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

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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.

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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 1st September 2007 and 1st 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

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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). Multinomial 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), 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

(1) Ngan SY, Burmeister B, Fisher RJ, Solomon M, Goldstein D, Joseph D, et al.
Randomized trial of short-course radiotherapy versus long-course
chemoradiation comparing rates of local recurrence in patients with T3 rectal
cancer: Trans-Tasman Radiation Oncology Group trial 01.04. J Clin Oncol 2012
Nov 1;30(31):3827-33.

(2) Corcos L, Jossic-Corcos C. Statins: perspectives in cancer therapeutics. Dig
Liver Dis 2013 Oct;45(10):795-802.

(3) Nielsen SF, Nordestgaard BG, Bojesen SE. Statin use and reduced cancer-
related mortality. N Engl J Med 2012 Nov 8;367(19):1792-802.

(4) Shao YY, Hsu CH, Yeh KH, Chen HM, Yeh YC, Lai CL, et al. Statin Use Is
Associated With Improved Prognosis of Colorectal Cancer in Taiwan. Clin
Colorectal Cancer 2015 Feb 21;14(3):177-84.

(5) Cardwell CR, Hicks BM, Hughes C, Murray LJ. Statin Use After Colorectal
Cancer Diagnosis and Survival: A Population-Based Cohort Study. J Clin Oncol
2014 Aug 4;32(28):3177-83.

(6) Bardou M, Barkun A, Martel M. Effect of statin therapy on colorectal cancer.
Gut 2010 Nov;59(11):1572-85.

(7) Gibot L, Follet J, Metges J, Auvray P, Simon B, Corcos L, et al. Human caspase

7 is positively controlled by SREBP-1 and SREBP-2. Biochem J 2009 May

27;420(3):473-83.

(8) Sassano A, Platanias LC. Statins in tumor suppression. Cancer Lett 2008 Feb

18;260(1-2):11-9.

(9) Gazzerro P, Proto MC, Gangemi G, Malfitano AM, Ciaglia E, Pisanti S, et al.

Pharmacological actions of statins: a critical appraisal in the management of

cancer. Pharmacol Rev 2012 Jan;64(1):102-46.

(10) Fritz G, Brachetti C, Kaina B. Lovastatin causes sensitization of HeLa cells to

ionizing radiation-induced apoptosis by the abrogation of G2 blockage. Int J

Radiat Biol 2003 Aug;79(8):601-10.

(11) Nubel T, Damrot J, Roos WP, Kaina B, Fritz G. Lovastatin protects human

endothelial cells from killing by ionizing radiation without impairing induction

and repair of DNA double-strand breaks. Clin Cancer Res 2006 Feb 1;12(3 Pt

1):933-9.

(12) Holler V, Buard V, Gaugler MH, Guipaud O, Baudelin C, Sache A, et al.

Pravastatin limits radiation-induced vascular dysfunction in the skin. J Invest

Dermatol 2009 May;129(5):1280-91.

(13) Haydont V, Gilliot O, Rivera S, Bourgier C, Francois A, Aigueperse J, et al.

Successful mitigation of delayed intestinal radiation injury using pravastatin is

not associated with acute injury improvement or tumor protection. Int J

Radiat Oncol Biol Phys 2007 Aug 1;68(5):1471-82.

(14) Follet J, Corcos L, Baffet G, Ezan F, Morel F, Simon B, et al. The association of

statins and taxanes: an efficient combination trigger of cancer cell apoptosis.

Br J Cancer 2012 Feb 14;106(4):685-92.

(15) Katz MS, Minsky BD, Saltz LB, Riedel E, Chessin DB, Guillem JG. Association of

statin use with a pathologic complete response to neoadjuvant

chemoradiation for rectal cancer. Int J Radiat Oncol Biol Phys 2005 Aug

1;62(5):1363-70.

(16) Mace AG, Gantt GA, Skacel M, Pai R, Hammel JP, Kalady MF. Statin therapy is

associated with improved pathologic response to neoadjuvant

chemoradiation in rectal cancer. Dis Colon Rectum 2013 Nov;56(11):1217-27.

(17) Armstrong DE, Raissouni S, Price Hiller JA, Mercer J, Powell ED, MacLean A, et

al. Predictors of pathologic complete response after neoadjuvant treatment

for rectal cancer: A multicenter study. J Clin Oncol 2014 32[suppl 3], abstr

397.

(18) Ng K, Ogino S, Meyerhardt JA, Chan JA, Chan AT, Niedzwiecki D, et al.

Relationship Between Statin Use and Colon Cancer Recurrence and Survival:

Results From CALGB 89803. J Natl Cancer Inst 2011 Aug 17;103(20):1540-51.

(19) Wedlake LJ, Silia F, Benton B, Lalji A, Thomas K, Dearnaley DP, et al.

Evaluating the efficacy of statins and ACE-inhibitors in reducing

gastrointestinal toxicity in patients receiving radiotherapy for pelvic

malignancies. Eur J Cancer 2012 Sep;48(14):2117-24.

(20)   Ng K, Meyerhardt JA, Chan AT, Sato K, Chan JA, Niedzwiecki D, et al. Aspirin

and COX-2 inhibitor use in patients with stage III colon cancer. J Natl Cancer

Inst 2015 Jan;107(1):345.

(21)   Algra AM, Rothwell PM. Effects of regular aspirin on long-term cancer

incidence and metastasis: a systematic comparison of evidence from

observational studies versus randomised trials. Lancet Oncol 2012

May;13(5):518-27.

(22)   Rothwell PM, Wilson M, Elwin CE, Norrving B, Algra A, Warlow CP, et al. Long-

term effect of aspirin on colorectal cancer incidence and mortality: 20-year

follow-up of five randomised trials. Lancet 2010 Nov 20;376(9754):1741-50.

(23)   Chan AT, Ogino S, Fuchs CS. Aspirin use and survival after diagnosis of

colorectal cancer. JAMA 2009 Aug 12;302(6):649-58.

(24)   Cardwell CR, Kunzmann AT, Cantwell MM, Hughes C, Baron JA, Powe DG, et

al. Low-dose aspirin use after diagnosis of colorectal cancer does not increase

survival: a case-control analysis of a population-based cohort.

Gastroenterology 2014 Mar;146(3):700-8.

(25)   Cancer Therapy Evaluation Program. Common Terminology Criteria for

Adverse Events v3.0 (CTCAE). Bethesda, ML, USA: National Cancer Institute

(USA); 2003.

(26) Bosset JF, Collette L, Calais G, Mineur L, Maingon P, Radosevic-Jelic L, et al. Chemotherapy with preoperative radiotherapy in rectal cancer. N Engl J Med 2006 Sep 14;355(11):1114-23.

(27) Bosset JF, Calais G, Mineur L, Maingon P, Radosevic-Jelic L, Daban A, et al. Enhanced tumorocidal effect of chemotherapy with preoperative radiotherapy for rectal cancer: preliminary results--EORTC 22921. J Clin Oncol 2005 Aug 20;23(24):5620-7.

(28) Zhong S, Zhang X, Chen L, Ma T, Tang J, Zhao J. Statin use and mortality in cancer patients: Systematic review and meta-analysis of observational studies. Cancer Treat Rev 2015 Jun;41(6):554-67.

(29) Ahern TP, Pedersen L, Tarp M, Cronin-Fenton DP, Garne JP, Silliman RA, et al. Statin prescriptions and breast cancer recurrence risk: a Danish nationwide prospective cohort study. J Natl Cancer Inst 2011 Oct 5;103(19):1461-8.

(30) Ling Y, Yang L, Huang H, Hu X, Zhao C, Huang H, et al. Prognostic Significance of Statin Use in Colorectal Cancer: A Systematic Review and Meta-Analysis. Medicine (Baltimore) 2015 Jun;94(25):e908.

(31) Kollmeier MA, Katz MS, Mak K, Yamada Y, Feder DJ, Zhang Z, et al. Improved biochemical outcomes with statin use in patients with high-risk localized prostate cancer treated with radiotherapy. Int J Radiat Oncol Biol Phys 2011 Mar 1;79(3):713-8.

(32) Tsai HK, Katz MS, Coen JJ, Zietman AL, Kaufman DS, Shipley WU. Association of statin use with improved local control in patients treated with selective bladder preservation for muscle-invasive bladder cancer. Urology 2006 Dec;68(6):1188-92.

(33) Scosyrev E, Tobis S, Donsky H, Wu G, Joseph J, Rashid H, et al. Statin use and the risk of biochemical recurrence of prostate cancer after definitive local therapy: a meta-analysis of eight cohort studies. BJU Int 2013 Mar;111(3 Pt B):E71-E77.

(34) Nubel T, Dippold W, Kaina B, Fritz G. Ionizing radiation-induced E-selectin gene expression and tumor cell adhesion is inhibited by lovastatin and all-trans retinoic acid. Carcinogenesis 2004 Aug;25(8):1335-44.

(35) Dimitrova Y, Dunoyer-Geindre S, Reber G, Mach F, Kruithof EK, de Moerloose P. Effects of statins on adhesion molecule expression in endothelial cells. J Thromb Haemost 2003 Nov;1(11):2290-9.

(36) Haydont V, Bourgier C, Pocard M, Lusinchi A, Aigueperse J, Mathe D, et al. Pravastatin Inhibits the Rho/CCN2/extracellular matrix cascade in human fibrosis explants and improves radiation-induced intestinal fibrosis in rats. Clin Cancer Res 2007 Sep 15;13(18 Pt 1):5331-40.

(37) Hoffmeister M, Jansen L, Rudolph A, Toth C, Kloor M, Roth W, et al. Statin use and survival after colorectal cancer: the importance of comprehensive confounder adjustment. J Natl Cancer Inst 2015 Jun;107(6):djv045.

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Table 1:   Patient Demographics

Median age at diagnosis		69	(range 19 – 86)
Gender			
Male		106	(75%)
Female	36	(25%)	
Ethnicity			
NZ European		99	(70%)
Maori		10	(7%)
Other European		18	(13%)
Not stated		15	(10%)
TNM Stage			
Stage I		4	(2.8%)
Stage II	35	(24.6%)	
Stage III		92	(64.8%)
Stage IV		11	(7.7%)
LCRT			
With concurrent chemo		129	(91%)
Without chemo		13	(9%)

Table 2: Statin and aspirin use during neo-adjuvant long-course radiation treatment

	On statins (n = 33)	Not on statins (n = 109)	On aspirin (n= 35)	Not on aspirin† (n = 106)
Gender				
Male	25 (76%)	81 (74%)	29 (83%)	76 (72%)
Female	8 (24%)	28 (26%)	6 (17%)	30 (28%)
Median age (range)	71 (59 – 84)	67 (19 – 86)	72 (54- 86)	67 (19 – 86)
MRI Stage				
Stage I	2 (6.1%)	2 (1.8%)	1 (2.9%)	3 (2.8%)
Stage II	14 (42.4%)	21 (19.3%)	12 (34.3%)	23 (21.7%)
Stage III	16 (48.5%)	76 (69.7%)	20 (57.1%)	71 (67%)
Stage IV	1 (3%)	10 (9.2%)	2 (5.7%)	9 (8.5%)
Concurrent chemotherapy				
Yes	28 (85%)	101 (93%)	27 (77%)	101 (95%)
No	5 (15%)	8 (7%)	8 (23%)	5 (5%)
Maximal bladder toxicity				
Grade 0	14 (42.4%)	43 (39.4%)	11 (31.4%)	46 (43.4%)
Grade 1	15 (45.5%)	47 (43.1%)	16 (45.7%)	45 (42.5%)
Grade 2	4 (12.1%)	17 (15.6%)	8 (22.9%)	13 (12.3%)
Grade 3	0 (0%)	1 (0.9%)	0 (0%)	1 (0.9%)
Unknown	0 (0%)	1 (0.9%)	0 (0%)	1 (0.9%)
Maximal rectal toxicity				
Grade 0	2 (6.1%)	8 (7.3%)	4 (11.4%)	6 (5.7%)
Grade 1	5 (15.1%)	35 (32.1%)	4 (11.4%)	36 (34%)
Grade 2	22 (66.7%)	50 (45.9%)	23 (65.7%)	48 (45.3%)
Grade 3	4 (12.1%)	15 (13.8%)	4 (11.4%)	15 (14.2%)
Unknown	0 (0%)	1 (0.9%)	0 (0%)	1 (0.9%)

Chemotherapy stopped due to toxicity				
Yes	13 (39.4%)	34 (31.2%)	13 (37.1%)	34 (32.1%)
No	15 (45.5%)	67 (61.5%)	14 (40%)	67 (63.2%)
Not on chemo	5 (15.1%)	8 (7.3%)	8 (22.9%)	5 (4.7%)
Radiation therapy stopped due to toxicity				
Yes	2 (6%)	5 (5%)	2 (6%)	5 (5%)
No	31 (94%)	104 (95%)	33 (94%)	101 (95%)
Pathological response				
Number assessable	33	102	33[‡]	101
Complete	3 (9.1%)	14 (13.7%)	6 (18.2%)	11 (10.9%)
Incomplete	30 (90.9%)	88 (86.3%)	27 (81.8%)	90 (89.1%)

† 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.

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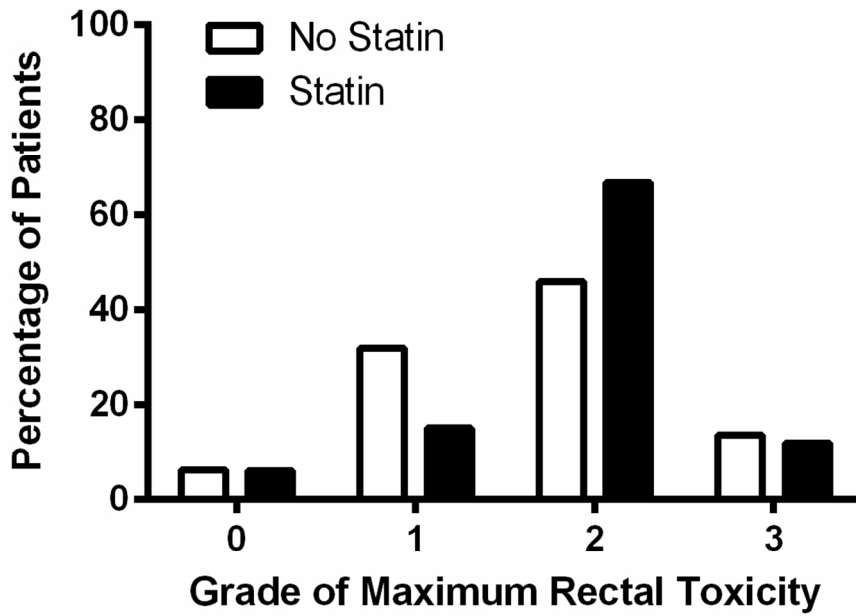50
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Figure 1. Distribution of maximum rectal toxicity grades during chemoradiation, according to statin use
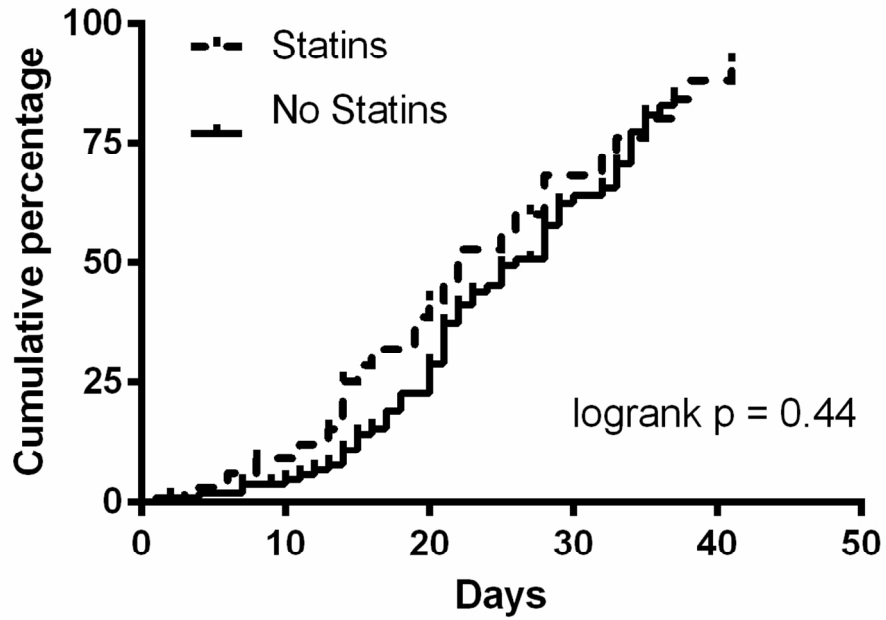(Spearman R not significant).
106x73mm (300 x 300 DPI)

Figure 2. Actuarial plot of time to maximum rectal toxicity in patients who had at least grade 2 toxicity.
105x73mm (300 x 300 DPI)