Effect of statin and aspirin use on toxicity and pathological complete response rate of neo-adjuvant chemo-radiation for rectal cancer
Effect of statin and aspirin use on toxicity and pathological complete
response rate of neo-adjuvant chemo-radiation for rectal cancer

Running title: Statin use in rectal cancer chemo-radiation

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Abstract

Aims: To retrospectively evaluate the potential impact of statin and aspirin use on acute toxicity and pathological complete response rate (pCR) in rectal cancer patients receiving neo-adjuvant long course radiation (LCRT) with concurrent chemotherapy.

Methods: A retrospective review was performed of all patients undergoing neo-adjuvant LCRT for rectal adenocarcinoma at the Regional Cancer Treatment Service between 1 September 2007 and 1 June 2011. Data obtained include demographic details; date and radiological TNM stage at diagnosis; medication taken at time of radiation therapy; toxicity during LCRT; and surgical histology to determine if a pCR was obtained following LCRT.

Results: Neo-adjuvant LCRT was administered to 142 patients for rectal cancer during this period; concurrent chemotherapy was omitted in 13 due to significant co-morbidities. TNM stage was 2 or 3 radiologically at diagnosis in 127 (89.4%) of patients. At the time of LCRT 23% were taking a statin and 25% were taking aspirin. Of 135 assessable patients, 34 (13%) achieved a pCR at surgery. On logistic regression pCR was not significantly associated with the use of chemotherapy, statins, aspirin, other NSAIDs, T-stage or N-stage. There was no significant correlation between statin or aspirin use with bladder or rectal toxicity. Actuarial time to maximum rectal toxicity was not different in statin users or non-users.
Conclusion: In contrast to other larger retrospective series, this study did not find improvements in toxicity or pCR rate through statin or aspirin use in rectal cancer patients undergoing LCRT. Their potential benefits in this setting would be best studied prospectively in a large randomised trial.

Keywords: chemo-radiation; rectal cancer; statin; aspirin
Introduction

While advances in the management of rectal cancer have reduced local relapse to less than 10% in most patients, those with TNM tumour stage T4 and higher-risk T3 node-positive tumours still have higher local relapse rates. In addition, distant relapse still occurs in 25-30%, with a similar proportion dying within 5 years (1). Statins are a class of drugs that inhibit the mevalonate pathway through inhibition of the rate-controlling enzyme, 3-hydroxy-3-methyl-glutaryl-CoA reductase. While they are commonly used to lower cholesterol, it appears that modulation of this signalling pathway may also improve cancer outcomes (2). A Danish population study of 295,925 cancer cases diagnosed between 1995 and 2007 revealed that the use of statins significantly improved overall survival (OS) in the whole cohort, and specifically within the colorectal cancer (CRC) group (HR 0.79, 95% CI 0.74–0.85) (3). Similarly a registry study of 17,115 CRC patients from Taiwan reported that multivariate cancer-specific mortality was significantly reduced in statin users (HR 0.77, p < 0.001)(4). More recently a population-based cohort study of 7657 patients with CRC in the United Kingdom showed that statin use improved CSS (fully adjusted HR, 0.71; 95% CI, 0.61 to 0.84) and all-cause mortality (fully adjusted HR, 0.75; 95% CI, 0.66 to 0.84) (5).

Preclinical studies have elaborated mechanisms that may contribute to improved cancer outcomes with statins, many of which relate to effects on cell signalling that are independent of cholesterol metabolism (6). These include mechanisms that can improve treatment efficacy as well as inhibition of radiation (RT)-induced gut and
skin toxicities (7-14). Thus there appears to be a specific and beneficial interaction of statins with RT.

This correlates with retrospective clinical studies in which patients taking statins during chemo-RT for rectal cancer at Memorial Sloan-Kettering Cancer Center (n=349), Cleveland Clinic (n=407) or 5 Canadian hospitals (n=891) had significantly higher rates of pathological complete response (pCR) on multivariate analysis, ranging from 1.7 to 4.5 (15-17). In contrast no benefit from statin use was seen in a large trial (n=842) of adjuvant chemotherapy for colon cancer (18). Furthermore, a prospective observational study of 308 patients at the Royal Marsden Hospital, London, treated with radical pelvic RT reported that those taking statins had significantly reduced RT-induced bowel toxicity, both during treatment (p=0.04) and one year later (19).

Aspirin’s inhibition of platelet activation, platelet-tumour cell adhesion, angiogenesis and metastasis, as well as therapeutic interactions with chemotherapy and RT, have demonstrated survival benefits in CRC patients in some series (20-23) though not all (24). Interestingly, even though statins and aspirin may both improve outcomes through inhibiting inflammation, the benefit of statins is still seen when controlling for aspirin use (4).

We retrospectively explored the potential benefit of using statin and/or aspirin or other non-steroidal anti-inflammatory drugs (NSAIDs) in the clinical setting of rectal
cancer patients receiving a standard course of neo-adjuvant long-course radiation therapy (LCRT) with concurrent chemotherapy (chemo-RT). We report the association of the use of statins and NSAIDS in this patient group with the acute toxicity of their treatment and the pCR rate found at the time of surgery.

Methods

The electronic oncology notes were reviewed of all patients diagnosed with rectal cancer between 1st September 2007 and 1st June 2011 who underwent LCRT for rectal cancer at the Regional Cancer Treatment Service (RCTS), Palmerston North Hospital. Hospital paper notes were reviewed when the electronic record was incomplete. Data was obtained regarding patient’s demographic details; date and radiological TNM stage at diagnosis; medication taken at time of radiation therapy; toxicity during LCRT; and surgical histology to determine if a pCR was obtained following LCRT. While the names of any statins and NSAIDs used during treatment was recorded, due to the retrospective nature of this study the details on dosage, duration of use and indication for these drugs were not available to the investigators.

The electronic oncology notes prospectively recorded weekly toxicity evaluation (graded according to the Common Toxicity Criteria Version 3.0 (25)) during LCRT, hospital admissions or if treatment was stopped early due to toxicity. For the purposes of this study, the most severe bowel and bladder toxicity that developed during radiation treatment was documented.
LCRT was offered to all patients who were node-positive on MRI staging of their rectal cancer and/or had a threatened circumferential resection margin. LCRT was also considered if the surgeon felt resection would be difficult due to tumour bulk. LCRT was delivered as a 3D conformal technique using 15MV photons in 2 phases: phase 1 delivered a dose of 45 Gray (Gy) in 25 fractions over 5 weeks to the pelvis; phase 2 delivered a boost dose to the rectal tumour of 5.4 Gy in 3 fractions over 3 days. Concurrent chemotherapy (capecitabine 825 mg/m$^2$ twice daily or continuous IV infusion of 5-fluorouracil [5FU] 225 mg/m$^2$/day) was administered with LCRT as standard practice, unless medical fitness or co-morbidities precluded this (in some of these patients bolus 5FU was given at a dose of 500mg/m$^2$ on days 1 – 5 of week 1 and week 5 of radiation treatment). On completion of LCRT, definitive surgery (either total mesorectal excision or abdomino-perineal resection) took place 6 – 8 weeks later.

Statistical analysis of this dataset was undertaken using Spearman correlation between patient, tumour and treatment parameters and toxicity and pCR rate. Logistic regression was used to evaluate the association of statin, aspirin, other NSAIDs or chemotherapy use on pCR rate, rectal toxicity grade and time to maximum toxicity. Actuarial analysis of time to maximum rectal toxicity was analysed using the Kaplan-Meier method and log-rank statistic. Under the significance level of 0.05 and two-sided testing, p<0.05 is assumed to be statistically significant.

Results
Between 1\textsuperscript{st} September 2007 and 1\textsuperscript{st} June 2011, 142 patients were diagnosed with rectal cancer and received LCRT at RCTS. Patient demographics of this group are outlined in Table 1. Concurrent chemotherapy was given to 129 (91\%) patients (106, 16 and 7 with capecitabine, infusional and bolus 5FU respectively); 13 did not receive concurrent chemotherapy due to co-morbidities. Eleven patients (7.7\%) were known to have metastatic disease at the time of diagnosis, of which nine had concurrent chemo-RT. Thirty three (23\%) patients were taking a statin at the time of their LCRT (see Table 2), 28 using simvastatin and 5 using atorvastatin. Thirty-five (25\%) patients were taking aspirin, 7 (5\%) were taking other NSAIDs and 19 (13\%) patients were taking both a statin and aspirin.

After completion of LCRT, only 140 patients went on to surgery as 2 patients died prior to their surgical procedure. In a further 5 patients the histological report was not obtainable and in all these cases their surgery was performed at a peripheral hospital. Of the 135 assessable patients, 17 (13\%) achieved a pCR at the time of surgery. On logistic regression pCR was not significantly associated with the use of chemotherapy, statins, aspirin, other NSAIDs, T-stage or N-stage.

Prospectively-recorded data was available on bladder and rectal toxicity during RT in 141 patients. The most severe toxicity recorded was grade 3 for both bladder and rectum, in 1 and 19 (13.5\%) patients respectively. Grade 1 and 2 bladder toxicities were recorded in 62 (44\%) and 21 (14.9\%) patients respectively, and grade 1 and 2 rectal toxicities in 40 (28.4\%) and 72 (51.1\%) patients respectively (Table 2). Of the 129 patients who received concurrent chemotherapy, this treatment had to be
discontinued during RT in 47 (36%) due to toxicity and 15 patients (12%) were
hospitalised for toxicity during treatment. RT was stopped earlier than scheduled in
7 patients (5%) due to toxicity.

Univariate analysis was performed of correlations between the following
parameters: age (as a continuous variable); tumour grade; T-, N- and M-stage; use of
chemotherapy, statins, aspirin or other NSAIDs; time to, and maximum grade of
bladder or rectal toxicity; early cessation of chemotherapy or RT; and pCR. A
significant correlation was seen between age and statin (r=0.19) or aspirin (r=0.29)
use and an inverse correlation with chemotherapy use (r=-0.38) and N-stage (r=-
0.24; all p< 0.05). Patients taking statins also had significantly lower N-stage (r=-
0.23) and those who received chemotherapy had significantly lower T-stage (r=-
0.21). Grade of rectal toxicity was significantly associated with early cessation of
chemotherapy (r=0.42).

There was no significant correlation between statin or aspirin use with bladder or
rectal toxicity (Figure 1). Multinominal logistic regression was used to evaluate
associations with grade of rectal toxicity: no interaction was seen with statin, aspirin
or NSAID use, whereas chemotherapy was strongly associated with grade 3 toxicity
(coefficient 15.3, p<0.00001). Actuarial time to maximum rectal toxicity was not
different in statin users or non-users, when analysing either all patients (log-rank
p=0.78) or those who had at least grade 2 toxicity (log-rank p= 0.44, Figure 2).

Discussion
We undertook this retrospective study to specifically evaluate the effect of statins and aspirin on acute treatment toxicity and pCR rates in rectal cancer patients being treated with neo-adjuvant LCRT, with or without concurrent chemotherapy. This was inspired by reports from other groups, in larger datasets, that statins appeared to reduce the acute toxicity of treatment and increased the pCR rate (15-17;19), while statins and aspirin were each associated with improved overall colorectal cancer outcomes (3;22). In this cohort of 142 patients, about a quarter of whom took either agent (13% took both), we were unable to demonstrate a significant benefit in either acute treatment-related toxicity or pCR rate from statin or aspirin use. In contrast, adding chemotherapy to LCRT substantially increased the severity of toxicity, consistent with other reports (26), though in this series we did not see the improved histological outcome reported by others (27).

While large population studies suggest that statins improve relapse and cancer-specific survival in various cancers including rectal cancer (3;4;28-30), there appear to be beneficial interactions with RT that are not apparent with other treatments. Retrospective clinical studies report that patients taking statins during RT or chemo-RT for rectal, bladder or prostate cancer had significantly higher rates of pathological complete response (pCR), local control and PSA progression-free survival, respectively (15-17;31-33). In contrast no benefit from statin use was seen in a meta-analysis of surgical treatment of prostate cancer (31;33) nor adjuvant chemotherapy for colon cancer (18). However, in a large breast cancer population the significantly-reduced relapse risk associated with statin use did not appear to
differ by specific cancer treatments, including RT, chemotherapy or endocrine therapy (29).

Mechanisms that may contribute to improved cancer outcomes with statins relate either to direct effects on tumours (including generation of pro-apoptotic, growth-inhibitory and pro-differentiation responses, radiosensitisation of tumour cells and inhibition of angiogenesis, invasion and metastasis) or to effects on normal tissues (reducing inflammation and inhibiting RT-induced intestinal and skin toxicities) (8-13). Statins can modify the acute RT-related normal tissue inflammatory response through inhibiting endothelial cell damage and activation, thus preventing recruitment of inflammatory cells into the tissues (11;12;34;35), with reduced late toxicities (and acute toxicities to a lesser extent) reported in preclinical models (12;13;36). A solitary prospective observational study evaluating this in patients receiving radical pelvic RT showed statins significantly reduced RT-induced bowel toxicity, both during treatment and one year later (19).

On the background of this significant body of preclinical and clinical work supporting potential clinically-significant benefits of statin use during RT, the lack of benefit in toxicity or pCR rate with statins found in this retrospective study is most likely due to its significant limitations. This single centre study has a small sample size and it was not possible retrospectively to collect data on ECOG performance status or other factors such as pre-treatment CEA levels which have been associated with higher odds ratios for pCR (17). Similarly we were not able to evaluate a possible
interaction between dose or duration of aspirin or statin use, nor the late toxicity of
treatment and disease outcome data. We also acknowledge that the logistic
regression analysis of the pCR rate and its association with other factors, including
aspirin and statin use, will be limited by the small number of events (n = 17).

Our results are also consistent with the possibility of there being no beneficial
interaction of statins with RT in rectal cancer patients, or indeed for colon or rectal
cancer overall, as reported by other authors (18;37). Larger patient numbers than
those we evaluated in this study are needed to discriminate the influence of statins
and NSAIDS on treatment toxicities and outcomes separate to other prognostic
variables. The true benefits of statins in this clinical setting can be best evaluated
with the least bias and confounding by large, prospective, well-designed,
randomised, placebo-controlled trials.

Conclusion

Although our study did not find improvements in toxicity or pCR rate through statin
or aspirin use in rectal cancer patients undergoing LCRT, the preclinical and clinical
data collectively present a compelling case for such trials to be conducted, especially
in cancer patients who are being treated with RT. Neo-adjuvant LCRT or chemo-RT
in rectal cancer patients is a setting in which efficacy of statins in reducing toxicities
can be combined with evaluating the histological, inflammatory and molecular
effects of these agents in normal and malignant tissues. The implications of such a
benefit at a population level are profound, offering improved tolerability of RT and
better cancer outcomes, using agents that have very low cost and toxicity.
References:

Reference List


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Enhanced tumorocidal effect of chemotherapy with preoperative 

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biochemical outcomes with statin use in patients with high-risk localized 
prostate cancer treated with radiotherapy. Int J Radiat Oncol Biol Phys 2011 


### Table 1: Patient Demographics

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<th>Category</th>
<th>Count</th>
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<td>Male</td>
<td>106</td>
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<td>(25%)</td>
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<tr>
<td>Maori</td>
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<tr>
<td>Other European</td>
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<td>(10%)</td>
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<tr>
<td>Stage II</td>
<td>35</td>
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<tr>
<td>Stage III</td>
<td>92</td>
<td>(64.8%)</td>
</tr>
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<td>Stage IV</td>
<td>11</td>
<td>(7.7%)</td>
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<tr>
<td>LCRT</td>
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<td></td>
</tr>
<tr>
<td>With concurrent chemo</td>
<td>129</td>
<td>(91%)</td>
</tr>
<tr>
<td>Without chemo</td>
<td>13</td>
<td>(9%)</td>
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Table 2: Statin and aspirin use during neo-adjuvant long-course radiation treatment

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<tr>
<th></th>
<th>On statins (n = 33)</th>
<th>Not on statins (n = 109)</th>
<th>On aspirin (n= 35)</th>
<th>Not on aspirin† (n = 106)</th>
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<td>Gender</td>
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<td></td>
<td></td>
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<tr>
<td>Male</td>
<td>25 (76%)</td>
<td>81 (74%)</td>
<td>29 (83%)</td>
<td>76 (72%)</td>
</tr>
<tr>
<td>Female</td>
<td>8 (24%)</td>
<td>28 (26%)</td>
<td>6 (17%)</td>
<td>30 (28%)</td>
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<tr>
<td>Median age (range)</td>
<td>71 (59 – 84)</td>
<td>67 (19 – 86)</td>
<td>72 (54- 86)</td>
<td>67 (19 – 86)</td>
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<td>MRI Stage</td>
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<td>2 (1.8%)</td>
<td>1 (2.9%)</td>
<td>3 (2.8%)</td>
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<tr>
<td>Stage II</td>
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<td>21 (19.3%)</td>
<td>12 (34.3%)</td>
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<td>Stage III</td>
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<td>76 (69.7%)</td>
<td>20 (57.1%)</td>
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<td>Stage IV</td>
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<td></td>
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<tr>
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<td>28 (85%)</td>
<td>101 (93%)</td>
<td>27 (77%)</td>
<td>101 (95%)</td>
</tr>
<tr>
<td>No</td>
<td>5 (15%)</td>
<td>8 (7%)</td>
<td>8 (23%)</td>
<td>5 (5%)</td>
</tr>
<tr>
<td>Maximal bladder</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>toxicity</td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>Grade 0</td>
<td>14 (42.4%)</td>
<td>43 (39.4%)</td>
<td>11 (31.4%)</td>
<td>46 (43.4%)</td>
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<td>Grade 1</td>
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<td>47 (43.1%)</td>
<td>16 (45.7%)</td>
<td>45 (42.5%)</td>
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<tr>
<td>Grade 2</td>
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<td>17 (15.6%)</td>
<td>8 (22.9%)</td>
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<tr>
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For Peer Review

Chemotherapy stopped due to toxicity

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<th>Group 2</th>
<th>Group 3</th>
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<td>13 (39.4%)</td>
<td>34 (31.2%)</td>
<td>13 (37.1%)</td>
<td>34 (32.1%)</td>
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<td>67 (61.5%)</td>
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<td>8 (7.3%)</td>
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Radiation therapy stopped due to toxicity

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<thead>
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<tr>
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<td>104 (95%)</td>
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<td>101 (95%)</td>
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Pathological response

<table>
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<td>102</td>
<td>33‡</td>
<td>101</td>
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<td>88 (86.3%)</td>
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† In 1 patient it was unknown if they were or were not taking aspirin

‡ 1 patient in the aspirin group died prior to surgery and 1 patient had an unknown surgical histology
Figure Legends:

Figure 1. Distribution of maximum rectal toxicity grades during chemoradiation, according to statin use (Spearman R not significant).

Figure 2. Actuarial plot of time to maximum rectal toxicity in patients who had at least grade 2 toxicity.
Figure 1. Distribution of maximum rectal toxicity grades during chemoradiation, according to statin use (Spearman R not significant).

106x73mm (300 x 300 DPI)
Figure 2. Actuarial plot of time to maximum rectal toxicity in patients who had at least grade 2 toxicity.

logrank p = 0.44