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FULL PAPER

The curative management of synchronous rectal and prostate cancer

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Objective: Neoadjuvant “long-course” chemoradiation is considered a standard of care in locally advanced rectal cancer. In addition to prostatectomy, external beam radiotherapy and brachytherapy with or without androgen suppression (AS) are well established in prostate cancer management. A retrospective review of ten cases was completed to explore the feasibility and safety of applying these standards in patients with dual pathology. To our knowledge, this is the largest case series of synchronous rectal and prostate cancers treated with curative intent.

Methods: Eligible patients had synchronous histologically proven locally advanced rectal cancer (defined as cT3–4Nx; cTxN1–2) and non-metastatic prostate cancer (pelvic nodal disease permissible). Curative treatment was delivered to both sites simultaneously. Follow-up was as per institutional guidelines. Acute and late toxicities were reviewed, and a literature search performed.

Results: Pelvic external beam radiotherapy (RT) 45–50.4 Gy was delivered concurrent with 5-fluorouracil (5FU). Prostate total dose ranged from 70.0 to 79.2 Gy. No acute toxicities occurred, excluding AS-induced erectile dysfunction. Nine patients proceeded to surgery, and one was managed expectantly. Three relapsed

with metastatic colorectal cancer, two with metastatic prostate cancer. Five patients have no evidence of recurrence, and four remain alive with metastatic disease. With a median follow-up of 2.2 years (range 1.2–6.3 years), two significant late toxicities occurred; G3 proctitis in a patient receiving palliative bevacizumab and a G3 anastomotic stricture precluding stoma reversal.

Conclusion: Patients proceeding to synchronous radical treatment of both primary sites should receive 45–50.4 Gy pelvic RT with infusional 5FU. Prostate dose escalation should be given with due consideration to the potential impact of prostate cancer on patient survival, as increasing dose may result in significant late morbidity. Review of published series explores the possibility of prostate brachytherapy as an alternative method of boost delivery. Frequent use of bevacizumab in metastatic rectal cancer may compound late rectal morbidity in this cohort.

Advances in knowledge: To our knowledge, this is the largest case series of synchronous rectal and prostate cancers treated with curative intent. This article contributes to the understanding of how best to approach definitive treatment in these patients.

INTRODUCTION

Prostate and colorectal cancers are the two most common cancers in males with 3014 and 1389 new cases diagnosed in Ireland per year, respectively. 23% of colorectal primaries are rectal in origin.¹ There are limited reports of the curative management of synchronous prostate and rectal

cancers. Neoadjuvant “long-course” chemoradiation (NACRT) and “short-course” external beam radiotherapy (EBRT) are considered standards of care in locally advanced rectal cancer.^{2,3} In addition to prostatectomy, EBRT and brachytherapy with or without androgen deprivation therapy (ADT) are firmly established in the treatment of

prostate cancer. A retrospective review of ten cases treated with radical intent was completed to explore the feasibility and safety of applying these standards to patients with synchronous dual pathology.

METHODS AND MATERIALS

Data were retrospectively collected from ten patients treated in three centres: St Luke's Radiation Oncology Network, Dublin; University College Hospital Galway; and Cork University Hospital, Dublin. For inclusion, all patients met the following criteria: dual diagnosis of locally advanced rectal (defined as cT3-4Nx; cTxN1-2) and non-metastatic prostate cancer (pelvic nodal disease attributed to prostate cancer permissible); both tumours histologically confirmed by an endoscopic rectal biopsy and either a trans-rectal or trans-perineal prostate biopsy; serum baseline prostate-specific antigen (PSA); clinical staging with digital rectal examination, rigid sigmoidoscopy, pelvic MRI (Figure 1); discussion at a multidisciplinary meeting and curative treatment delivered for both cancers simultaneously. Metastatic disease was excluded by isotope bone scan. MRI staging influenced overall staging if evidence of extracapsular extension or seminal vesicle (SV) invasion was detected. Patients were followed up according to institutional guidelines for both cancers. Patient toxicity during radiotherapy (RT) was assessed on treatment by medical and/or nursing staff and documented in medical notes and recreated retrospectively using the National Cancer Institute common terminology criteria of adverse events v. 4.0 grading sheets for both acute and late genitourinary and gastrointestinal toxicities. Metastatic relapse was determined on interval CT scanning of the thorax, abdomen and pelvis. Descriptive statistics were used to analyse the data in light of the retrospective nature of this review.

RESULTS

Patient characteristics and treatment details are summarized in Table 1. Median follow-up is 2.2 years from initial diagnosis (range 1.18–6.34 years). The median age in our patient cohort was 68 years (range 47–79 years). All cases had locally advanced rectal cancer. Patients 1 and 4 had low rectal tumours (0–5 cm from anal

verge). Patients 3, 5, 6, 9 and 11 had mid-rectal tumours (6–10 cm), and Patients 2, 7 and 8 had upper rectal tumours (11–15 cm). Patients 6 and 10 had low-risk prostate cancers as per the National Comprehensive Cancer Network risk stratification;⁴ Patients 2, 3 and 5 had intermediate-risk disease; Patient 9 had high risk; and the remainder very-high risk by virtue of clinical tumour stage (T stage) 3b disease (Patients 1, 4, 7 and 8). Median-presenting PSA was 13 ng ml^{-1} (range $1.79\text{--}82 \text{ ng ml}^{-1}$). Prostate histology revealed Gleason scores ranging from 5 (3 + 2) to 9 (5 + 4). Rectal biopsies showed grade 2 adenocarcinoma in all cases except for Patient 10 in whom high-grade dysplasia was seen. This was discordant with MRI appearances of the primary rectal cancer and is included in our cohort, as the multidisciplinary meeting concluded there to be adequate diagnostic information to safely assume this was an adenocarcinoma. Patients 1, 7, 8 and 9 were prescribed combined androgen blockade at diagnosis. Patients 1 and 7 were treated as node-positive prostate cancer, without histological confirmation, and were prescribed life-long ADT.

All patients were CT simulated in the supine or prone positions. When prone, additional immobilization was achieved with a bellyboard. The use of bladder filling or rectal preparation was not standardized across patients; bladder filling alone (Patients 6, 7 and 10), rectal preparation and bladder filling (Patient 1), neither specified (Patients 2, 4 and 5). No bladder filling or rectal preparation details were available for Patients 3, 8 and 9. Pelvic doses of 45–50.4 Gy in 1.8–2 Gy per fraction were prescribed. The total dose delivered to the prostate ranged between 70.0 and 79.2 Gy. An inverse planned intensity-modulated RT solution was adopted for Patients 4, 8 and 10. The remainder received three-dimensional conformal RT (CRT). The majority were treated in two phases; Phase I consisted of a pelvic nodal volume and Phase II encompassed the prostate with a margin (Figure 2a,b). Treatment was delivered in three phases for Patients 1, 4 and 6 and in five phases for Patient 8. In the case of Patient 8, EBRT was delivered in five “shrinking” phases. Planning target volume 1 (PTV 1) contained the pelvic nodal volume; PTV 2: the prostate, SVs and mesorectum plus margin; PTV 3: PTV2 excluding the mesorectum; PTV 4: the prostate and SV plus margin; and PTV 5: the prostate and SV excluding rectum. With one exception, patients received 5-fluorouracil (5FU) concurrent with pelvic radiotherapy. 5FU was omitted in the case of Patient 9 following an ischaemic cardiac event requiring angioplasty. Both infusional and bolus delivery of chemotherapy were used. For infusional regimens, 225 mg m^{-2} 5FU was prescribed. The alternative was a bolus regimen of 1 g given intravenously Days 1–4 in the first and last weeks of RT. Patients 1 and 8 received bolus 5FU. No grade 3 acute gastrointestinal (GI) or urinary toxicities were recorded apart from grade 3 erectile dysfunction in patients receiving ADT (Table 2).

Nine of the ten patients proceeded to surgery. Patient 8 declined surgery and had expectant management. The majority underwent anterior resection (AR). An abdominoperineal resection (APR) was performed for Patient 6. Patient 1 underwent pelvic exenteration involving rectal resection and cystoprostatectomy with formation of an intestinal urinary conduit 13 months post CRT. In the latter case, a residual rectal ulcer was

Figure 1. Sagittal reconstruction of a T_2 weighted MRI showing a rectal tumour (red arrow) and a prostate tumour (white arrow).

Table 1. Patient characteristics

Patient	1	2	3	4	5	6	7	8	9	10
Age (years)	47	73	78	66	61	65	56	71	79	70
TNM (R)	T3N2	T3N2	T3N1	T3Nx	T2N2	T3/4N1	T3N1	T3Nx	T3N2	T4N2
TNM (P)	T3bN1	T2cN0	TxN0	T3bNx	T1cN0	T1cN0	T3bN1	T3bNx	T1cNx	T2cNx
PSA	58	16.4	14.3	1.8	6.8	8.9	82	20	12.6	6
GS	9	6	3 + 4	3 + 4	3 + 4	2 + 3	9	9	9	6
Pelvis (Gy) ^a	50.4	50.4	45	50	50	50	46	45	50.4	50
Prostate (Gy) ^b	73.8	73.8	73.8	74	70	74	74	79.2	70.4	74
5FU	Bolus	Infusional	Infusional	Infusional	Infusional	Infusional	Infusional	Bolus	–	Infusional
ADT	+	–	–	–	–	–	+	+	+	–
Surgery	Ex	AR	AR	AR	AR	APR	AR	–	AR	AR
ypTNM	T3N0	T3N1	T3N0	T2N0	T2N1	T2N0	T3N0	–	T3N0	T4bN0
CT	–	FOLFOX	FOLFOX	–	FOLFOX	FOLFOX	FOLFOX	FOLFOX	FOLFOX	FOLFOX
Status	NED	M1/R	RIP/R	NED	M1/R	NED	M1/P	M1/P	NED	NED

5FU, 5-fluorouracil; ADT, androgen deprivation therapy; APR, abdominoperineal resection; AR, anterior resection; CT, adjuvant chemotherapy; Ex, exenteration; FOLFOX, folinic acid/fluorouracil/oxaliplatin; GS, Gleason score; M1/P, metastatic prostate cancer; M1/R, metastatic rectal cancer; NED, no evidence of disease; P, prostate cancer; PSA, prostate-specific antigen; R, rectal cancer; RIP/R, rest in peace metastatic rectal cancer; yp, pathological stage following neoadjuvant therapy.

^aDose prescribed to the pelvic nodal volume (Phase I).

^bDose delivered to prostate inclusive of all phases.

Figure 2. A dose distribution for a representative 2 phase plan displayed in colour wash. The 95% coverage of the Phase 1 and 2 volumes are shown in blue and red, respectively: (a) sagittal plane and (b) axial plane.

seen at the time of endoscopy following CRT. There was no histological evidence of residual malignancy on biopsy. The patient was deemed to have had a complete clinical response and was followed closely with serial lower GI endoscopies. He ultimately proceeded to salvage surgery upon detection of local recurrence. All surgical procedures yielded negative proximal and distal margins. Patient 3 had a close circumferential resection margin (1 mm). All except Patients 1 and 4 received adjuvant folinic acid/fluorouracil/oxaliplatin (FOLFOX) chemotherapy. During subsequent follow-up, five patients failed systemically. Patients 2, 3 and 5 developed pulmonary metastases of colorectal origin (histologically confirmed). Patient 3 failed with oligometastatic lung metastasis following a disease-free interval of 48 months and proceeded to metastectomy. The patient subsequently developed further lung and liver metastases and died from disseminated disease within 2 years of the initial presentation. Patients 7 and 8 developed sclerotic bone

metastases of presumed prostatic origin. This occurred after a period of non-compliance with adjuvant ADT in Patient 7. Patient 8 developed castrate-resistant disease during adjuvant ADT. Both of these patients had high-risk prostate cancer at the outset. In total, nine patients remain alive either with no evidence of disease (Patients 1, 4, 6, 9 and 10) or living with metastatic disease (Patients 2, 5, 7 and 8). Significant late toxicity is recorded for two patients. Patient 2 developed grade 3 proctitis. Of note, this patient received palliative bevacizumab. Rectal symptoms occurred during bevacizumab therapy 27 months post CRT and resolved 8 months following its discontinuation. Patient 3 developed a grade 3 anastomotic stricture 18 months post CRT precluding future stoma reversal.

DISCUSSION

Given the rarity of this presentation, past publications are limited to individual case reports and case series. To our knowledge, this is the largest case series of synchronous rectal and prostate cancers treated with curative intent. Two recent articles have discussed potential treatment paradigms incorporating RT in this rare cohort. Qiu *et al*⁵ at the Johns Hopkins (Baltimore, MD) have published a case series describing pelvic EBRT and brachytherapy boost in four patients with synchronous rectal and prostate cancers. Their cohort received 45–50.4 Gy to the pelvis followed by caesium-137 (¹³⁷Cs) implantation after a 4- to 5-week interval from the end of EBRT. Brachytherapy boosts ranged from 80 to 90 Gy. Rectal cancer surgery was performed after an interval ranging from 5 weeks to 2 months; all patients underwent AR. One patient experienced a grade 3 GI toxicity.⁵ Kavanagh *et al*⁶ published a treatment paradigm for all patients presenting with synchronous rectal and prostate cancers inclusive of those with metastatic disease at diagnosis. Five patients in their cohort received radical treatment; one patient had a prostatectomy followed by neoadjuvant CRT and AR; the remaining four patients were treated similarly to our cohort with shrinking field RT, chemotherapy and surgery with the only reported morbidity being post-operative wound infections in two patients. Siu *et al*⁷ in Stanford (Stanford, CA) have documented their management of two medically inoperable patients. One received CRT; 50.4 Gy with concurrent 5FU followed by a second phase delivering a total dose of 60.4 Gy to the prostate. The second patient received 45 Gy to the pelvis with a 20-Gy boost to the prostate. With 1 and 2 years follow-up, respectively, both patients were alive with PSA readings $<1.0 \text{ ng ml}^{-1}$ and no rectal cancer recurrence. Two further case reports document the delivery of multiple-phase neoadjuvant RT and concomitant 5FU, including the use of hypofractionated RT to the prostate. The patient treated with hypofractionation experienced grade 2 enteritis.^{8,9} Primary surgical management with radical retro-pubic prostatectomy and AR or APR has been described in two separate case series.^{10,11}

When faced with a patient with synchronous rectal and prostate cancers, the validity of treating both sites must be questioned on an individual patient basis. Many prostate cancers will not be clinically relevant in a patient's lifetime. For lower risk prostate cancers, older patients or where a patient's life expectancy is likely to be limited by a high-risk rectal cancer and/or

Table 2. Acute and late radiotherapy toxicity (maximum reported grade)

Patient	Acute	Late
1	G1 proctitis	Rectal ulceration
	G1 frequency/urgency	
2	No toxicity reported	Anastomotic stricture
3	No toxicity reported	No toxicity reported
4	No toxicity reported	No toxicity reported
5	G1 frequency/urgency	No toxicity reported
	G1 cystitis	
6	G1 diarrhoea	No toxicity reported
	G1 rectal pain	
7	G1 frequency/urgency	No toxicity reported
8	G1 proctitis	No toxicity reported
9	G1 hesitancy	No toxicity reported
	G1 urgency	
	G1 nocturia	
10	No toxicity reported	No toxicity reported

G1, grade 1 as per National Cancer Institute common terminology criteria of adverse events v 4.0.

comorbidities, it may be difficult to justify a prostate boost. Locally advanced rectal cancer in which NACRT is considered are by definition staged as IIIB for which reported 5-year overall survival (OS) is 30–60%. Disease-specific survival in low- and intermediate-risk prostate cancers ranges from 75% to 86% and 34% in high-risk disease.¹² Proceeding with neoadjuvant treatment of a rectal cancer in isolation without addressing the known prostate cancer could in the event of prostate cancer progression complicate further RT delivery. Salvage surgery would be challenging in a previously irradiated pelvis. Experience from salvage prostatectomy after EBRT for prostate cancer reports increased morbidity compared with primary prostatectomy, as tissue planes become difficult to traverse secondary to fibrosis and scarring. Two series report rates between 22% and 30% for bladder neck contractures and rectal injury as high as 25%.¹³ However, these considerations are tempered by the reality that a proportion of patients treated will relapse with metastatic rectal cancer.

Applying standards of care for rectal and prostate cancer in patients diagnosed with synchronous tumours is achievable with NACRT and a prostate boost. A prostate boost can be delivered by EBRT or brachytherapy. We recommend for appropriate patients proceeding to synchronous radical treatment of both primary sites that all patients should receive pelvic CRT with infusional 5FU as standard. Pelvic doses of 45–50.4 Gy in 1.8 Gy per fraction or 50 Gy in 2 Gy per fraction are feasible as demonstrated in our series.

Dose escalation to the prostate should be addressed with due consideration to the potential impact of prostate cancer on

patient's estimated OS and in the knowledge that increasing dose may result in significant late morbidity. An increased incidence of GI toxicity in higher dose groups has been reported in randomized control trials examining dose escalation in prostate cancer,^{14–16} and its incidence is strongly correlated to the volume of rectum receiving >70 Gy.¹⁵

Ultimately, GI toxicity is a function of technique, dose, treated volume and reported end point. A lower EBRT boost to the prostate would minimize GI toxicity because in the absence of a demonstrable OS benefit from dose escalation, it may be difficult to justify higher doses to the prostate in light of potential dose-dependent toxicity. Most importantly, we recommend that any prostate boost be considered and justified in light of patient age and comorbidity, likelihood of future metastatic rectal cancer and risk category of prostate cancer.

The potential for rectal toxicity resulting from the interaction between the high-dose boost region and (future) bevacizumab should be considered when planning synchronous strategies, especially for patients with higher-risk rectal cancer. This was doubtless the aetiology of rectal ulceration for Patient 2. In a prospective observational cohort study Sugrue et al¹⁷ noted previous pelvic radiotherapy as a baseline characteristic present in the majority of patients with metastatic colorectal cancer receiving bevacizumab plus first-line chemotherapy with evidence of GI perforation; however, this did not reach statistical significance.¹⁸ Investigators in the Mayo Clinic confirmed this risk of serious bowel injury (SBI) for patients receiving both RT and vascular endothelial growth factor inhibitor (VEGFI) therapy. In 76 patients treated with abdominal stereotactic body radiation therapy (SBRT) to a median dose of 50 Gy in 5 fractions only patients who had received VEGFI therapy before SBRT experienced SBI. A statistically significant correlation between SBI and VEGFI therapy within 3 months of SBRT was demonstrated.¹⁹ The majority of patients with metastatic rectal cancer will receive bevacizumab at some stage in their care, and this may compound late rectal morbidity.

Published series in prostate brachytherapy report late grades 2 and 3 GI complications ranging from 3.7% to 18% and <1–8%.²⁰ Therefore, following 50.4-Gy EBRT to the pelvis, a prostate brachytherapy boost is an attractive treatment paradigm as reported by Qiu et al.⁵ ¹³¹Cs with a photon energy similar to iodine-125 but with a significantly shorter half-life of 9.6 days compared with 59.4 days may be an effective method of delivering a prostate boost in suitable patients, and with a shorter half-life, it is more favourable for pre-operative use. If ¹³¹Cs seeds are not available then iodine or palladium brachytherapy is not recommended. A technique not explored in case series to date is EBRT with a single-fraction high-dose-rate brachytherapy boost.²¹ This technique would remove the radiation protection hazard for surgeons and may reduce the delay in proceeding to surgery that was associated with seed implants.

Patient 3 experienced an anastomotic stricture. This may have been the result of an overlap with the high-dose region of the prostate boost. "Anastomotic Planning" should be undertaken in

consultation with the surgeon to determine the likely location of the anastomosis in relation to the high-dose region of the prostate boost. Clearly for patients who will require APR, there will not be an anastomosis, and this complication cannot occur.

CONCLUSION

EBRT for synchronous rectal and prostate cancers is relatively straightforward to plan and deliver. It appears to be well tolerated in the acute setting, but there is potential for significant late rectal morbidity. The required dose can be delivered to both tumour

sites by multiple-phase EBRT or EBRT and a brachytherapy boost. Not all patients benefit from delivery of the standard high dose to the prostate. Despite small numbers, our series highlights important considerations in this unusual cohort.

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