# Associations of clinical and dosimetric parameters with late rectal toxicities after radical intensity-modulated radiation therapy for prostate cancer: a single-centre retrospective study

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## ABSTRACT

**Introduction:** This study assessed the incidence of late rectal toxicities and evaluated potential predictive factors for late proctitis in patients treated with prostate-specific intensity-modulated radiotherapy in Hong Kong.

**Methods:** This retrospective longitudinal observational study included patients with localised prostate cancer who were treated with intensity-modulated radiation therapy in an oncology unit in Hong Kong between January 2007 and December 2011, and who had >1 year of follow-up. Clinical, pharmacological, and radiation parameters were recorded. Toxicities were measured by Common Terminology Criteria for Adverse Events version 4.

**Results:** In total, 232 patients were included in this analysis. The mean follow-up time was 7.3 ± 2.1 years and 46.5% of the patients had late rectal toxicities. Late proctitis occurred in 30.5% of patients; 25% of the patients with late proctitis exhibited grade ≥2 toxicity. Median onset times for late proctitis and rectal bleeding were 15 and 18.4 months, respectively. Multivariable regression showed increased odds for the occurrence of late proctitis in patients with older age (odds ratio [OR]=1.11, 95% confidence interval [CI]=1.04-1.19, P=0.003), higher V70 (OR=1.08, 95% CI=1.01-1.15, P=0.027), and presence of acute rectal toxicities (OR=4.47, 95% CI=2.37-8.43, P<0.001). Antiplatelet use was not significantly associated with the occurrence of late proctitis (OR=1.98, 95% CI=0.95-4.14, P=0.07).

**Conclusions:** The incidence of late rectal toxicities was considerable among patients in this study. Clinicians should consider the possibility of late proctitis for patients with older age, acute rectal toxicities, and higher V70. High doses to rectal volumes should be limited because of the significant association with V70.


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**New knowledge added by this study**

- Age, V70, and the presence of acute rectal toxicities were identified as potential predictive factors for the occurrence of late proctitis in prostate cancer patients who undergo treatment with intensity-modulated radiotherapy.
- This is the first study in Hong Kong to describe the incidence of late rectal toxicities over time and to identify associations between pharmacological factors and the occurrence of late proctitis in patients with prostate cancer who undergo treatment with intensity-modulated radiotherapy with radical intent.

**Implications for clinical practice or policy**

- Clinicians should closely monitor patients for the development of late rectal toxicities, including proctitis, following intensity-modulated radiotherapy for prostate cancer.
- Clinicians should promptly investigate any rectal symptoms that develop after radiotherapy in patients who exhibit factors predictive of high risk, including older age, the presence of acute rectal toxicities, and higher V70.
- During radiotherapy planning for patients with prostate cancer, clinicians should attempt to limit the applications of high doses to rectal volumes.

 

## 前列腺癌患者在接受根治性強度調控放射治療後出現與直腸相關的長期併發症與臨床及電療設計因素的相關性：一所腫瘤科中心的回顧性研究

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**引言：**回顧列腺癌患者在接受根治性強度調控放射治療後出現與直腸相關的長期併發症的出現率，以及評估可預計其出現的臨床及電療設計因素。

**方法：**這項縱向觀察式研究納入2007年1月至2011年12月期間在一所腫瘤科中心接受根治性強度調控放射治療後覆檢超過一年的前列腺癌病人並檢視他們的臨床、用藥及電療設計因素，以及出現與直腸相關長期併發症的情況。

**結果：**本研究納入232名病人進行分析，平均覆檢時間為7.3 ± 2.1年。46.5%患者出現與直腸相關的長期併發症。長期直腸炎的出現率為30.5%，當中25%為第2級以上，出現長期直腸炎及直腸出血的中位數時間分別為15個月及18.4個月。多元線性迴歸分析發現年紀愈大（比值比=1.11，95%置信區間=1.04-1.19，P=0.003）、愈高V70值（比值比=1.08，95%置信區間=1.01-1.15，P=0.027）及出現短期直腸併發症（比值比=4.47，95%置信區間=2.37-8.43，P<0.001）的病人較大機會出現長期直腸炎。研究未能証明抗血小板藥物與長期直腸炎相關（比值比=1.98，95%置信區間=0.95-4.14，P=0.07）。

**結論：**與直腸相關長期併發症的出現率不容忽視。醫生應留意年紀較大、高V70值與及曾出現短期直腸併發症的病人出現幅射性腸炎的可能性。因應V70與直腸炎的關係，在電療設計上應盡量避免直腸進入高劑量範圍。

## Introduction

Radical radiotherapy is a standard treatment option for patients with early-stage and locally advanced non-metastatic prostate cancer. Advances in radiotherapy in the past 20 years include the use of androgen deprivation therapy for patients with this type of cancer, as well as the application of more precise radiotherapy techniques.[1,2] Intensity-modulated radiation therapy (IMRT) has emerged as the standard radiotherapy technique.[3] Its benefits have been explored in terms of the effects of dose escalation or hypofractionation on survival outcomes.[4,5] For patients undergoing this type of treatment, toxicities are the primary concern. Long-term side-effects (ie, complications occurring ≥3 months after radiotherapy) have a major impact on the quality of life for affected patients; this is particularly important for patients with genitourinary or rectal toxicities. Late rectal toxicities, including per-rectal bleeding, faecal incontinence, and proctitis, have been reported to occur at rates of 5% to 21%.[1,3-9]

Associations have been reported between late rectal toxicities and various clinical and dosimetric parameters; however, most data were collected using the conventional three-dimensional conformal technique.[8,10-12] In addition, there have been limited reports of such associations among patients in Hong Kong. In particular, Poon et al[8] reported that 8% of patients exhibited grade ≥2 late rectal toxicities following IMRT in a retrospective cohort study. Although several clinical parameters were assessed, most failed to show statistically significant associations, with the exception of the presence of acute rectal toxicities.[8] To the best of our knowledge, pharmacological parameters following IMRT for prostate cancer have not yet been studied in local populations. Some previous reports showed a significant association between anticoagulant use and late rectal toxicities, whereas an association between antiplatelet use and androgen deprivation was inconsistent among studies.[12-14]

Multiple strategies have been used for the treatment of late rectal toxicities. The use of hyperbaric oxygen has shown promising results in some retrospective studies, but it has not been available in Hong Kong until recently.[12,15,16] Treatments with sucralfate, prednisolone enaema, short-chain fatty acids, and antifibrinolytics have been evaluated in small trials.[17-19] Thus far, no standard approach has been established, and there are no published data regarding local management practices.

Late rectal toxicities may represent clinically significant complications because of their non-negligible incidences. Insights regarding any factors predictive of their occurrence could aid in improved treatment planning and early identification of toxicity. This study was performed to assess the incidence of late rectal toxicities and to identify factors predictive for late proctitis in patients treated with prostate-specific IMRT in Hong Kong.

## Methods

### Study design and patients

This retrospective longitudinal observational study included patients with prostate cancer who received IMRT with radical intent in a tertiary referral institution in Hong Kong from January 2007 to December 2011. Patients were excluded if they were followed up for fewer than 12 months from the start of radiotherapy, if they did not complete the course of radiotherapy, if they were not at risk of proctitis (eg, those with post-abdominoperineal resection), or if they did not have a retrievable radiotherapy plan due to technical difficulties. The cut-off date for data collection was 31 December 2018.

Patients underwent treatment with a comfortably full bladder and an empty rectum, with laxatives administered 1 day prior to simulation computed tomography. Patients were asked to empty the bladder prior to attending the radiotherapy suite, and then drink a comfortable volume of water. A pelvic thermoplastic mould was used for immobilisation. Intravenous contrast was administered prior to computed tomography. Re-simulation was performed automatically if bladder volume was below 150 cc, if

prominent rectal gas was present, or upon request by the attending oncologist. Contouring was performed by designated oncologists with confirmation by at least one specialist. Tumour and whole prostate were contoured as a single volume; the clinical target volume (CTV) was the volume of the tumour, whole prostate, and base of the seminal vesicle (defined as 1 cm of the central seminal vesicle proximal to the base of the prostate). Whole seminal vesicle was included in the CTV if seminal vesicle involvement was observed. Planning target volume (PTV) was determined by expanding the CTV by a radial margin of 1.5 cm, except posteriorly where a smaller margin was used (0.7 cm). Pelvic lymph node irradiation was not performed. Patients received 70 Gy in 35 daily fractions over 7 weeks at 100% of the isodose level. Rectal volume was contoured in accordance with the Radiation Therapy Oncology Group Consensus Contouring Guidelines for normal male pelvic tissue. Dose constraints for organs at risk followed our departmental protocol: for the rectum, we classified the plan as fulfilling the first, second, or third criteria. First criteria were satisfied if V40 (% of organ volume receiving 40 Gy) <35% or V65 (% of organ volume receiving 65 Gy) <17%; second criteria were satisfied if V53 (% of organ volume receiving 53 Gy) <45% or V68 (% of organ volume receiving 68 Gy) <20%; and third criteria were satisfied if V60 (% of organ volume receiving 60 Gy) <50%, V65 (% of organ volume receiving 65 Gy) <35%, or V70 (% of organ volume receiving 70 Gy) <25%. Hormonal treatment was administered based on the risk stratification used in the United Kingdom National Institute for Health and Care Excellence guidelines. Patients were followed up at 3–6-month intervals until the patient died or defaulted, and data were censored at the last recorded follow-up. Dose distributions, doses administered to organs at risk, and dose volume histograms were evaluated by the Eclipse and Planning System (Varian Medical Systems; Palo Alto [CA], United States).

### Data collection

For each patient, basic demographic data were documented, including age; Eastern Cooperative Oncology Group performance score; smoking habit; pretreatment albumin level; co-morbidities such as hypertension, diabetes, lipid disorder, history of cerebrovascular disease, ischaemic heart disease, and/or chronic renal impairment; medical history of abdominal surgery; drug history including antihypertensives, oral glycaemic agents, antiplatelets, anticoagulants, lipid-lowering agents, and antipurine agents; androgen deprivation therapies, including medical or surgical castration; and use of immunosuppressants. Tumour characteristics were also recorded, including pretreatment prostate-specific antigen level, clinical T-staging determined by clinical and radiological findings (based on AJCC 7th edition[20]), and Gleason score.

Acute and late rectal toxicities, including proctitis, incontinence, and per-rectal bleeding, were recorded and classified in accordance with Common Terminology Criteria for Adverse Events version 4.[21] Late rectal toxicities were defined as those that occurred at least 3 months after the completion of radiotherapy. Late proctitis was defined as either the presence of rectal symptoms listed in Common Terminology Criteria for Adverse Events version 4, or colonoscopy findings of proctitis (eg, telangiectasia, ulcers, or inflammation). If a patient presented with per-rectal bleeding, colonoscopy findings were referenced whenever present to differentiate proctitis or other causes of bleeding, such as diverticulosis or haemorrhoids. Per-rectal bleeding only was recorded if no endoscopic proctitis features were present; otherwise, both per-rectal bleeding and proctitis were recorded. Additional parameters recorded included time of onset of late rectal toxicities, as well as treatment modalities used.

Dosimetric parameters (eg, V40, V50, V60, V70, Dmax [maximum dose], mean dose to rectum, and contoured rectal volume) were evaluated with the radiotherapy planning system. The use of static beam or volumetric arc technique was recorded, as was the compliance with rectal dose constraints.

### Statistical analysis and research ethics

Incidences of grade ≥1 late rectal toxicities with 95% confidence interval (CI) were calculated at 1, 2, and 5 years after treatment. The Kaplan-Meier curve method was used to illustrate the time to onset of late rectal toxicities. The Chi squared test, Fisher's exact test, independent *t* test, or Mann-Whitney *U* test were used to compare baseline patient characteristics, pharmacological and dosimetric parameters between patients in grades 0 and ≥1 late toxicities, as well as in patients with late proctitis. The association of each parameter with late proctitis was examined using a multivariable binary logistic regression model with a backward stepwise selection method, including variables with $P<0.1$ in univariable regression analyses. The presence of multicollinearity was determined by using variance inflation factors. Statistical analyses were performed using SPSS (Windows version 22.0; IBM Corp, Armonk [NY], United States). The threshold of statistical significance was set at $P<0.05$. The STROBE checklist was followed to ensure standardised reporting.

## Results

From January 2007 to December 2011, a total of 238 patients with prostatic cancer received radical radiotherapy in our institution. As shown in the Figure, 232 patients were included in the analysis. The mean age of patients was 72.3 ± 4.8 years at

time of radiotherapy (Table 1). The mean follow-up period was 7.3 ± 2.1 years, and there were 157 (67.7%) surviving patients at the cut-off date for data collection. Forty-two (18.1%) patients had been diagnosed with biochemical recurrence during the study period, based on the Phoenix definition.[22] In total, 229 patients received a PTV dose of ≤70 Gy. Owing to genuine bowel invasion, or as a component of individualised dose escalation, four patients received a PTV dose of 66 to 76 Gy, of which three were >70 Gy. Colonoscopy was performed in 103 (44.4%) patients during follow-up. Among patients with per-rectal bleeding, 93 (88.6%) had undergone colonoscopy.

Occurrences of acute and late rectal toxicities throughout the study period are shown in Table 2. The rates of all-grade acute and late rectal toxicities were 36.2% and 46.5%, respectively; the rates of grade ≥2 late rectal toxicities and proctitis were 28.4% and 25.0%, respectively. Nineteen (8.2%) patients had grade 3 per-rectal bleeding, with 15 (78.9%) requiring blood transfusion and eight (42.1%) requiring endoscopic coagulation. The cumulative incidences of rectal toxicities at 1, 2, and 5 years after treatment are shown in Table 3. The median times of onset of late proctitis, late faecal incontinence, and late per-rectal bleeding were 15, 21.8, and 18.4 months, respectively.

Patients' detailed demographic, pharmacological, and dosimetric parameters are listed in Table 1. Factors including history of haemorrhoid, PTV dose, and V70 were significantly different between patients with and without late rectal toxicities. In addition, age was the sole demographic factor significantly associated with late proctitis. There was no significant association between antiplatelet use and late rectal toxicities (P=0.066). No associations were found between late proctitis and other demographic or pharmacological characteristics (eg, PTV dose and history of haemorrhoid) in this study.

Univariable and stepwise multivariable analyses were performed to identify factors predictive of late proctitis (Table 4). In univariable analysis, the presence of acute rectal toxicities, antiplatelet use, age at radiotherapy, Dmax, and dose/volume histogram parameters (ie V50, V60, V70, and rectal constraints) were identified as potential risk factors. In the regression model with all potential risk factors included, multicollinearity was detected among the dose/volume histogram parameters (variance inflation factors of 7.21, 8.69, 3.05, and 4.97 for V50, V60, V70, and rectal constraints, respectively). Compared to V50 and V60, V70 (ie, the high-dose region) showed a stronger association with late proctitis in univariable analysis. Multicollinearity was resolved by exclusion of V50 and V60 from the multivariable regression model. The final multivariable regression model revealed increased odds of late proctitis in patients with older age, higher V70, and the presence of acute rectal toxicities. Antiplatelet use tended to show higher odds, but this finding was not statistically significant (odds ratio=1.98, 95% CI=0.95-4.14). Dmax and satisfaction of the 3rd criteria alone were associated with late proctitis in univariable analysis, but the associations were not significant in multivariable analysis.

Common treatment modalities among patients with grade ≥2 late proctitis were also recorded. Topical agents such as Ultraproct® (commercial preparation of fluocortolone pivalate, fluocortolone hexanoate, and cinchocaine hydrochloride), bismuth ointment, or an antifibrinolytic agent (eg, tranexamic acid) are commonly used as first-line treatment.[23] More than half (53.4%) of the patients had been administered an antifibrinolytic agent, while 77.6% and 19% of the patients were prescribed Ultraproct® and bismuth, respectively. Prednisolone enaema was also administered in 22 (37.9%) patients; the median duration of enaema use was 3.5 months (interquartile range, 1-7.25 months). Subjective improvement was reported by eight (36.4%) patients who received enaema treatment.

## Discussion

Radiation proctitis and other long-term rectal toxicities are clinically significant complications of radiotherapy to the prostate, due to their detrimental effects on patients' quality of life, as well as the expected long duration of post-treatment survival. In our cohort, the incidences of late proctitis (30.2%) and overall rectal toxicities (46.5%) were slightly higher than those in previous reports (5%-21%).[1,3-9] Comparison of baseline characteristics showed that more patients had ≥T3 disease in our cohort, although we found no statistically significant association between T-staging and a higher incidence of proctitis; similarly, no association between these parameters were reported in other studies.[8,12] Other variables with possible interactions were similar between our study and prior studies; these included

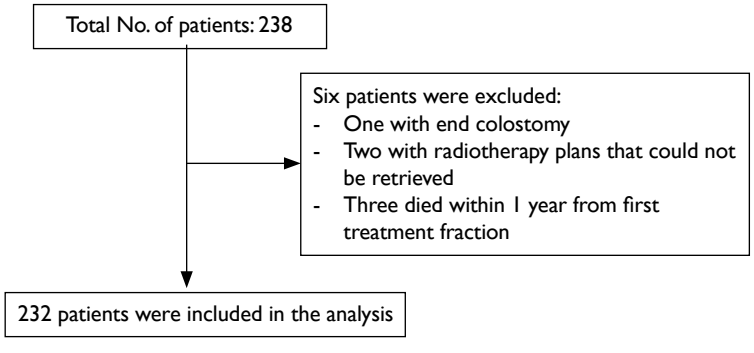


FIG. Patient recruitment

TABLE 1. Baseline clinical, pharmacological, and dosimetric parameters of prostate cancer patients treated with intensity-modulated radiation therapy, stratified by severity of late rectal toxicities and late proctitis*

| | All (n=232) | Late rectal toxicities | | P value† | Late proctitis | | P value† |
|---|---|---|---|---|---|---|---|
| | | Grade 0 (n=124) | Grade ≥1 (n=108) | | Grade 0 (n=162) | Grade ≥1 (n=70) | |
| Clinical parameters | | | | | | | |
| Age (years) | 72.3 ± 4.8 | 71.8 ± 5.1 | 72.9 ± 4.5 | 0.090 | 71.8 ± 4.8 | 73.6 ± 4.6 | 0.007 |
| >75 years | 60 (25.9%) | 29 (23.4%) | 31 (28.7%) | 0.356 | 37 (22.8%) | 23 (32.9%) | 0.110 |
| Smoking‡ | 123/213 (57.7%) | 61/113 (54.0%) | 62/100 (62.0%) | 0.237 | 82/148 (55.4%) | 41/65 (63.1%) | 0.297 |
| ECOG | | | | 0.423 | | | 0.736 |
| 0 | 157 (67.7%) | 88 (71.0%) | 69 (63.9%) | | 112 (69.1%) | 45 (64.3%) | |
| 1 | 69 (29.7%) | 34 (27.4%) | 35 (32.4%) | | 46 (28.4%) | 23 (32.9%) | |
| 2 | 6 (2.6%) | 2 (1.6%) | 4 (3.7%) | | 4 (2.5%) | 2 (2.9%) | |
| Hypertension | 148 (63.8%) | 85 (68.5%) | 63 (58.3%) | 0.106 | 107 (66.0%) | 41 (58.6%) | 0.277 |
| Diabetes | 67 (28.9%) | 35 (28.2%) | 32 (29.6%) | 0.814 | 46 (28.4%) | 21 (30.0%) | 0.804 |
| Ischaemic heart disease | 28 (12.1%) | 14 (11.3%) | 14 (13.0%) | 0.696 | 17 (10.5%) | 11 (15.7%) | 0.263 |
| Haemorrhoid | 4 (1.7%) | 0 | 4 (3.7%) | 0.046 | 2 (1.2%) | 2 (2.9%) | 0.586 |
| History of bowel surgery | 5 (2.2%) | 1 (0.8%) | 4 (3.7%) | 0.187 | 3 (1.9%) | 2 (2.9%) | 0.639 |
| Hyperlipidaemia | 32 (13.8%) | 20 (16.1%) | 12 (11.1%) | 0.269 | 26 (16.0%) | 6 (8.6%) | 0.129 |
| Chronic renal injury | 30 (12.9%) | 15 (12.1%) | 15 (13.9%) | 0.685 | 23 (14.2%) | 7 (10.0%) | 0.382 |
| Cerebrovascular disease | 27 (11.6%) | 16 (12.9%) | 11 (10.2%) | 0.520 | 17 (10.5%) | 10 (14.3%) | 0.408 |
| Inflammatory bowel disease | 2 (0.9%) | 1 (0.8%) | 1 (0.9%) | 1.000 | 2 (1.2%) | 0 | 1.000 |
| Albumin (g/dL) | 38.5 ± 3.4 | 38.9 ± 3.3 | 38.1 ± 3.5 | 0.332 | 38.6 ± 3.5 | 38.4 ± 3.2 | 0.985 |
| Gleason score (by TRUS) | | | | 0.303 | | | 0.195 |
| ≤6 | 103 (44.4%) | 55 (44.4%) | 48 (44.4%) | | 67 (41.4%) | 36 (51.4%) | |
| 7 | 68 (29.3%) | 32 (25.8%) | 36 (33.3%) | | 53 (32.7%) | 15 (21.4%) | |
| 8-10 | 61 (26.3%) | 37 (29.8%) | 24 (22.2%) | | 42 (25.9%) | 19 (27.1%) | |
| T stage | | | | 0.906 | | | 0.973 |
| T1c | 45 (19.4%) | 23 (18.5%) | 22 (20.4%) | | 31 (19.1%) | 14 (20.0%) | |
| T2 | 65 (28.0%) | 36 (29.0%) | 29 (26.9%) | | 45 (27.8%) | 20 (28.6%) | |
| T3 or above | 122 (52.6%) | 65 (52.4%) | 57 (52.8%) | | 86 (53.1%) | 36 (51.4%) | |
| Pretreatment PSA level | | | | 0.289 | | | 0.234 |
| Pharmacological parameters | | | | | | | |
| Antiplatelet | 46 (19.8%) | 25 (20.2%) | 21 (19.4%) | 0.891 | 27 (16.7%) | 19 (27.1%) | 0.066 |
| Antihypertensives | 130 (56.0%) | 75 (60.5%) | 55 (50.9%) | 0.143 | 96 (59.3%) | 34 (48.6%) | 0.132 |
| Oral glycaemic agents | 50 (21.6%) | 28 (22.6%) | 22 (20.4%) | 0.683 | 36 (22.2%) | 14 (20.0%) | 0.706 |
| Anticoagulants | 6 (2.6%) | 3 (2.4%) | 3 (2.8%) | 1.000 | 4 (2.5%) | 2 (2.9%) | 1.000 |
| Immunosuppressants | 4 (1.7%) | 3 (2.4%) | 1 (0.9%) | 0.625 | 3 (1.9%) | 1 (1.4%) | 1.000 |
| Lipid-lowering agents | 32 (13.8%) | 14 (11.3%) | 18 (16.7%) | 0.236 | 20 (12.3%) | 12 (17.1%) | 0.331 |
| Gouty medications | 10 (4.3%) | 6 (4.8%) | 4 (3.7%) | 0.755 | 9 (5.6%) | 1 (1.4%) | 0.289 |
| Pretreatment hormonal treatment | 175 (75.4%) | 95 (76.6%) | 80 (74.1%) | 0.654 | 122 (75.3%) | 53 (75.7%) | 0.947 |
| Dosimetric parameters | | | | | | | |
| PTV dose | | | | 0.038 | | | 0.128 |
| ≤70 Gy | 229 (98.7%) | 124 (100%) | 105 (97.2%) | 0.099 | 161 (99.4%) | 68 (97.1%) | 0.217 |
| >70 Gy | 3 (1.3%) | 0 | 3 (2.8%) | | 1 (0.6%) | 2 (2.9%) | |
| Technique | | | | 0.373 | | | 0.986 |
| Static beam IMRT | 199 (85.8%) | 104 (83.9%) | 95 (88.0%) | | 139 (85.8%) | 60 (85.7%) | |
| Rapid arc | 33 (14.2%) | 20 (16.1%) | 13 (12.0%) | | 23 (14.2%) | 10 (14.3%) | |
| Rectal constraint | | | | 0.171 | | | 0.092 |
| 1 | 58 (25.0%) | 36 (29.0%) | 22 (20.4%) | | 46 (28.4%) | 12 (17.1%) | |
| 2 | 124 (53.4%) | 66 (53.2%) | 58 (53.7%) | | 86 (53.1%) | 38 (54.3%) | |
| 3 | 50 (21.6%) | 22 (17.7%) | 28 (25.9%) | | 30 (18.5%) | 20 (28.6%) | |
| Dmax (Gy) | 73.0 ± 0.8 | 72.9 ± 0.9 | 73.1 ± 0.8 | 0.134 | 73.0 ± 0.8 | 73.2 ± 0.8 | 0.091 |
| V40 (%) | 57.6 ± 17.7 | 56.8 ± 17.7 | 58.4 ± 17.7 | 0.520 | 56.4 ± 17.6 | 60.3 ± 17.6 | 0.118 |
| V50 (%) | 42.8 ± 14.2 | 41.5 ± 13.2 | 44.3 ± 15.2 | 0.238 | 41.4 ± 13.7 | 46.0 ± 14.9 | 0.030 |
| V60 (%) | 30.3 ± 10.0 | 29.5 ± 10.4 | 31.2 ± 9.5 | 0.090 | 29.3 ± 10.1 | 32.5 ± 9.4 | 0.004 |
| V70 (%) | 13.8 ± 4.7 | 13.2 ± 4.8 | 14.5 ± 4.5 | 0.031 | 13.2 ± 4.6 | 15.2 ± 4.6 | 0.003 |
| Mean rectal dose (Gy) | 43.5 ± 7.7 | 43.2 ± 7.5 | 43.9 ± 7.8 | 0.515 | 43.0 ± 7.6 | 44.8 ± 7.6 | 0.104 |
| Rectal volume ($cm^3$) | 60.8 ± 22.5 | 59.8 ± 20.8 | 61.9 ± 24.4 | 0.754 | 60.7 ± 22.0 | 60.9 ± 23.8 | 0.718 |

Abbreviations: ECOG = Eastern Cooperative Oncology Group; IMRT = intensity-modulated radiation therapy; PSA = prostate-specific antigen; PTV = planning target volume; TRUS = transperineal ultrasound

* Data are shown as No. (%) of patients or mean ± standard deviation, unless otherwise indicated

† Pearson Chi squared test, Mann-Whitney *U* test, Fisher's exact test, or independent *t* test, as appropriate

‡ Smoking status was available for 213 patients

age, dosimetric parameters (eg, V70, which was 14% in our study and 10% to 23% in previous studies), and the use of antiplatelets.[8,11,12]

There are two possible explanations for the higher incidences of late proctitis and overall rectal toxicities. First, our study involved frequent utilisation of colonoscopy for any rectal symptoms, which may lead to a higher rate of recognition; notably, the rate of utilisation was not reported in previous studies. Second, our study had a relatively long follow-up period. Previous studies described the incidence of toxicity throughout the study period. The mean follow-up period in our study was 7.3 years, whereas that of most previous studies was 38.9 to 66 months; in one notable exception, the follow-up period was 8.4 years (the incidence was 21% in that study).[3] The longer study period may also have contributed to a higher number of late rectal toxicities.

Previous reports suggested that a variety of parameters are associated with late proctitis; knowledge of these parameters could help clinicians to predict the risk of proctitis in each patient. In our study, age, and dosimetric parameters including V50, V60, and V70 were associated with late proctitis; history of haemorrhoid and V70 were associated with overall late rectal toxicities. These findings are consistent with the results of previous studies.[10-14,24] Some factors identified in prior studies, including diabetes, previous abdominal surgery, and the use of antiandrogen or anticoagulant medication,[11,13,25] failed to demonstrate any associations in the present study. Of note, <10% of the patients in our study had a history of abdominal surgery or inflammatory bowel disease; this could have influenced our ability to identify a statistically significant association. Recall bias, incomplete documentation of coexisting

TABLE 2. Occurrences of acute and late rectal toxicities during the study period (n=232)

| | Proctitis | | Per-rectal bleeding | | Faecal incontinence | | Overall rectal toxicities | |
|---|---|---|---|---|---|---|---|---|
| | Acute | Late | Acute | Late | Acute | Late | Acute | Late |
| Grade 0 | 162 (69.8%) | 162 (69.8%) | 204 (87.9%) | 127 (54.7%) | 229 (98.7%) | 228 (98.3%) | 148 (63.8%) | 124 (53.4%) |
| Grade 1 | 62 (26.7%) | 12 (5.2%) | 25 (10.8%) | 41 (17.7%) | 3 (1.3%) | 2 (0.9%) | 74 (31.9%) | 42 (18.1%) |
| Grade ≥2 | 8 (3.4%) | 58 (25.0%) | 3 (1.3%) | 64 (27.6%) | 0 | 2 (0.9%) | 10 (4.3%) | 66 (28.4%) |

TABLE 3. Incidences of grade ≥1 late rectal toxicities at selected time points

| | Year 1 | | Year 2 | | Year 5 | |
|---|---|---|---|---|---|---|
| | Count | Incidence (95% CI) | Count | Incidence (95% CI) | Count | Incidence (95% CI) |
| Late proctitis | 10/232 | 4.3% (2.36%-7.75%) | 45/227 | 19.8% (15.16%-25.49%) | 68/208 | 32.7% (26.68%-39.33%) |
| Late per-rectal bleeding | 30/232 | 12.9% (9.21%-17.86%) | 81/228 | 35.5% (29.6%-41.93%) | 102/212 | 48.1% (41.48%-54.81%) |
| Late faecal incontinence | 2/231 | 0.9% (0.24%-3.10%) | 2/226 | 0.9% (0.24%-3.17%) | 3/200 | 1.5% (0.51%-4.32%) |
| Overall late rectal toxicities | 32/232 | 13.8% (9.94%-18.82%) | 84/228 | 36.8% (30.85%-43.27%) | 104/212 | 49.1% (42.4%-55.74%) |

Abbreviation: 95% CI = 95% confidence interval

TABLE 4. Association with grade ≥1 late proctitis: binary logistic regression

| | Univariable | | Multivariable* | |
|---|---|---|---|---|
| | OR (95% CI) | P value | OR (95% CI) | P value |
| Presence of acute rectal toxicities | 3.91 (2.17-7.06) | <0.001 | 4.47 (2.37-8.43) | <0.001 |
| Antiplatelet use | 1.86 (0.95-3.64) | 0.069 | 1.98 (0.95-4.14) | 0.070 |
| Age at radiotherapy (years) | 1.09 (1.02-1.16) | 0.011 | 1.11 (1.04-1.19) | 0.003 |
| V50 (%) | 1.02 (1.00-1.04) | 0.027 | - | - |
| V60 (%) | 1.03 (1.00-1.06) | 0.032 | - | - |
| V70 (%) | 1.09 (1.03-1.16) | 0.005 | 1.08 (1.01-1.15) | 0.027 |
| Rectal constraints (Ref: 1st criteria) | | | | |
| 2nd criteria | 1.69 (0.81-3.55) | 0.163 | - | - |
| 3rd criteria | 2.56 (1.09-5.98) | 0.031 | - | - |
| Dmax (Gy) | 1.40 (0.95-2.07) | 0.089 | - | - |

Abbreviations: 95% CI = 95% confidence interval; OR = odds ratio

* Multivariable analysis using backward stepwise selection method with variables including presence of acute rectal toxicities, antiplatelet use, age at radiotherapy, V70, rectal constraints, and Dmax

medical conditions and pharmacological histories, and the relatively small sample size in our cohort may have influenced our conclusions regarding factors associated with overall late rectal toxicities and/or late proctitis.

Several dosimetric parameters and dose/volume histogram data (including V50, V60, and V70) were also associated with late proctitis, as in previous studies.[8] Our in-house rectal constraints did not demonstrate significant associations with the occurrence of proctitis (P=0.092). Notably, in the present study, the PTV dose was associated with overall late toxicities, but not with late proctitis specifically. Most patients received 70 Gy in this study; therefore, the effects of PTV dose on complications were difficult to establish.

Regression analysis was used to predict the odds of late proctitis among patients in our study. As shown in Table 4, higher V70, older age, and the presence of acute rectal toxicities were found to increase the odds of late proctitis. Poon et al[8] also reported similar findings concerning acute rectal toxicities; however, they did not find associations with V70 or age. The increased incidence of late proctitis in our study may have enhanced our ability to identify significantly associated factors. Nevertheless, both our present study and the study of Poon et al[8] demonstrated that patients with acute rectal toxicities during radiotherapy had higher incidences of late proctitis than patients without acute rectal toxicities. Similar results were reported by Fellin et al.[11] Taken together, the present and prior results indicate that the presence of acute toxicities is predictive for late proctitis. Clinicians should be vigilant and perform prompt investigations when patients with acute toxicities report any rectal symptoms during subsequent follow-up.

Theoretically, dosimetric parameters are expected to be associated with late proctitis. In our study, the dosimetric parameters exhibited modest associations with late proctitis. Notably, we did not find a significant association between our in-house rectal constraints and the occurrence of late proctitis. Fellin et al[11] demonstrated similar associations between late proctitis and V70, as well as other dosimetric parameters, in their cohort. This suggests that the presence of confounding factors may reduce the strength of associations with late proctitis. A notable factor is the inter-fractional variation of rectal and bladder filling; specifically, Miralbell et al[26] found that rectal filling was significantly associated with late rectal toxicities. Imaging-guided radiotherapy with inter-fractional bowel and bladder control has been suggested in accordance with the nomogram designed by Delobel et al[9]; this type of therapy could reduce the risks of acute and late rectal toxicities. In our study, there was no strict inter-fractional bowel or imaging control for bladder and rectal volumes during the course of IMRT. Although we found no statistically significant difference in the mean rectal volume during simulation computed tomography between patients with and without late proctitis, we could not retrieve the inter-fractional variation in rectal volumes for analysis in this study; this factor was also excluded from analysis in the study by Fellin et al.[11] Although identical instructions were provided to patients during simulation and treatment, inter-fractional variations may have been statistically significant. To further confirm whether dosimetric parameters are predictive of late proctitis, a prospective study is needed in which strict inter-fractional rectal and bladder control are performed, in combination with improved treatment verification strategies (eg, the use of cone beam computed tomography).

There were a few weaknesses in this study. First, this was a retrospective study in which incomplete reporting may have occurred and data might have been missing. Second, the small sample size and the low prevalences of some clinical factors and events may have affected the statistical power to determine associations between rates of complications and potential predictive factors (eg, use of anticoagulants and presence of inflammatory bowel disease). Third, confounding factors might have been present as mentioned earlier in the Discussion, and could not be controlled because of the retrospective nature of this study. However, this study did identify factors that clinicians could use to predict the occurrence of late proctitis. The significant association of V70 with late proctitis should be applied to radiotherapy planning, in that high doses to the rectal volume should be limited where possible.

In summary, late rectal toxicities were frequent among patients in this study in Hong Kong. The occurrence of late proctitis was associated with age, V50, V60, and V70; the occurrence overall late rectal toxicities was associated with a history of haemorrhoid, PTV dose, and V70. Multivariable regression analysis suggested that age, V70, and the presence of acute rectal toxicities could predict the occurrence of late proctitis. Clinicians should closely monitor patients for the occurrence of late proctitis if they exhibit these high-risk factors.

## Author contributions

All authors had full access to the data, contributed to the study, approved the final version for publication, and take responsibility for its accuracy and integrity.

Concept or design: BYH Ng, ACK Cheng.
Acquisition of data: BYH Ng.
Analysis or interpretation of data: BYH Ng, ELM Yu, TTS Lau.
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Critical revision for important intellectual content: BYH Ng, ELM Yu, KS Law, ACK Cheng.

## Conflicts of interest

All authors have disclosed no conflict of interest.

## Declaration

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## Ethics approval

This study was approved by the Kowloon West Cluster research ethics committee (Ref KW/EX-19-020(131-08)) and the requirement for patient consent was waived by the committee.

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