Author/s:
Kong, JC;Ryan, J;Akhurst, T;Ngan, SY;Michael, M;Tie, J;Warrier, SK;Heriot, AG

Title:
The predictive value of PET/CT for distant recurrences in locally advanced rectal cancer treated with neoadjuvant chemoradiotherapy

Date:
2021-12-01

Citation:
Kong, J. C., Ryan, J., Akhurst, T., Ngan, S. Y., Michael, M., Tie, J., Warrier, S. K. & Heriot, A. G. (2021). The predictive value of PET/CT for distant recurrences in locally advanced rectal cancer treated with neoadjuvant chemoradiotherapy. Journal of Medical Imaging and Radiation Oncology, 65 (7), pp.917-924. https://doi.org/10.1111/1754-9485.13315.

Persistent Link:
https://hdl.handle.net/11343/298877

DR. JOSEPH CHERNG KONG (Orcid ID : 0000-0002-1392-2480)

Article type : Original Article

The predictive value of PET/CT for distant recurrences in locally advanced rectal cancer treated with neoadjuvant chemoradiotherapy

Joseph C. Kong, MBChB, FRACS, PhD,[1,5-6]* Jennifer Ryan, FRACS, MS,[1,6]* Timothy Akhurst, MD,[4] Samuel Y. Ngan, MBBS, FRANZCR,[3,6] Michael Michael, FRACP, MD,[2,5-6] Jeanne Tie, MBChB, FRACP, MD, [2,5-7] Satish K Warrier, MBBS, FRACS, MS,[1,5-6] Alexander G. Heriot, FRACS, MD,[1,5-6]

[1]Division of Cancer Surgery, [2]Division of Medical Oncology, [3]Division of Radiation Oncology, [4]Division of Nuclear Medicine and [5]Division of Cancer Research, Peter MacCallum Cancer Centre, Melbourne, Victoria, Australia

[6]Sir Peter MacCallum Department of Oncology, University of Melbourne, Parkville, Victoria, Australia

[7]Division of Prsonalised Oncology, Walter and Eliza Hall Institute of Medical Research, Parkville, Victoria, Australia

* JCK and JR are co-first authors and have contributed equally to this study

Correspondence to: Dr Joseph Cherng Kong, Division of Cancer Surgery, Peter MacCallum Cancer Centre, 305 Grattan Street, Melbourne, Victoria, 3000, Australia, e-mail: joekong@gmail.com

Reprint: Dr Joseph Cherng Kong, Division of Cancer Surgery, Peter MacCallum Cancer Centre, 305 Grattan Street, Melbourne, Victoria, 300, Australia, e-mail: joekong@gmail.com

Short running head: PET/CT long-term prognosis in rectal cancer

Disclaimer: We have no conflict of interest.

Source of support: None

Author's contribution

Contributions	**By which author**
Substantial contributions to the conception and design, acquisition of data, or analysis and interpretation of data	Joseph Kong Jennifer Ryan
Drafting and revising the article	All authors
Final approval of the version to be published	All authors

Appropriate category for the paper: Colorectal/anal neoplasia

Abstract

Background

It is well recognized that pathological complete response (pCR) for locally advanced rectal cancer after neoadjuvant chemoradiotherapy (CRT) confers a positive survival advantage. Despite this, a small proportion of patients can develop distant recurrence, and these are the patients that will likely benefit from adjuvant therapy. This study aims to investigate the role of PET/CT as a functional imaging to stratify patients according to their risk of distant recurrence.

Methods

This is a retrospective analysis of a prospectively maintained database in a single quaternary teaching hospital from 2010 to 2019. All consecutive cases of locally advanced rectal cancer with restaging PET/CT were included. The primary outcome measure was 5-year OS and distant recurrence free survival.

Results

A pCR and complete metabolic response (CMR) were identified in 47 (18%) patients and 73 (27.4%) patients respectively. Of these, 26 patients had both pCR and CMR and these patients remained free of local and distant recurrence at their last censored date. Patients with both pCR and CMR achieved the highest 5-year overall survival of 96.2%, followed by those with pCR and incomplete CMR (iCMR) of 85.7%, non-pCR and CMR of 85.1% and non-pCR and iCMR of 83.1%. Independent predictors for 5-year distant recurrence free survival were pathological and PET metabolic response, nodal staging and lymphovascular invasion (LVI).

Conclusion

In conclusion, a PET/CT has the potential to better stratify patients of their risk of distant metastasis. However, a larger validation cohort is required before these findings can be translated to clinical utility.

Introduction

The widespread adoption of standardized quality surgery and neoadjuvant CRT in the management of locally advanced rectal cancer has resulted in significant improvement in local recurrence rates.[1, 2] Although neoadjuvant treatment allows for locoregional control, an estimated 30% of patients develop distant metastases after a curative rectal cancer resection.[2] In order to mitigate the risk of distant metastases, various international guidelines recommend adjuvant chemotherapy for a total of 3-6 months for stage II/III rectal cancers irrespective of the response to neoadjuvant therapy.[3] Despite these recommendations the usage remains controversial, with studies demonstrating inconsistent benefits on long-term survival and risk of metastases.[4-6]

Current selection criteria for adjuvant chemotherapy are largely extrapolated from colon cancer studies, with high-risk features including lymph node positivity, lymphovascular invasion and/or advanced depth of invasion.[7, 8] However, recently the adjuvant oxaliplatin in rectal cancer (ADORE) trial reported significant 6-year disease-free survival (DFS) benefit of 68.2% favoring FOLFOX, compared to 56.8% in the 5-fluoracil and leucovorin arm. Their sub-group analysis also showed an improved in 6-year OS in the FOLFOX arm for patients with ypN2 and minimally regressed tumor.[9]

Although the ADORE trial showed a DFS benefit in high-risk rectal cancer patients, there remained doubt the benefits can be extrapolated to patients with pCR. Patients with pCR inherently has good OS and DFS. Moreover, subgroup analysis on those with pCR suggested no additional benefit from post-operative chemotherapy,[5] even though these patients have a risk of distant metastases as high as 11%.[10] It is likely that this small subset of patients (who had a pCR but suffers from distant failure) may benefit from additional therapy, the selection criteria remain elusive. A potential biomarker is PET/CT, a functional imaging modality that measures the intensity of fluorodeoxyglucose (FDG) uptake by tumor cells. A CMR following neoadjuvant chemoradiotherapy has been shown to be associated with improved long-term survival and prognosis.[11, 12] Hence, the aim of this study is to evaluate the utility of the FDG-PET/CT as a functional imaging for identifying risk of distant recurrence, as a way to stratify patients (into high and low risk of distant metastasis) with good response to receive adjuvant chemotherapy.

Methods

A retrospective study from a prospectively maintained database was performed. All consecutive locally advanced primary rectal cancer (Stage II and III) or T2 rectal cancers that will likely need an abdominoperineal resection at a quaternary teaching hospital between January 2010 and December 2018 were identified. All data has been collected prospectively, and follow-up performed by research fellows as part of the translational research program in our institution. Routine pre- and post-CRT MRI and PET/CT were also performed before radical surgery.

The inclusion criteria were; i) completion of neoadjuvant CRT ii) had pre- and post-treatment PET/CT, iii) undergone total mesorectal excision (TME) for curative intent. Data collected prospectively were; sex, age, patient comorbidities (smoking history, peripheral vascular disease, ischemic heart disease, arrythmias, heart failure, stroke history, diabetes, renal function, chronic obstructive pulmonary disease, hypercholesterolemia), pre- and post-chemoradiation treatment staging by

Computerised Tomography (CT), Magnetic Resonance Imaging (MRI) and PET/CT, surgical approach, pathology, post-operative complications, local and distant recurrence.

All patients were treated with long course chemoradiotherapy consisting of 50.4 Gy in 28 fractions over 5 weeks with concurrent chemotherapy; either continuous infusion of 5-flurouracil, 225 mg/m^2 per day or oral capecitabine 1650 mg/m^2 per day throughout the patient's radiotherapy session. PET/CT acquisition of images and processing were performed on a dedicated scanner (GE Discovery LS, GE Medical Systems, Milwaukee, WI) at a median of six weeks following the completion of neoadjuvant CRT. Images were acquired one hour after injection of approximately 400 MBq FDG with CT for attenuation correction and lesion localization. Bladders were generally catheterized, and a diuretic was administered to minimize urinary activity. Images were acquired from the neck to the upper thigh. A single nuclear medicine specialist blinded to the clinical response and prior to histological examination determined metabolic response. Qualitative analysis of metabolic response was determined from visual inspection of images according to a binary visual scale of complete response or incomplete response. CMR was defined as no identifiable activity in all previously defined sites of ^{18} FDG activity or where ^{18} FDG uptake was indistinguishable from or less than any diffuse bowel activity immediately adjacent to the original site of uptake on pre-treatment images and within the radiation treatment volume. For the purposes of this study, partial metabolic response, stable metabolic disease and progressive metabolic disease were combined and considered to be an iCMR.

Histological examination was performed by a specialist gastrointestinal pathologist, blinded to radiological response. A pathological complete response was defined as complete regression with absence of residual cancer cells. For a patient to be classified as a pCR, a complete response had to be achieved in both the primary tumor and lymph nodes (T0N0). Histological assessment of response was performed at a median of 10 weeks following the completion of neoadjuvant CRT.

The American Joint Committee on Cancer (AJCC) fifth edition was used for TNM staging due to the historical nature of the database (initiated back in 2010). Length of follow up, time to recurrence, DFS and OS were calculated in years from date of surgery. Patients who were free from local and/or distant recurrence at the time of last contact had their time to recurrence censored at this date. Patients who died were censored at their death date. Patients alive at the last contact date had their survival time censored at the date of last contact.

The primary outcome measure was to assess the predictive value of pCR (from histological assessment) and CMR by PET/CT for 5-year OS and 5-year distant recurrence free survival. Hence, a 5-year Kaplan Meir survival curve and log rank test were performed; initially comparing PET response alone followed by further stratification in accordance to both histological and PET response which yield four groups: pCR and CMR, pCR and iCMR, non-pCR and CMR and non-pCR and iCMR. Pearson chi-square was performed to compare the four groups.

Following this, a multivariate Cox regression analysis was performed for both 5-year OS and distant recurrence free survival in order to eliminate any confounders and to determine whether both histological and PET responses as a group remained a significant independent predictor. A p-value of <0.05 was considered significant. All statistical analysis was performed using the IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp.

Ethics approval was obtained from Human Research Ethics Committees at Peter MacCallum Cancer Centre.

Results

There were 319 consecutive locally advanced primary rectal cancer identified from the rectal cancer database. Of these, 266 patients (83.4%) were included into the final

analysis as 25 patients did not receive neoadjuvant chemoradiotherapy, 14 were deemed inoperable, nine had incomplete neoadjuvant therapy and five did not have restaging PET/CT. The median follow-up was 5.5 years (range 0.4-16.4 years).

The baseline patient characteristics are shown in Table 1. A pCR (T0N0) was confirmed in 47 patients (17.7%), with an additional four patients who had complete response only in their primary tumour but not nodal basin (T0N+, Stage III). In those with pCR, 26 (9.8%) had CMR and 21 (7.9%) had iCMR. Altogether, there were 73 (27.4%) who had CMR. A total of 178 patients (66.9%) completed adjuvant chemotherapy, with 26 (9.8%) local recurrences and 39 (14.7%) distant metastases.

In the assessment of long-term survival according to histological and metabolic response, those with pCR had a 5-year OS of 91.5% compared to 83.6% for those with non-pCR (p=0.259) whereas those with CMR had a 5-year OS of 89% compared to 83.4% for iCMR (p=0.042, see Figure 1a). Similarly, there was statistical difference seen between CMR and iCMR for 5-year distant recurrence free survival (p=0.005) as shown in Figure 1b.

Patients with both pCR and CMR achieved the highest 5-year overall survival of 96.2%, followed by those with pCR and iCMR of 85.7%, non-pCR and CMR of 85.1% and non-pCR and iCMR of 83.1% (see Table 2 and Figure 2(a)) but did not reach statistical significance. Despite the lack of difference in 5-year OS, those with both pCR and CMR did not develop any local or distant recurrence after a median follow-up of 7.8 years (range 2.2 to 16.4 years) for this cohort. This had translated to a significant difference in 5-year distant recurrence free survival as shown in Figure 2(b) but not 5-year OS (p=0.167, see Figure 2(a)).

Independent predictors for 5-year distant recurrence free survival (see Table 3) were increasing combined pathological and metabolic responses on histology and PET/CT with a hazard ratio (HR) of 2.17 (95% CI 1.13-4.18, p=0.021), increasing nodal

staging (p<0.001) and lymphovascular invasion with a HR 2.39 (95% CI 1.24-4.6, p=0.009).

Discussion

The current non-randomized data from a quaternary hospital, highlights the role of PET/CT as a functional measure of tumour response. It shows that if a patient had a CMR, they would have a low risk of distant recurrence which is comparable to those with pCR. Furthermore, patients with both pCR and CMR harbor an almost negligible risk of local recurrence or distant recurrence. Although no statistically significant difference was identified in 5-year OS, it is clinically significant as shown in significant difference in 5-year distant recurrence free survival.

The "watch and wait" strategy has increasing being reported in the literature since its inception by Habr-Gama in 2004.[13] It is a strategy that spares low rectal cancers from radical surgery, therefore avoiding the immediate adverse events after surgery, the functional consequence of rectal surgery and most important to a patient, the ability to avoid having a permanent stoma. However, the clinical assessment to determine a patient had clinical complete response where there is no identifiable tumour on endoscopy and imaging has a risk of regrowth of approximately 30%.[14]

One of the imaging modalities that has been investigated is the PET/CT, to assess its accuracy in predicting pCR. It has been shown by the pioneering Brazilian group for "watch and wait", clinical assessment alone had an accuracy of 91% but with the addition of PET/CT; it can improve the accuracy to 96%.[15] Others has not shown a consistent accuracy between PET/CT and pCR including this study.[16]A number of reasons has been postulated for the false negative result, which includes shrinkage of tumour volume, an inherent decrease in metabolic activity after treatment or histology consistent with mucinous subtype.[17] Despite the lack of clinical short-term prediction,

it does however help prognosticate and gives a guide to the risk of recurrence and long-term survival.

In our study, the ability to predict an improvement in long-term survival was boosted if patients had concurrent CMR on PET/CT. The 26 patients who had both pCR and CMR remained disease free during follow up (median >5 years) with neither local nor distant recurrence. Moreover, there were twelve patients who did not receive adjuvant chemotherapy and remained disease free to date. These findings likely reflect good tumor biology. Such a finding can be informative, as there is currently no consensus on the role of adjuvant chemotherapy after neoadjuvant CRT and surgery.

Two meta-analyses investigating this,[18, 19] found administrating chemotherapy after surgery for all patients irrespective of histological response of limited survival benefit. Other authors have investigated the role of adjuvant chemotherapy in those with pCR and found the patients who will benefit the most are those who had positive nodal staging before neoadjuvant treatment.[5, 18] Nonetheless, the current recommendation by National Comprehensive Cancer Network is to advocate adjuvant chemotherapy for patients with pathological stage II and III rectal cancers.[20]

Our results can potentially allow clinicians to tailor adjuvant treatment based on response to neoadjuvant chemoradiotherapy. As shown, the combination of a pCR and complete metabolic response on PET/CT may provide additional prognostic information to stratify the use of adjuvant chemotherapy and therefore avoid the potential toxicity associated with chemotherapy of limited benefit. Conversely, nearly 20% of the patients who had no evidence of pCR and CMR suffered from distant metastasis. Therefore, it is in this subset of patients that will most likely benefit from chemotherapy. It is still uncertain the clinical implications of those with pCR without CMR or non-pCR with CMR, with equivalent risk of distant metastasis of approximately 9% in those groups as the numbers are small and a larger sample is required to gauge the true long-term effect.

There were several limitations to this study, such as the retrospective nature of the analysis, the small number of patients with both pathologic and metabolic complete response, the small number of distant metastasis in both pCR and CMR group and even lower number of patients who did not receive adjuvant chemotherapy to make any firm conclusions. Moreover, the interval time from the patients' last dose of chemoradiation to performing PET/CT can be a confounding factor that may mask the true effects of tumour response. Despite this, it did identify a novel finding that may be clinically relevant to assist in decision making regarding adjuvant chemotherapy. However, this finding needs to be validated with a larger cohort of patients.

In conclusion, restaging PET/CT has the potential to better stratify patients on their risk of distant metastasis. Further clinical research is required to further validate these positive findings.

Figure legend

Table 1: Patient, tumour staging and treatment characteristics

Table 2: Long-term survival outcomes stratified according to histological and functional (PET/CT) response

Table 3: Multivariate cox regression analysis for Stage I-III rectal cancer

Figure 1: Kaplan Meier survival curve for a) 5-year OS (p=0.042) and b) 5-year Distant Recurrence Free Survival (p=0.005) based on PET response after neoadjuvant chemoradiotherapy

Figure 2: Kaplan Meier survival curve for a) 5-year overall survival (p=0.167) and b) 5-year distant recurrence free survival (p=0.015) based pathological and metabolic PET/CT response after neoadjuvant chemoradiotherapy

Reference

[1] Heald RJ. The 'Holy Plane' of rectal surgery. *Journal of the Royal Society of Medicine*. 1988; 81:503-8.

[2] Sauer R, Becker H, Hohenberger W, et al. Preoperative versus postoperative chemoradiotherapy for rectal cancer. *The New England journal of medicine*. 2004; 351:1731-40.

[3] Poulsen L, Qvortrup C, Pfeiffer P, Yilmaz M, Falkmer U, Sorbye H. Review on adjuvant chemotherapy for rectal cancer - why do treatment guidelines differ so much? *Acta oncologica (Stockholm, Sweden)*. 2015; 54:437-46.

[4] Sun Y, Wu X, Zhang Y, et al. Pathological complete response may underestimate distant metastasis in locally advanced rectal cancer following neoadjuvant chemoradiotherapy and radical surgery: Incidence, metastatic pattern, and risk factors. *European Journal of Surgical Oncology*. 2019; 45:1225-31.

[5] Lim YJ, Kim Y, Kong M. Adjuvant chemotherapy in rectal cancer patients who achieved a pathological complete response after preoperative chemoradiotherapy: a systematic review and meta-analysis. *Scientific reports*. 2019; 9:10008.

[6] Breugom AJ, van Gijn W, Muller EW, et al. Adjuvant chemotherapy for rectal cancer patients treated with preoperative (chemo)radiotherapy and total mesorectal excision: a Dutch Colorectal Cancer Group (DCCG) randomized phase III trial[†]. *Annals of Oncology*. 2015; 26:696-701.

[7] Gray R, Barnwell J, McConkey C, Hills RK, Williams NS, Kerr DJ. Adjuvant chemotherapy versus observation in patients with colorectal cancer: a randomised study. *Lancet*. 2007; 370:2020-9.

[8] Moertel CG, Fleming TR, Macdonald JS, et al. Levamisole and fluorouracil for adjuvant therapy of resected colon carcinoma. *The New England journal of medicine*. 1990; 322:352-8.

[9] Hong YS, Kim SY, Lee JS, et al. Oxaliplatin-Based Adjuvant Chemotherapy for Rectal Cancer After Preoperative Chemoradiotherapy (ADORE): Long-Term Results of a Randomized Controlled Trial. *Journal of Clinical Oncology*. 2019; 37:3111-23.

[10] Kong JC, Guerra GR, Warrier SK, et al. Prognostic value of tumour regression grade in locally advanced rectal cancer: a systematic review and

meta-analysis. *Colorectal disease : the official journal of the Association of Coloproctology of Great Britain and Ireland*. 2018; 20:574-85.

[11] Choi M, Kollepara SLS, Heilbrun LK, Smith D, Shields AF, Philip PA. PET scans as a predictive marker of survival in advanced colorectal cancer. *Clinical colorectal cancer*. 2015; 14:35-40.

[12] Okuno T, Kawai K, Koyama K, et al. Value of FDG-PET/CT Volumetry After Chemoradiotherapy in Rectal Cancer. *Diseases of the colon and rectum*. 2018; 61:320-7.

[13] Habr-Gama A, Perez RO, Nadalin W, et al. Operative versus nonoperative treatment for stage 0 distal rectal cancer following chemoradiation therapy: long-term results. *Annals of surgery*. 2004; 240:711-7; discussion 7-8.

[14] Kong JC, Guerra GR, Warrier SK, Ramsay RG, Heriot AG. Outcome and Salvage Surgery Following "Watch and Wait" for Rectal Cancer after Neoadjuvant Therapy: A Systematic Review. *Diseases of the colon and rectum*. 2017; 60:335-45.

[15] Perez RO, Habr-Gama A, Gama-Rodrigues J, et al. Accuracy of positron emission tomography/computed tomography and clinical assessment in the detection of complete rectal tumor regression after neoadjuvant chemoradiation: long-term results of a prospective trial (National Clinical Trial 00254683). *Cancer*. 2012; 118:3501-11.

[16] Ryan JE, Warrier SK, Lynch AC, Heriot AG. Assessing pathological complete response to neoadjuvant chemoradiotherapy in locally advanced rectal cancer: a systematic review. *Colorectal disease : the official journal of the Association of Coloproctology of Great Britain and Ireland*. 2015; 17:849-61.

[17] Flavell RR, Naeger DM, Aparici CM, Hawkins RA, Pampaloni MH, Behr SC. Malignancies with Low Fluorodeoxyglucose Uptake at PET/CT: Pitfalls and Prognostic Importance: Resident and Fellow Education Feature. *Radiographics*. 2016; 36:293-4.

[18] Petrelli F, Coinu A, Lonati V, Barni S. A systematic review and meta-analysis of adjuvant chemotherapy after neoadjuvant treatment and surgery for rectal cancer. *International journal of colorectal disease*. 2015; 30:447-57.

[19] Bujko K, Glimelius B, Valentini V, Michalski W, Spalek M. Postoperative chemotherapy in patients with rectal cancer receiving preoperative

radio(chemo)therapy: A meta-analysis of randomized trials comparing surgery +/- a fluoropyrimidine and surgery + a fluoropyrimidine +/- oxaliplatin. *European journal of surgical oncology : the journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology*. 2015; 41:713-23.

[20] Benson AB, Venook AP, Al-Hawary MM, et al. Rectal Cancer, Version 2.2018, NCCN Clinical Practice Guidelines in Oncology. *Journal of the National Comprehensive Cancer Network : JNCCN*. 2018; 16:874-901.

Table 1: Patient, tumour staging and treatment characteristics

Variables	n (%)
Sex	
Male	179 (67.3)
Female	87 (32.7)
Pre-operative Staging	
T1	1 (0.4)
T2	22 (8.3)
T3	164 (61.7)
T4	79 (29.7)
N0	62 (23.3)
N1	126 (47.4)
N2	78 (29.3)
Pre-operative MRI features	
Threatened CRM	50 (18.8)
EMVI positivity	46 (17.3)

Surgical Entry	
Open	146 (54.9)
Laparoscopic	64 (24.1)
Laparoscopic conversion to open	12 (4.5)
Robotic	44 (16.5)
Tumour site	
Upper	77 (28.9)
Mid	78 (29.3)
Low	111 (41.7)
PET CMR	
No	193 (72.6)
Yes	73 (27.4)
Pathological Staging	
T0	51 (19.2)
T1	13 (4.9)
T2	51 (19.2)
T3	116 (43.6)
T4	35 (13.2)

N0	181 (68)
N1	67 (25.2)
N2	18 (6.8)
AJCC Stage 0	47 (17.7)
AJCC Stage 1	52 (19.5)
AJCC Stage 2	82 (30.8)
AJCC Stage 3	85 (32)
CRM positivity	12 (4.5)
DRM positivity	2 (0.8)
Adjuvant therapy	
No	88 (33.1)
Yes	178 (66.9)
Total	266 (100)
Median follow up in years	5.5 (0.4-16.4)
Median time to local recurrence in years	1.3 (0.4-4.3)
Mean time to distant recurrence in years	1.4 (0.3-3.6)

CMR – complete metabolic response on PET/CT, pCR – pathological complete response, AJCC – American Joint Committee on Cancer, nCRT – neoadjuvant chemoradiotherapy

Table 2: Long-term survival outcomes stratified according to histological and functional (PET/CT) response

	pCR and CMR (%)	pCR and iCMR (%)	non-pCR and CMR (%)	Non-pCR and iCMR (%)	p-value
pT stage					
0	26 (100)	21 (100)	1 (2.1)	3 (1.7)	
1	0	0	5 (10.6)	8 (4.7)	
2	0	0	15 (31.9)	36 (20.9)	
3	0	0	24 (51.1)	92 (53.4)	
4	0	0	2 (4.3)	33 (19.2)	<0.001
pN stage					
0	26 (100)	21 (100)	25 (53.2)	109 (63.4)	
1	0	0	19 (40.4)	48 (27.9)	
2	0	0	3 (6.4)	15 (8.7)	<0.001
Adjuvant chemotherapy					
No	12 (46.2)	8 (38.1)	13 (27.7)	55 (32)	
Yes	14 (53.8)	13 (61.9)	34 (72.3)	117 (68)	0.397
Local recurrence					
No	26 (100)	20 (95.2)	43 (91.5)	148 (86)	
Yes	0	1 (4.8)	4 (8.5)	24 (14)	0.115

Distant recurrence					
No	26 (100)	19 (90.5)	43 (91.5)	139 (80.8)	
Yes	0	2 (9.5)	4 (9.5)	33 (19.2)	0.027
5-year survival	25 (96.2)	18 (85.7)	40 (85.1)	143 (83.1)	0.167

pCR – pathological complete response from resected surgical specimen, CMR – complete metabolic response from restaging PET, iCMR – incomplete metabolic response from restaging PET

Table 3: Multivariate cox regression analysis for Stage I-III rectal cancer

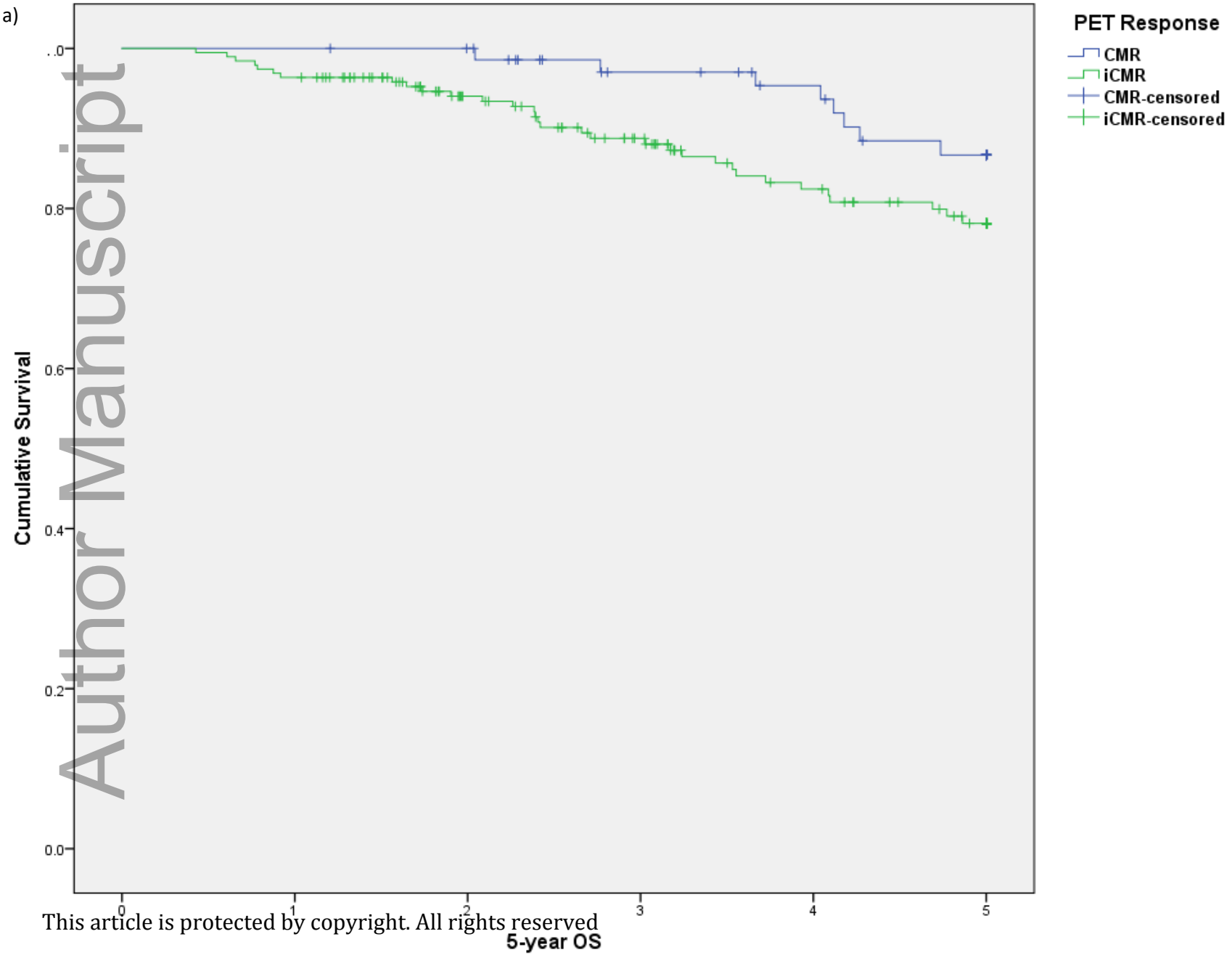
5-year Overall Survival			
pN stage	**Hazard ratio**	**95% confidence interval**	**p**
0	1		
1	2.99	1.46-6.12	
2	4.4	1.76-10.9	0.001
Lymphovascular invasion	2.51	1.28-4.94	0.008
5-year Distant Recurrence Free Survival			
Pathological and PET metabolic response *	2.17	1.13-4.18	0.021
pN stage			

0	1		
1	3.56	1.81-7.02	
2	5.91	2.42-14.4	<0.001
Lymphovascular invasion	2.39	1.24-4.6	0.009

* This is stratifying patients tumour response according to pCR and CMR, pCR and iCMR, non-pCR and CMR, non-pCR and iCMR

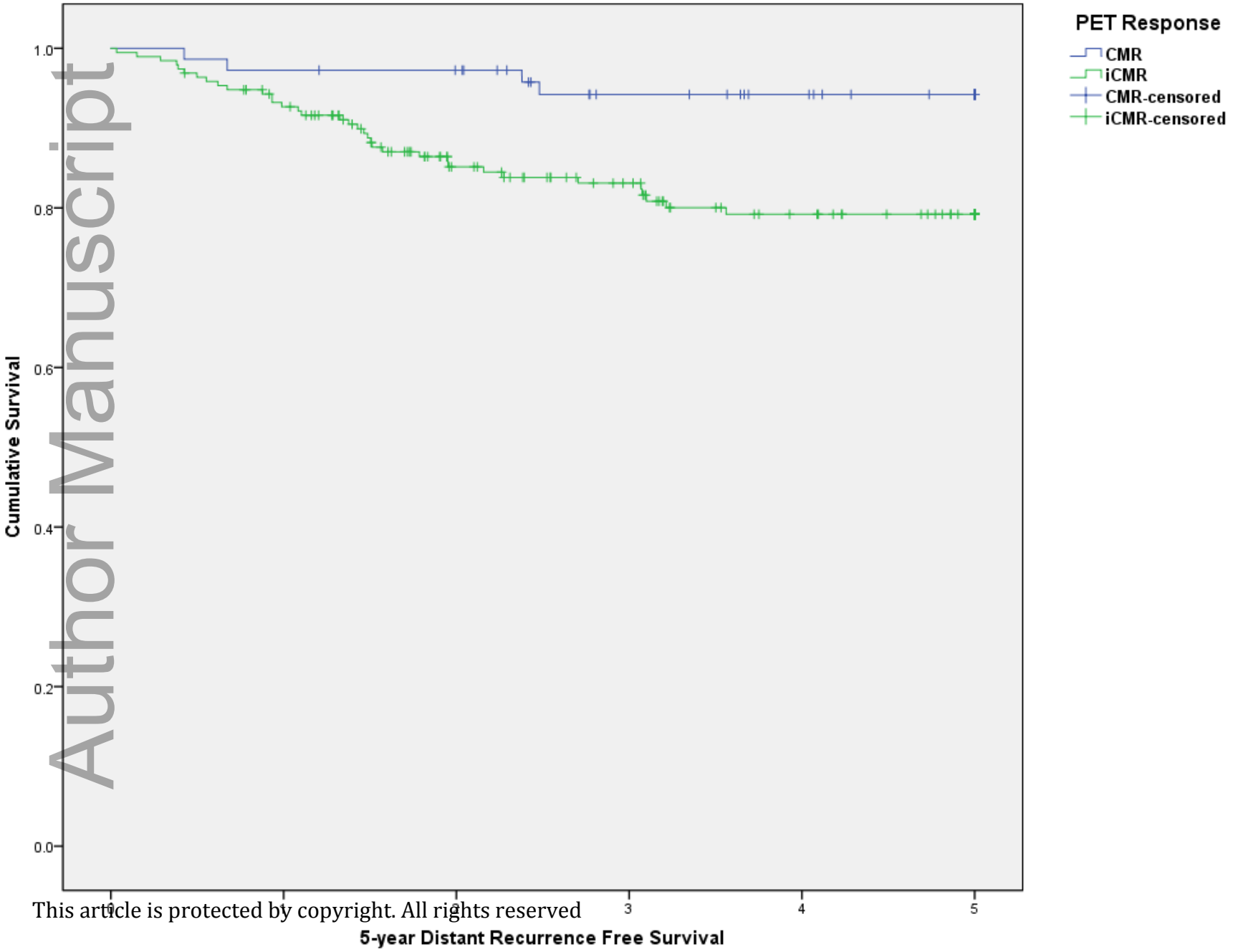
Figure 1: Kaplan Meier survival curve for a) 5-year OS (p=0.042) and b) 5-year Distant Recurrence Free Survival (p=0.005) based on PET response after neoadjuvant chemoradiotherapy

a)



No. at risk	1-year	2-year	3-year	4-year	5-year
CMR	73	71	63	59	57
iCMR	193	159	143	128	118

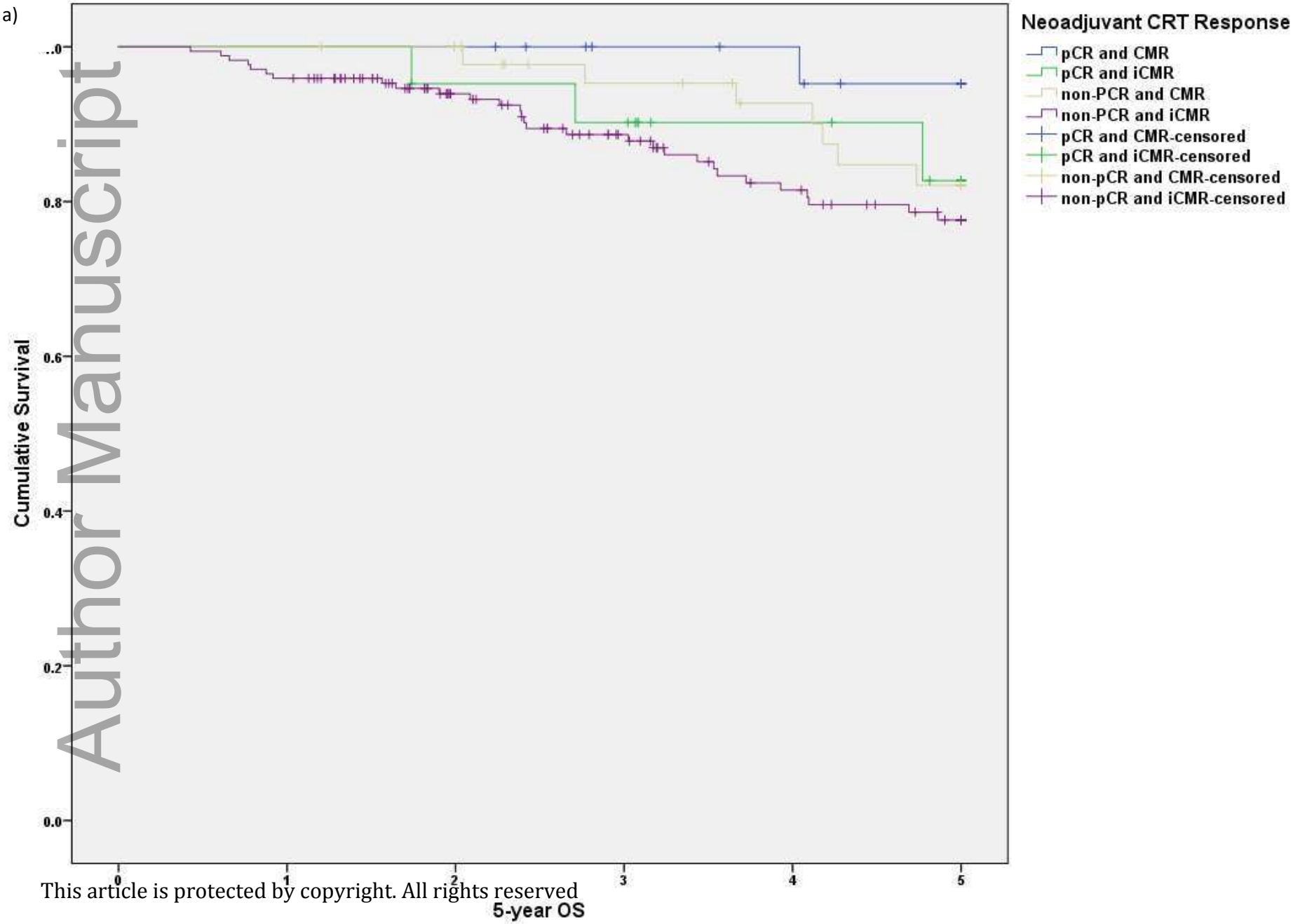
b)



No. at risk	1-year	2-year	3-year	4-year	5-year
CMR	71	69	59	54	52
iCMR	175	141	131	117	114

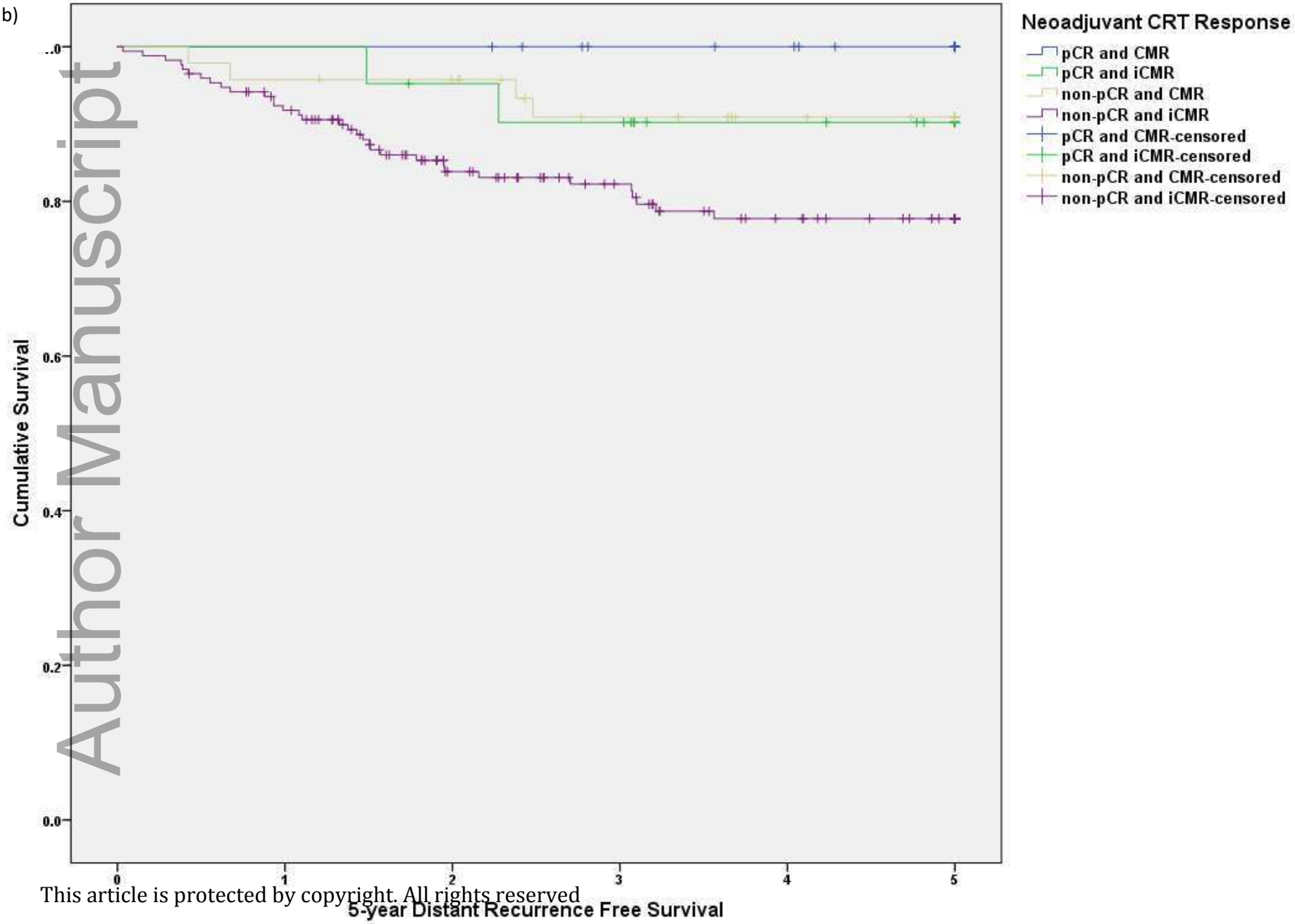
Figure 2: Kaplan Meier survival curve for a) 5-year overall survival (p=0.167) and b) 5-year distant recurrence free survival (p=0.015) based pathological and metabolic PET/CT response after neoadjuvant chemoradiotherapy

a)



No. at risk	1-year	2-year	3-year	4-year	5-year
pCR and CMR	26	26	22	21	19
pCR and iCMR	21	20	20	15	13
Non-pCR and CMR	47	45	41	38	38
Non-pCR and iCMR	172	139	123	113	105

b)



No. at risk	1-year	2-year	3-year	4-year	5-year
pCR and CMR	26	26	22	21	18
pCR and iCMR	21	20	20	15	12
Non-pCR and CMR	45	43	37	33	34
Non-pCR and iCMR	154	121	111	102	102

Abbreviations:
pCR – pathological complete response, CMR – complete metabolic response on PET, iCMR – incomplete metabolic response on PET