information. These patients not referred to CancerCare Manitoba were substantially older, had more aggressive disease, and half did not receive any treatment (data not shown). 391 patients had late stage ovarian cancer (III, IV and unknown) and 210 patients had early stage ovarian cancer (I and II). Unknown stage was included in the late stage cohort because they exhibited very similar survival to stage IV patients. The following analyses were conducted on the 391 late stage patients, whose descriptive statistics are included (Table 1). This was because late stage patients are frequently treated with both cytoreductive surgery and chemotherapy, whereas most early stage patients can be solely treated with surgery. As such, late stage patients have a very different survival prognosis as compared to early stage patients. I focused on entering and validating the data input for chemotherapy treatment, as well as surgical and chemotherapy-related toxicities.

While the data was being entered for the MOCO database, I also developed a number of clinical questions related to treatment modalities for ovarian cancer, specifically pertaining to the

neoadjuvant and adjuvant chemotherapy populations. The first of these questions addressed whether or not certain variables were associated with neoadjuvant chemotherapy treatment.

What factors, if any, predict treatment with neoadjuvant chemotherapy vs adjuvant chemotherapy? The first series of investigations conducted were focused on determining which factors, if any, were associated with receiving neoadjuvant over adjuvant chemotherapy. These were aimed to establish whether or not poorer outcomes in the neoadjuvant population were due to treatment selection bias, whereby more aggressive disease was treated with neoadjuvant chemotherapy. A multivariable analysis was conducted that adjusted for age, tumour histotype and time from suspicion to diagnosis (Table 2). It was determined that with respect to tumour histotype, clear-cell, endometrioid, mucinous and serous carcinoma are statistically significantly more likely to receive treatment with adjuvant chemotherapy than unclassified epithelial. 'Other' tumour histotypes (epithelial-stromal, and miscellaneous and non-specified) are also more likely to receive treatment with adjuvant chemotherapy; however, these findings were not statistically significant (p=0.0841; Table 2). By contrast, unclassified epithelial tumour histotype is more likely to receive neoadjuvant chemotherapy treatment than adjuvant therapy. In addition, it was determined that as patients aged, they were more likely to receive neoadjuvant chemotherapy (OR=0.71, 95% CI=0.55-0.92, p=0.0108; Table 2). Last, it was established that if the time from suspicion to diagnosis of malignancy takes 50 or more days, then the patient is more likely to receive adjuvant chemotherapy (Figure 1). However, if the time from suspicion to diagnosis of malignancy takes less than 50 days, then the patient is more likely to receive neoadjuvant chemotherapy (Figure 1).

Supplementary analyses were conducted on the late stage patient cohort in order to determine what patient characteristics were associated with a short time from suspicion to diagnosis of malignancy. It was determined that patients with a short time period from suspicion to diagnosis of malignancy were more likely to be diagnosed with unclassified epithelial tumour histotype, thus suggesting more severe disease (Figure 2). In addition, patients diagnosed with stage III disease were less likely to have unclassified epithelial tumour histotype ovarian cancer compared to patients diagnosed with stage IV disease (OR=0.455, 95% CI=0.28-0.73, p=0.0056). The same analyses also established that as patients aged, they were more likely to be diagnosed with stage IV/unknown disease (Figure 3). Furthermore, patients with unclassified epithelial tumour histotype were more likely to be diagnosed with stage IV/unknown disease compared to other tumour histotypes (OR=2.119, 95% CI=1.38-3.25, p=0.0006). Here, 'other' refers to all epithelial ovarian cancer histotypes besides unclassified epithelial.

Does residual tumour post surgery in the neoadjuvant population have an effect on their survival? The effects of residual tumour post surgery on overall patient survival were analyzed. The reference group chosen was adjuvant chemotherapy with less than 1 cm, but more than 0 cm of residual disease post surgery, in order to provide a less biased comparison for neoadjuvant therapy. Multivariable analysis was conducted, and of particular interest was the finding that neoadjuvant chemotherapy patients with no residual tumour remaining post surgery had non-significantly lower survival than adjuvant patients with less than 1 cm, but greater than 0 cm of residual disease (HR=1.983, 95% CI=1.00-3.95, p=0.0510).

Do neoadjuvant chemotherapy patients experience an increased incidence of chemotherapy related toxicities, chemotherapy dose reduction, or treatment interruption? The incidence of chemotherapy toxicities, dose reduction, and treatment interruption between the adjuvant and neoadjuvant populations was compared in order to determine whether or not neoadjuvant patients experienced an increased incidence of these events. The incidences of these events were reported in both populations at three months into

first line treatment (Table 3). With respect to chemotherapy toxicities, it was determined that neoadjuvant chemotherapy patients did not experience an increased incidence of chemotherapy toxicities. In fact, it was established that at three months of first line chemotherapy, 53.4% of adjuvant chemotherapy patients experienced pain toxicities, in comparison to 32.0% of neoadjuvant patients (Table 3). This corresponded to a statistically significant increased incidence of pain toxicities in the adjuvant population (p<0.001; Table 3). Furthermore, with respect to 'other' toxicities, adjuvant chemotherapy patients also experienced an increased incidence of these toxicities (p=0.001; Table 3) relative to neoadjuvant patients. The term 'other' refers to toxicities that could not be classified under the defined toxicity headings in Table 3. Despite the fact there was no evidence suggesting that neoadjuvant patients experience more chemotherapy toxicities than adjuvant patients, it is important to note that many patients from both populations do experience toxicities. Specifically, 96.6% of adjuvant chemotherapy patients and 93.7% of neoadjuvant patients reported a minimum of 1 chemotherapy toxicity after three months of first line treatment (Table 3).

The cumulative incidence of dose reduction and treatment interruption was examined in both the neoadjuvant and adjuvant chemotherapy populations. With respect to the cumulative incidence of dose reduction, it was determined that there was no statistically significant difference in the incidence of chemotherapy dose reduction of >20% between the neoadjuvant and adjuvant treatment groups (p=0.145; Table 3). In both the neoadjuvant and adjuvant populations, the incidence of dose reduction was less than 10% in each group, with 8.9% of adjuvant and 6.4% of neoadjuvant patients experiencing dose reductions of >20% (Table 3). However, there was a statistically significant difference (p=0.036; Table 3) in the cumulative incidence of treatment interruption (7 days) between the neoadjuvant and adjuvant populations. Specifically, the adjuvant treatment group experienced a higher incidence of treatment interruption (12.6% of patients), than the neoadjuvant treatment group (2.8% of patients) (Table 3). Nonetheless, the incidence of dose reduction was less than 15% in each group.

Do chemotherapy patients who experience certain chemotherapy toxicities, dose reduction or treatment interruption exhibit worse survival compared to their counterparts who do not? The investigations of these events included only first line chemotherapy. The first of the analyses conducted examined the effects of chemotherapy toxicities on patient survival, and it was found that within the neoadjuvant chemotherapy group, patients who experienced fatigue toxicities had lower survival than those who did not (HR=1.628, 95% CI=1.08-2.45, p=0.0200). Within the adjuvant chemotherapy group, patients who experienced skin toxicities had better survival than those who did not (HR=0.358, 95% CI=0.16-0.78, p=0.0101). However, it is highly likely that one of these findings is not a truly significant relationship, but rather randomly significant due to the high number of comparisons. Thus, it appears that regardless what kind of chemotherapy treatment patients receive, there is no evidence suggesting that toxicities during treatment affects overall survival, nor does it explain why neoadjuvant patients have worse survival.

It was also hypothesized that the toxicities experienced by patients undergoing neoadjuvant chemotherapy were so severe that their treatments were delayed or required dose reduction for patients to complete treatment, which may adversely affect their survival. Consequently, the effects of chemotherapy dose reduction and interruption on survival were analyzed. It was determined that within the adjuvant and neoadjuvant groups, chemotherapy dose reduction of at least 20% did not significantly affect patient survival (adjuvant: p=0.8079; neoadjuvant: p=0.8511). In addition, chemotherapy interruptions of 1 and 2 weeks also did not significantly affect patient survival in either treatment group (neoadjuvant 1 week delay: p=0.7956; neoadjuvant 2 week delay: p=0.5100; adjuvant 1 week delay: p=0.5395; adjuvant 2 week delay:

p=0.8049).

Is there a difference in neoadjuvant patient survival compared to adjuvant patient survival when controlling for the number of cycles chemotherapy? A comparison of the number of chemotherapy cycles between patients receiving 6 cycles of adjuvant therapy (the gold standard treatment) with different treatment groups was conducted by Cox regression analyses to predict overall survival (Table 4). As previously mentioned, when referring to 'cycles' of neoadjuvant or adjuvant chemotherapy, this denotes the total number of cycles of chemotherapy within one line, which includes all chemotherapy cycles occurring before and after surgery. In comparison to 6 cycles of first line adjuvant chemotherapy, 6 cycles of first line neoadjuvant therapy (a total of 6 cycles) demonstrated significantly decreased survival (HR=1.893, 95% CI=1.07-3.35, *p*=0.0286; Table 4). This analysis included all tumour histotypes. When adjusted for other variables including income, comorbidities, time from suspicion to diagnosis, and incidental finding of malignancy, neoadjuvant survival was still worse than adjuvant (HR=1.747, 95% CI=0.98-3.13, *p*=0.0606; Table 4), but not significantly different.

The standard number of cycles within first line neoadjuvant chemotherapy in Manitoba is 9 cycles, which includes 3 cycles before surgical debulking, followed by 6 cycles after surgery. The standard number of cycles within first line adjuvant chemotherapy in Manitoba is 6 cycles after surgery. In order to compare standard first line adjuvant treatment to standard first line neoadjuvant treatment, a sensitivity analysis was conducted. A multivariable analysis was generated, which adjusted for the following variables: income, comorbidities, time from suspicion to diagnosis of malignancy, incidental finding of malignancy, age at diagnosis and ER presentation at suspicion of malignancy. It was established that 9 cycles of first line neoadjuvant treatment demonstrated significantly worse survival than 6 cycles of adjuvant treatment (HR=2.179, 95% CI=1.43-3.32, *p*=0.0003).

To increase the homogeneity between neoadjuvant and adjuvant patients, some analysis was done exclusively for serous ovarian cancer histotype. Serous histotype is the most common tumour histotype of the cohort studied in this thesis. It was determined that serous carcinoma treated with 6 cycles of first line neoadjuvant chemotherapy exhibited statistically significant lower survival than that treated with 6 cycles of first line adjuvant chemotherapy (HR=3.746, 95% CI=1.67-8.39, *p*=0.0013; Table 4~~)~~. When incorporating time from suspicion to diagnosis into the analysis, neoadjuvant survival slightly improved (HR=3.585, 95% CI=1.58-8.15, *p*=0.0023; Table 4). Again, to compare standard neoadjuvant to adjuvant treatment for serous histotype, a sensitivity analysis comparing 6 cycles of adjuvant to 9 cycles of neoadjuvant chemotherapy was conducted through multivariable analysis that incorporated time from suspicion to diagnosis and incidental finding of malignancy. It was established that 9 cycles of neoadjuvant chemotherapy had significantly worse survival than 6 cycles of adjuvant chemotherapy within the serous histotype cohort (HR=2.564, 95% CI=1.51-4.35, *p*=0.0005).

The aforementioned analyses were focused on first line chemotherapy and in light of this information another series of investigations were conducted in order to determine whether or not neoadjuvant patients were more likely to receive more than one line of chemotherapy. A multivariable competing risk model incorporating treatment type and stage was generated. A competing risk model looks at predicting the first occurrence of two events, the event of interest (in this case, second line chemotherapy) or the competing risk (in this case, death). This model indicated that neoadjuvant patients are more likely to receive second line chemotherapy than adjuvant patients [sub-hazard ratio (SHR)=4.334, 95% CI=2.51-7.50, *p*<0.0001] and that the risk of this decreases over time [SHR (for time interaction)=0.446, 95% CI=0.29-0.68,

p=0.0002]. Furthermore, both adjuvant and neoadjuvant patients had the same risk of death, when taking death into account as a competing risk.

Discussion

This study was initiated because the MOCO study group had previously determined that ovarian cancer patients treated with neoadjuvant chemotherapy have worse survival outcomes than those treated with adjuvant chemotherapy after surgery. This prompted an investigation of factors that may be affecting neoadjuvant patient survival, and to identify variables that predict neoadjuvant treatment.

With respect to predictive factors of adjuvant vs neoadjuvant chemotherapy, if the time from suspicion to diagnosis of malignancy takes 50 or more days, then the patient is more likely to receive adjuvant chemotherapy. But, if the time from suspicion to diagnosis of malignancy is under 50 days, then the patient is more likely to receive neoadjuvant chemotherapy. This may be due to the fact that a shorter diagnostic time period is correlated with more clinically apparent, aggressive ovarian cancer that is more easily and quickly diagnosed. Another factor that predicted treatment with neoadjuvant chemotherapy was more advanced age. This is not surprising, considering that older patients tend to have more comorbidities, which makes them less ideal surgical candidates. It may be the case that in older patients with more comorbidities, the safest treatment option is to lessen disease severity with neoadjuvant chemotherapy, so they at some point in the future may become surgical candidates. In addition, it was determined that unclassified epithelial tumour histotype patients were less likely to receive adjuvant chemotherapy; it would be interesting to further analyze the unclassified epithelial histotype population alone, in order to see if there is a difference in survival between adjuvant and neoadjuvant patients. Currently, the number of patients in the MOCO database with unclassified epithelial histotype is too small to conduct any such analyses with adequate power. However, serous histotype only analyses were conducted, which determined that neoadjuvant survival was poorer.

Next, in order to test the hypothesis that a short time period from suspicion to diagnosis of malignancy is correlated with severe disease, a multivariable analysis was conducted. It was determined that unclassified epithelial histotype was correlated with a shorter time from suspicion to diagnosis of malignancy and with stage IV disease presentation. Previous unpublished analyses from the MOCO group demonstrated that serous and clear cell/endometrioid histotypes had significantly higher survival than unclassified epithelial (HR=0.698, 95% CI=0.52-0.93, *p*=0.0131; HR=0.423, 95% CI=0.22-0.83, *p*=0.0120, respectively). Thus, it appears that unclassified epithelial histotype is associated with more severe disease. Other centres have also observed such findings, whereby high-grade serous tumours, unspecified adenocarcinomas and undifferentiated carcinomas demonstrated a significantly higher incidence of advanced disease than low-grade serous, mucinous, endometrioid and clear cell tumours[12]. Consequently, the data indicates that a shorter time period from suspicion to diagnosis of malignancy is associated with unclassified epithelial histotype, and therefore more severe disease.

From a socio-economic and population health perspective, and based on the factors examined in this retrospective chart review, income and place of residence did not significantly affect the likelihood of receiving adjuvant vs neoadjuvant chemotherapy. These results are reassuring because as previously mentioned, neoadjuvant chemotherapy is associated with worse patient survival, and thus it is good to have analyses showing that there does not appear to be any inequities based upon the factors analyzed. There is the possibility that factors exist

that we did not examine which might affect the treatments provided to certain patient populations; however, there was no apparent difference between income groups and residence groups.

The effects of residual tumour post-surgery on overall patient survival were also examined. Because the neoadjuvant patients likely had disease treatment prior to surgery, the reference group chosen for comparison was adjuvant chemotherapy with less than 1 cm, but greater than 0 cm of residual tumour post-surgery. When looking at the effects of residual tumour post-surgery on overall patient survival, neoadjuvant chemotherapy with no residual tumour had worse survival than adjuvant chemotherapy with less than 1 cm, but greater than 0 cm of residual tumour post-surgery. The result was very near statistical significance (p=0.0510), which may be confirmed with a larger sample size. It is possible that the best scenario for patients entering neoadjuvant chemotherapy will still have a worse outcome than patients receiving adjuvant chemotherapy with some residual disease. On a general clinical note, this highlights the importance of properly identifying patients best suited for treatment with neoadjuvant chemotherapy. Specifically, it is imperative for clinicians to use their best clinical judgment when creating a treatment plan, such that only patients whose disease truly warrants neoadjuvant therapy receive it. In order to accomplish this, clinicians must have the necessary serologic, radiological, imaging, and surgical tools in order to predict the resectability of advanced ovarian cancer. A systematic review of modalities for primary cytoreductive surgery for advanced ovarian cancer indicated that the rates of optimal cytoreduction vary among surgeons, and more importantly, a universal clinical model that can predict which patients will undergo optimal cytoreduction currently does not exist[13]. This is problematic, as it suggests that there is the possibility for certain patients to have their cytoreductive potential underestimated, which may lead to them receiving clinically inappropriate neoadjuvant chemotherapy. The MOCO group does not suspect clinically inappropriate neoadjuvant therapy use in this patient cohort, but rather treatment selection bias as a cause of lower neoadjuvant survival. Nonetheless, further research is needed to evaluate the value and role of prognostic variables in predicting surgical outcome, such as the use of imaging to assess disease burden[13]. Ultimately, the goal is for patients to receive optimal surgical treatment that is most appropriate for their clinical disease state.

In addition, the incidence of chemotherapy toxicities in the neoadjuvant and adjuvant population was evaluated, as it was thought that perhaps neoadjuvant patients experienced more chemotherapy toxicities. The analyses demonstrated that for all the types of chemotherapy toxicities analyzed, neoadjuvant patients do not experience an increased incidence of toxicities, thus disproving this hypothesis. Needless to say, both adjuvant and neoadjuvant populations experience high numbers of chemotherapy toxicities within the first three months of their first line chemotherapy treatment. It is possible that neoadjuvant toxicities are underreported because these patients are generally more ill, and therefore may not attribute these toxicities to their chemotherapy regimen. It was also hypothesized that the toxicities experienced by neoadjuvant patients might be the cause of their poorer survival. The effects of 11 different chemotherapy toxicities on survival were analyzed in the neoadjuvant and adjuvant treatment groups (22 comparisons in total). With respect to the effects of various chemotherapy toxicities experienced during the first line of chemotherapy on patient survival within the different groups, 2 significant relationships were found: lower neoadjuvant survival associated with fatigue, and better adjuvant survival associated with skin toxicities. Because of the number of comparisons analyzed, it is expected that one of the relationships may be randomly significant. In order to determine which, if any, of these are truly significant, another independent population would be required. On a clinical note, it is important that both adjuvant and neoadjuvant ovarian cancer patients be made aware that they almost certainly will experience some kind of

chemotherapy toxicity during their treatment; however, despite the fact that such toxicities can be physically painful and emotionally distressing, they likely will not affect their overall survival.

It had also been hypothesized that neoadjuvant patient survival may be worse than adjuvant survival due to increased incidence of dose reduction and treatment interruption. However, it was shown that there was no statistically significant difference in the incidence of dose reduction between the neoadjuvant and adjuvant populations, but there was a significantly increased incidence of treatment interruption of 7 days in the adjuvant population compared to the neoadjuvant population. Thus, neoadjuvant patients do not experience an increased incidence of chemotherapy dose reduction, and in fact, adjuvant patients experience a higher incidence of treatment interruption. Furthermore, within these groups, patients who reported chemotherapy dose reduction or chemotherapy interruption did not exhibit lower survival when compared to members of their groups who did not report these events. Consequently, there is no evidence suggesting that either chemotherapy dose reduction or chemotherapy treatment interruption are related to lower survival in the neoadjuvant population.

The final set of analyses conducted focused on comparing survival between patients who received 6 cycles of first line neoadjuvant chemotherapy to those who received 6 cycles of first line adjuvant therapy (this included all patients that may have progressed onto further lines of chemotherapy). Multivariable analysis established that when controlling for income, comorbidities, time from suspicion to diagnosis and incidentally finding the cancer, survival in the neoadjuvant population was non significantly worse than adjuvant survival. This is likely an effect of the sample size and may have been limited by power. However, it is important to recognize that neoadjuvant patients might have worse survival than adjuvant patients when receiving the same number of cycles. Thus, a larger population would be required to confirm this observation.

Because tumour histotype is a factor in the choice of receiving adjuvant vs neoadjuvant therapy, a serous only tumour histotype analysis was conducted. The serous only histotype survival analysis was useful in confirming that 6 cycles of neoadjuvant has lower survival than 6 cycles of adjuvant chemotherapy. This was similar to what was observed in our ‘all tumour histotype’ survival analyses. Furthermore, because serous carcinoma is the most common ovarian cancer tumour histotype, a comparison of standard neoadjuvant to standard adjuvant chemotherapy was conducted for serous tumour histotype alone. Within the serous histotype patients, it was determined that standard neoadjuvant patients had worse survival than standard adjuvant patients. It was important to run this analysis because these are treatments that will be administered to much of the ovarian cancer population.

Additional analyses were run and it was determined that neoadjuvant patients are more likely to receive more than one line of chemotherapy compared to adjuvant patients; however, this risk decreases over time. When taking into account death as a competing risk, both the neoadjuvant and adjuvant populations had the same risk of death. Thus, it is unlikely that more adjuvant patients are dying and consequently not reaching second line chemotherapy. Overall, the data indicates that part of the reason neoadjuvant patients have an additional risk of death compared to adjuvant patients is because they have a higher risk of requiring more than one line of chemotherapy, which indicates the possibility of a neoadjuvant population with poorer health. Alternatively, it is also possible that neoadjuvant patients, who are more likely to have unclassified epithelial histotype, have a greater incidence of platinum-resistant disease, which is defined as recurrence of disease less than 6 months after completion of chemotherapy treatment[6]. Potentially, unclassified epithelial histotype might have certain molecular characteristics that make it more resistant to platinum based chemotherapy agents. However, a

literature search did not generate any results relating platinum-resistant epithelial ovarian cancer to tumour histotype. It is also possible that there are other unidentified factors, which may or may not be modifiable, contributing to the worsened neoadjuvant survival, in addition to the fact that neoadjuvant patients have greater disease severity than adjuvant patients and as a result require more than one line of chemotherapy.

As previously mentioned, other observational studies have indicated poorer neoadjuvant survival[8,9], consistent with what has been determined in this study, while randomized controlled trials suggest neoadjuvant and adjuvant chemotherapy are not significantly different in terms of overall survival[10,14]. A literature search of observational studies from centres reporting worse neoadjuvant survival did not generate any data regarding the effects of chemotherapy toxicities, dose reduction or treatment interruption on neoadjuvant and adjuvant patient survival, nor did they analyze any predictors of neoadjuvant treatment[8,9,15]. Thus, to the MOCO group's knowledge it appears that this retrospective chart review is the first to have analyzed specific predictors of neoadjuvant chemotherapy treatment of ovarian cancer, as well as the effects of chemotherapy toxicities, dose reduction and treatment interruption on adjuvant and neoadjuvant patient survival. Another literature search of clinical trials comparing neoadjuvant and adjuvant chemotherapy on ovarian cancer patient survival identified numerous studies indicating that neoadjuvant survival is not statistically significantly worse than adjuvant survival for late stage (minimum stage III) ovarian cancer[10,14,16,17]. A systematic review consisting of randomized controlled trials of women with advanced epithelial ovarian cancer (stages III/IV) who were randomly allocated to treatment groups comparing platinum-based chemotherapy before cytoredutive surgery to platinum-based chemotherapy following cytoreductive surgery did not find neoadjuvant chemotherapy prior to debulking surgery superior to adjuvant chemotherapy. It was suggested that in bulky disease, the use of neoadjuvant chemotherapy in women with stage IIIc/IV is a reasonable alternative to primary debulking surgery. However, in women with stage IIIa and IIIb ovarian cancer, primary debulking surgery is standard. Furthermore, when selecting candidates who will benefit from neoadjuvant chemotherapy, treatment should be specifically tailored to the individual patient and should take into account resectability, age, histology, stage and performance status[18].

The reason behind the differences seen between observational studies and randomized controlled trials are not fully known. One possible reason may be that retrospective chart reviews generally encompass a time frame of many years, during which practice guidelines may have changed. It is possible that for a certain time period treatment guidelines purported neoadjuvant therapy as the preferred modality, and consequently was administered to patients who may have benefitted more from adjuvant therapy. However, prior studies from the MOCO group tracked the incidence of adjuvant and neoadjuvant therapy use. From 1992-2011 there was increased use of neoadjuvant chemotherapy in ovarian cancer treatment, while adjuvant chemotherapy saw a decrease in usage. Thus, potential guideline changes did impact the incidence of neoadjuvant and adjuvant therapy use in Manitoba. Although neoadjuvant treatment use increased over time, there was no correlation with worse survival in the Manitoba epithelial ovarian cancer population. Consequently, it is unlikely that treatment guideline changes are the cause behind poor neoadjuvant patient survival. It is also a possibility that certain variables were not collected and therefore the dataset used for this chart review does not contain the relevant information, such as specific comorbidities. In this study a comorbidity index was used as a control variable, however in the future, individual comorbidities could be used to identify treatment with neoadjuvant over adjuvant therapy. It is suspected that such variables would be related to clinical selection bias, likely relating to the greater disease severity characterizing the neoadjuvant population. Physician treatment preference may also play a role, depending on how the physician personally feels about neoadjuvant treatment. This would likely

just affect the incidence of neoadjuvant and adjuvant therapy use and probably not affect patient survival. However, the main findings outlined in this thesis are largely associated with the potential for clinical selection bias in neoadjuvant patients, which becomes evident in retrospective observational studies, and has manifested itself as apparent worse neoadjuvant survival. This is in contrast to randomized clinical trials, which do not indicate worse neoadjuvant survival, whereby patients are randomly selected to receive neoadjuvant or adjuvant therapy and thus eliminating the potential for clinical selection bias.

Overall, the findings highlighted in this thesis suggest that the following are not substantial factors causing worse neoadjuvant patient survival: chemotherapy dose reduction, chemotherapy dose interruption, chemotherapy toxicities and the absence of residual tumour post surgery. Some important results that may help explain the worse survival in the neoadjuvant population include the factors that predict neoadjuvant treatment over adjuvant, those being older age, unclassified epithelial tumour histotype, and a short time period from suspicion to diagnosis of malignancy. Specifically, if the time from suspicion to diagnosis of malignancy takes 0-50 days, then the patient is less likely to receive adjuvant chemotherapy. This means that patients whose illness is more clinically apparent and possibly more severe, potentially making them worse surgical candidates, are more likely to be treated with neoadjuvant chemotherapy than patients whose diagnosis takes more than 50 days, and may have less severe disease. This was confirmed by establishing that a short time period from suspicion to diagnosis of malignancy was associated with unclassified epithelial histotype and that unclassified epithelial histotype was associated stage IV disease on presentation. Because this study determined that numerous chemotherapy treatment and surgery related factors were not likely causes behind poorer neoadjuvant survival, it is clear that one possible reason neoadjuvant patients have poorer survival is that patients with a short time period from suspicion to diagnosis of malignancy, presenting with potentially more severe disease, are more likely to receive neoadjuvant chemotherapy.

Thus, it is clear that this retrospective population is heterogeneous, as evidenced by the differences detected between the adjuvant and neoadjuvant groups. Specifically, the variables that predicted neoadjuvant over adjuvant treatment, including older age, unclassified tumour histotype and short time from suspicion to diagnosis of malignancy, indicate that neoadjuvant patients are the not same as adjuvant patients. In fact, these variables suggest that patients who receive neoadjuvant treatment tend to have greater disease severity than adjuvant patients, which is indicative of some clinical selection bias with respect to neoadjuvant therapy. Currently, it cannot definitively be said that clinical selection bias is the sole reason behind the worse survival in neoadjuvant patients. However, the data suggests that what is likely occurring in this patient cohort is that neoadjuvant patients with worse disease are receiving the best care possible, that being neoadjuvant treatment, and are dying because of their severe disease.

In summary, because neoadjuvant patients appear to have more severe disease than their adjuvant counterparts, logically, more neoadjuvant patients will die compared to adjuvant patients. Furthermore, to the knowledge of the MOCO group, this thesis is the first retrospective observational study that investigated specific predictors of neoadjuvant chemotherapy treatment, as well as the effects of chemotherapy toxicities, dose reduction and treatment interruption on neoadjuvant patient survival. Finally, it is very encouraging for the MOCO group and for Manitoban women in general that the data from this retrospective chart review supports the fact that there appears to be clinically appropriate use of neoadjuvant therapy for the treatment of epithelial ovarian cancer in Manitoba.

Table 1: Baseline characteristics and clinical features of the late stage (stages III, IV, unknown) patient cohort (n=391)

Variable		Count	%
Age	Mean (SD)	66 (14.01)	
Stage	III	200	51.15
	IV	120	30.69
	Unknown	71	18.16
Morphology	Serous Carcinoma	159	40.66
	Unclassified Epithelial	145	37.08
	Clear cell	13	3.32
	Endometrioid	5	1.28
	Mucinous	9	2.30
	Other	60	15.35
Residence	Winnipeg	219	56.01
	Outside Winnipeg	172	43.99
Treatment	No treatment	50	12.79
	Chemotherapy only	97	24.81
	Chemotherapy followed by surgery	108	27.62
	Surgery followed by chemotherapy	119	30.43
	Surgery only	17	4.35
Residual tumour	No surgery	147	37.60
	≥1 cm	105	26.85
	<1 cm	65	16.62
	0 cm	55	14.07
	Missing	19	4.86
Period of diagnosis	2008 and later	166	42.46
	2007 and earlier	225	57.54
Income	R1-R3	96	24.55
	R4-R5	61	15.60
	U1-U3	154	39.39
	U4-U5	73	18.67
	Missing	7	1.79
Comorbidities (resource utilization band)	Low	17	4.35
	Moderate	231	59.08
	High	100	25.58
	Very high	43	11.00
Deaths		340	
Follow-up (years)	Median (Q1-Q3)	1.54 (0.56-4.35)	

* Other = epithelial-stromal, and miscellaneous and unspecified

* R = rural, U = urban, 1 = lowest income, 5 = highest income

* Q1 = 25^{th} percentile, Q2 = 50^{th} percentile, Q3 = 75^{th} percentile

Table 2: Logistic regression predicting adjuvant chemotherapy (reference group = neo-adjuvant chemotherapy; stages III, IV, unknown)

Variable		Univariable			Multivariable		
		OR	95% CI	*p*	OR	95% CI	*p*
Age at diagnosis	(in 10 year increments)	0.825	0.66-1.04	0.0974	0.710	0.55-0.92	0.0108
Stage	III	1.548	0.82-2.91	0.1750			
	IV	1.167	0.47-2.88	0.7384			
	Unknown	1					
Histotypes	Clear-cell /endometrioid/mucinous	6.564	2.10-20.49	0.0012	6.964	2.02-24.03	0.0021
	Other	3.446	1.22-9.71	0.0193	2.684	0.88-8.23	0.0841
	Serous carcinoma	2.995	1.44-6.21	0.0032	2.720	1.25-5.92	0.0116
	Unclassified epithelial	1			1		
Type	II	0.377	0.15-0.94	0.0371			
	I	1					
Time from suspicion to diagnosis	‘	1.033	1.02-1.05	<0.0001	1.039	1.02-1.06	<0.0001
	‘’	0.958	0.94-0.98		0.951	0.93-0.97	
ER at first suspicion	Yes	0.689	0.38-1.25	0.2200			
	No	1					
Income	U4-U5	0.782	0.38-1.59	0.4972			
	U1-U3	1					
	R4-R5	1.024	0.45-2.35	0.9549			
	R1-R3	1					
Residence	Winnipeg	0.849	0.50-1.44	0.5443			
	Outside Winnipeg	1					
Period	2008-onward	0.568	0.33-0.97	0.0374			
	Prior to 2008	1					
Comorbidities (resource utilization band)	High/very high	1.136	0.63-2.05	0.6718			
	Moderate and lower	1					
Gynecologic oncologist encounter	After diagnosis	0.469	0.27-0.81	0.0065			
	Before diagnosis	1					
Tumour size	‘	0.982	0.96-1.00	0.1065			
	‘’	1.030	1.00-1.06				

* The control variables including stage, type, ER at first suspicion, income, residence, period, comorbidities, gynecologic oncology encounter and tumour size were not included in the final multivariable analysis because they did not significantly improve the model
* Time from suspicion to diagnosis: parameters from the restricted cubic splines
* Tumour size: parameters from the restricted cubic splines
* Other = epithelial-stromal, and miscellaneous and unspecified
* Type: determined using grade and histology information

Table 3: Cumulative incidence of chemotherapy toxicities, chemotherapy dose reduction and chemotherapy treatment interruption at 3 months of first line chemotherapy

Variable		Adjuvant	Neoadjuvant	*p*-value*
Toxicities	Overall	0.966	0.937	0.491
	Abdominal	0.130	0.084	0.185
	Blood	0.113	0.047	0.089
	Constipation	0.359	0.338	0.716
	Diarrhea	0.114	0.056	0.138
	Chest	0.078	0.065	0.544
	Fatigue	0.333	0.217	0.101
	Nausea/vomiting	0.557	0.589	0.315
	Neuropathy	0.411	0.383	0.385
	Pain	0.534	0.320	<0.001
	Skin	0.122	0.113	0.806
	Other	0.349	0.160	0.001
Dose reduction (>20%)		0.089	0.064	0.145
Treatment Interruption (7 days)		0.126	0.028	0.036

* log-rank test

Table 4: Overall survival of first line cycles of chemotherapy for all tumour histotypes and for serous carcinoma only (stages III, IV, unknown)

All tumour histotypes							
Treatment	**Cycles**	**Univariable**			**Multivariable**		
		HR	95% CI	*p*	HR	95% CI	*p*
No treatment		7.666	4.84-12.15	<0.0001	11.785	6.97-19.93	<0.0001
Chemotherapy only	1-5	4.546	2.70-7.64	<0.0001	4.916	2.90-8.34	<0.0001
Chemotherapy only	6	2.466	1.48-4.10	0.0005	2.507	1.48-4.25	0.0007
Chemotherapy only	7+	3.317	1.97-5.58	<0.0001	3.069	1.81-5.21	<0.0001
Neoadjuvant chemotherapy	1-5	2.231	0.86-5.80	0.0997	2.416	0.93-6.29	0.0707
Neoadjuvant chemotherapy	6	1.893	1.07-3.35	0.0286	1.747	0.98-3.13	0.0606
Neoadjuvant chemotherapy	7+	2.117	1.46-3.07	0.0001	1.826	1.24-2.68	0.0022
Surgery only		1.837	1.04-3.25	0.0367	2.101	1.19-3.72	0.0110
Adjuvant chemotherapy	1-5	1.568	0.83-2.96	0.1668	1.756	0.93-3.32	0.0836
Adjuvant chemotherapy	6	1			1		
Adjuvant chemotherapy	7+	1.523	0.93-2.51	0.0980	1.287	0.77-2.15	0.3340
Serous carcinoma only							
Treatment	**Cycles**	**Univariable**			**Multivariable**		
		HR	95% CI	*p*	HR	95% CI	*p*
No treatment		2.795	0.36-21.37	0.3313	1.838	0.24-14.20	0.5597
Chemotherapy only	1-5	3.397	0.90-12.87	0.0720	2.772	0.75-10.19	0.1248
Chemotherapy only	6	2.522	0.97-6.56	0.0578	2.162	0.83-5.66	0.1163
Chemotherapy only	7+	2.630	1.09-6.34	0.0312	3.177	1.30-7.75	0.0110
Neoadjuvant chemotherapy	1-5	7.414	1.78-30.85	0.0059	6.683	1.57-28.45	0.0102
Neoadjuvant chemotherapy	6	3.746	1.67-8.39	0.0013	3.585	1.58-8.15	0.0023
Neoadjuvant chemotherapy	7+	3.139	1.94-5.08	<0.0001	2.555	1.55-4.22	0.0002
Surgery only		3.024	1.36-6.74	0.0068	3.383	1.50-7.62	0.0033
Adjuvant chemotherapy	1-5	2.628	1.09-6.36	0.0322	2.798	1.14-6.88	0.0250
Adjuvant chemotherapy	6	1			1		
Adjuvant chemotherapy	7+	1.659	0.95-2.91	0.0768	1.599	0.91-2.82	0.1052

* All tumour histotypes: multivariable analysis is controlled for income, comorbidities, time from suspicion to diagnosis and incidental finding of malignancy

* Serous carcinoma only: multivariable analysis is controlled for time from suspicion to diagnosis

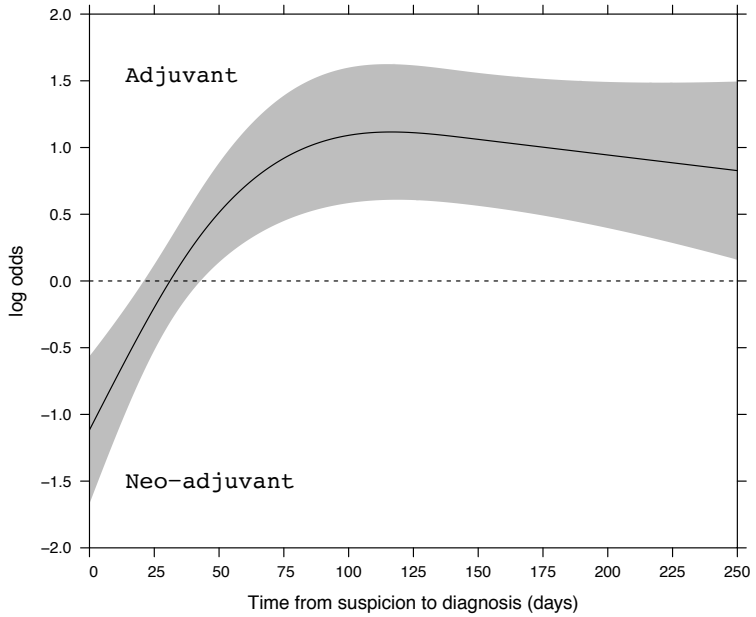

Figure 1: Plot showing the likelihood of receiving adjuvant or neoadjuvant chemotherapy as it relates to time from suspicion to diagnosis of malignancy. The predicted values were adjusted for age and tumour histotype.

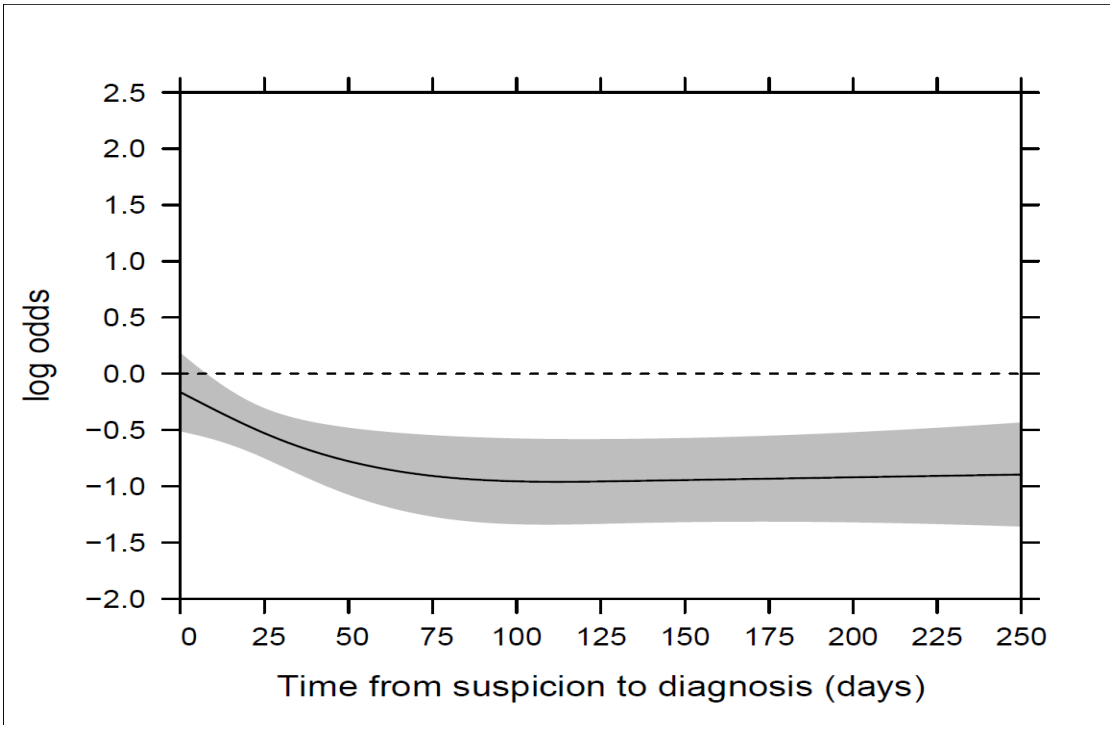

Figure 2: Plot showing the likelihood of diagnosis of unclassified epithelial tumour histotype as it relates to time from suspicion to diagnosis. The predicted values were adjusted for disease stage.

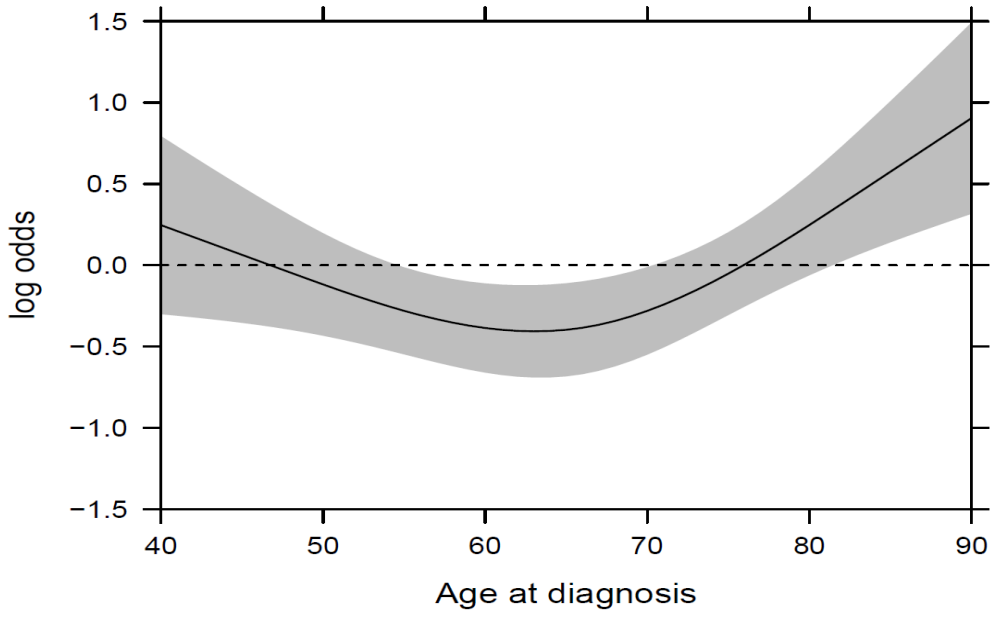

Figure 3: Plot showing the likelihood of diagnosis of stage IV/unknown disease as it relates to age at diagnosis of malignancy. The predicted values adjusted for tumour histotype.

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