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ORIGINAL CONTRIBUTION

Re-resection of Microscopically Positive Margins Found on Intra-Operative Frozen Section Analysis Does Not Result in a Survival Benefit in Patients Undergoing Surgery and Intraoperative Radiation Therapy for Locally Recurrent Rectal Cancer

Short Running head: Intraoperative frozen section in recurrent rectal cancer

James Ansell, M.D.[1] • William R. G. Perry, M.B.Ch.B.[2] • Kellie L Mathis, M.D.[2] • Fabian Grass, M.D.[3] • Jennifer Yonkus, M.D.[2] • Christopher Hallemeier, M.D.[4] • Michael Haddock, M.D.[4] • Graham Rondell, M.B.B.S.[5] • Amit Merchea, M.D.[2] • Dorin T. Colibaseanu, M.D.[2] • Nitin Mishra, M.D.[2] • Scott R. Kelley, M.D.[2] • David W. Larson, M.D.[2] • Eric J. Dozois, M.D.[2]

1 University Hospital of Wales, Cardiff, United Kingdom

2 Division of Colon and Rectal Surgery, Mayo Clinic, Rochester, Minnesota

3 Chuv, Lausanne University Hospital, Lausanne, Switzerland

4 Division of Radiation Oncology, Mayo Clinic, Rochester, Minnesota

5 Division of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, Minnesota

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Correspondence: Kellie L Mathis, M.D., Division of Colon and Rectal Surgery, Mayo Clinic, 200 First St. SW, Rochester, MN. Email: Mathis.Kellie@mayo.edu

ABSTRACT

BACKGROUND: Intraoperative frozen section analysis provides real-time margin resection status which can guide intraoperative decisions made by the surgeon and radiation oncologist. For patients with locally recurrent rectal cancer undergoing surgery and intraoperative radiation therapy, intraoperative re-resection of positive margins to achieve negative margins is common practice.

OBJECTIVE: To assess if re-resection of positive margins found on intraoperative frozen section analysis improves oncological outcomes.

DESIGN: This is a retrospective cohort study.

SETTINGS: This study was an analysis of a prospectively maintained multicenter database.

PATIENTS: All patients who underwent surgical resection of locally recurrent rectal cancer with intraoperative radiation therapy between 2000 and 2015 were included and followed for 5 years. Three groups were compared: initial R0 resection (IR0), initial R1 converted to R0 after re-resection (IR1-R0) and initial R1 that remained R1 after re-resection (IR1-R1). Grossly positive margin resections (R2) were excluded.

MAIN OUTCOME MEASURES: The primary outcome measures were 5-year overall survival, recurrence-free survival, and local re-recurrence.

RESULTS: A total of 267 patients were analyzed (initial R0 resection n=94, initial R1 converted to R0 after re-resection n=95, initial R1 that remained R1 after re-resection n=78). Overall survival was 4.4 years for initial R0 resection, 2.7 years for initial R1 converted to R0 after re-resection and 2.9 years for initial R1 that remained R1 after re-resection (p=0.01). Recurrence free survival was 3.0 years for initial R0 resection and 1.8 years for both initial R1 converted to R0 after re-resection and initial R1 that remained R1 after re-resection ($p \leq 0.01$).

Overall survival did not differ for patients with R1 and re-resection R1 or R0 (p=0.62). Recurrence-free survival and freedom from local re-recurrence did not differ between groups.

LIMITATIONS: Heterogeneous patient population, restricted to those receiving intraoperative radiation therapy

CONCLUSIONS: Re-resection of microscopically positive margins to obtain R0 status does not appear to provide a significant survival advantage or prevent local re-recurrence in patients undergoing surgery and intraoperative radiation therapy for locally recurrent rectal cancer. See **Video Abstract** at http://links.lww.com/DCR/B886 .

LA RE-RESECCIÓN DE LOS MÁRGENES MICROSCÓPICAMENTE POSITIVOS ENCONTRADOS DE MANERA INTRAOPERATORIA MEDIANTE LA TÉCNICA DE CRIOSECCIÓN, NO DA COMO RESULTADO UN BENEFICIO DE SUPERVIVENCIA EN PACIENTES SOMETIDOS A CIRUGÍA Y RADIOTERAPIA INTRAOPERATORIA PARA EL CÁNCER RECTAL LOCALMENTE RECIDIVANTE

ANTECEDENTES: El análisis de la ténica de criosección para los margenes positivos encontrados de manera intraoperatoria proporciona el estado de la resección del margen en tiempo real que puede guiar las decisiones intraoperatorias tomadas por el cirujano y el oncólogo radioterapeuta. Para los pacientes con cáncer de recto localmente recurrente que se someten a cirugía y radioterapia intraoperatoria, la re-resección intraoperatoria de los márgenes positivos para lograr márgenes negativos es una práctica común.

OBJETIVO: Evaluar si la re-resección de los márgenes positivos encontrados en el análisis de la ténica por criosecciónde manera intraoperatorios mejora los resultados oncológicos.

DISEÑO: Estudio de cohorte retrospectivo.

AJUSTES: Análisis de una base de datos multicéntrica mantenida de forma prospectiva.

POBLACIÓN: Todos los pacientes que se sometieron a resección quirúrgica de cáncer de recto localmente recurrente con radioterapia intraoperatoria entre 2000 y 2015 fueron incluidos y seguidos durante 5 años. Se compararon tres grupos: resección inicial R0 (IR0), R1 inicial convertido en R0 después de la re-resección (IR1-R0) y R1 inicial que permaneció como R1 después de la re-resección (IR1-R1). Se excluyeron las resecciones de márgenes macroscópicamente positivos (R2).

PRINCIPALES MEDIDAS DE RESULTADO: Supervivencia global a cinco años, supervivencia sin recidiva y recidiva local.

RESULTADOS: Se analizaron un total de 267 pacientes (resección inicial R0 n = 94, R1 inicial convertido en R0 después de la re-resección n = 95, R1 inicial que permaneció como R1 después de la re-resección n = 78). La supervivencia global fue de 4,4 años para la resección inicial R0, 2,7 años para la R1 inicial convertida en R0 después de la re-resección y 2,9 años para la R1 inicial que permaneció como R1 después de la re-resección (p = 0,01). La supervivencia libre de recurrencia fue de 3,0 años para la resección inicial R0 y de 1,8 años para el R1 inicial convertido en R0 después de la re-resección y el R1 inicial que permaneció como R1 después de la re-resección ($p \leq 0,01$). La supervivencia global no difirió para los pacientes con R1 y re-resección R1 o R0 (p = 0,62). La supervivencia libre de recurrencia y la ausencia de recurrencia local no difirieron entre los grupos.

LIMITACIONES: Población de pacientes heterogénea, restringida a aquellos que reciben radioterapia intraoperatoria.

CONCLUSIONES: La re-resección de los márgenes microscópicamente positivos para obtener el estado R0 no parece proporcionar una ventaja de supervivencia significativa o prevenir la recurrencia local en pacientes sometidos a cirugía y radioterapia intraoperatoria para el cáncer de recto localmente recurrente. Consulte **Video Resumen** en http://links.lww.com/DCR/B886 .

(Traducción—Dr Daniel Guerra)

KEY WORDS: Frozen section; Pathological margins; Recurrent rectal cancer.

INTRODUCTION

Surgery for locally recurrent rectal cancer (LRRC) is technically challenging and carries a significant risk of morbidity.[1–5] An aggressive surgical approach is the only curative option and may require en-bloc resection of pelvic viscera, musculoskeletal and neurovascular structures.[5–12] In addition to surgery, a multi-modality approach that includes chemotherapy and external beam radiation has evolved to improve local control of disease and prevent distant metastases.[4,13,14] Several centers also utilize intraoperative radiation therapy (IORT) to the tumor bed to further reduce the risk of local re-recurrence in cases where the resection margin is close or positive.[12–15] The most important positive prognostic factor in patients undergoing surgery for LRRC is the ability to achieve a negative-margin (R0) resection.[2,6,7,11,12] Patients with R0 resection have been reported to survive, on average, 3.2 to 4.4 years longer than those with R1 or R2 margins respectively.[7] Given the evidence supporting the survival advantage of an R0 resection, some centers utilize intraoperative frozen section (IOFS) to assess margin status. If the initial resection is R1 (IR1) on IOFS, re-resection may be undertaken in an attempt to obtain a subsequent R0 margin. This re-resection, however, may introduce further risk of surgical complications.
As such, we aimed to assess whether re-resection of an IR1 margin to obtain R0 status conferred any oncologic benefit when IORT is utilized.

MATERIALS AND METHODS

Data source and study subjects

The Mayo Clinic recurrent rectal cancer database is a retrospectively collected electronic database of demographics, disease characteristics, treatment and outcome information for patients with LRRC who proceed to surgical resection. Following ethical approval from the

institutional review board, data from patients who underwent surgery and IORT for LRRC between 2000 and 2015 were analyzed.

This included demographic information, primary tumor TNM stage, exposure to initial external beam radiation therapy (EBRT) and chemotherapy for primary disease, age at time of first recurrence, time from original surgery to first recurrence, and location of recurrence. Location of recurrence was defined as central, lateral (iliac vessels, piriformis, obturator internus, lumbosacral plexus), anterior (uterus, bladder, vagina, prostate) and posterior (sacrum, sacral nerves), with further delineation by whether the recurrence was above or below the third sacral body (S3). All patients had prior resection of a primary rectal tumor within 12 cm of the anorectal verge. Tumor staging included CT chest, abdominal and pelvis, pelvic MRI, colonoscopy, and histologic confirmation of recurrence. All study participants received IORT. If deemed safe, patients found to have an R1 margin on IOFS underwent re-resection in an attempt to achieve a negative margin as describe in prior studies from our institution.[4] Patients were regularly followed up in the outpatient setting for 5 years, unless death occurred prior.

Intraoperative frozen section (IOFS)

Based on our standard practice protocol, frozen-section analysis is performed on all resected specimens. The operating surgeon brings the specimen to the pathology lab and orients the pathologist to the surgical specimen. The surgeon reviews areas of concern such as tethered sites so the at-risk margins can be clearly delineated and analyzed. The specimens are assessed macroscopically with determination of the gross distance between lesion(s) and the identified surgical margins. Tissue sections are then taken for histologic assessment of the margins and for confirmation of the diagnosis. The turnaround time for pathology to process, analyze and report the results to the surgical team is approximately 30 - 45 minutes. This quick turnaround is due to

the close proximity of the pathology lab to the operating room, experienced technicians and pathologists and prioritizing analysis when specimens come to the lab.

Tissue sections are submitted as per the lab-developed protocol initially published by Wilson with minor modifications to the freezing microtomes and the tissue stain.[16] In brief, the tissue is frozen using a freezing microtome with compressed Freon gas and sectioned at a 5-10 micron thickness. The section is then transferred to a water bath and stained with toluidine blue and after staining transferred to a glass slide for histologic review. Resection margins are then categorized as: R0 (tumor cells >1mm from the surgical resection margin), R1 (tumor cells at or within 1 mm, of the surgical resection margin), and R2 (tumor seen macroscopically at the surgical resection margin).

Intraoperative radiotherapy

Our treatment protocol for patients with LRRC is outlined in Figure 1 and includes neoadjuvant chemotherapy, EBRT and IORT. When criteria are met, IORT is delivered through circular or elliptical acrylic applicators as previously described.[13] In this series all patients received IORT due to close or positive margin status. The radiation dose given intraoperatively to the tumor resection bed was dependent on the margin status at the time of resection and follows the protocol outlined in prior studies,[13] negative but close margins were given 1000-1250 cGy, R1 margins were given 1250-1500 cGy and gross residual margins were given 1500–2000 cGy.

Primary and secondary outcomes

Three groups were compared: initial R0, IR1 that were re-resected to achieve R0 (IR1-R0) and IR1 where R0 was not achieved despite re-resection (IR1-R1). In all cases, the re-resection took place the time of the same operation following IOFS analysis. Primary outcomes measures were 5-year overall survival (OS), recurrence free survival and freedom from local re-recurrence.

Statistical analysis

Descriptive statistics were reported as median (interquartile range [IQR]) or mean ± standard error as appropriate for continuous variables and absolute or relative frequencies for categorical variables. Continuous variables were compared using the Student's *t* test; categorical variables through Wilcoxon (chi squared) test. Chi squared tests were used to assess tumor location with margin status. Survival comparisons were generated using the log-rank test and Kaplan-Meier estimates. Subgroup analyses are presented as risk ratios. A p value of < 0.05 was considered statistically significant. Data analysis was performed with the Statistical Software for the Social Sciences SPSS Advanced Statistics 22 (IBM Software Group, Chicago, IL, USA).

RESULTS

A total of 267 patients were included in this analysis, of which 189 (71%) ultimately received an R0 resection (R0 94 (35%), IR1-R0 n=95 (36%), IR1-R1 n=78 (29%)) (Table 1). Demographic data was comparable between all 3 groups for the vast majority of variables including age at time of tumor recurrence, time from original surgery to recurrence and distribution of primary tumor according to TNM grade. Patients in the IR1-R1 group were more likely to receive both EBRT and chemotherapy than those in the IR1-R0 and IR0 groups. Intraoperative frozen section analysis was concordant with permanent section analysis in all but 2 patients.

Tumor location and relation to S3 were not significantly associated with initial resection margin status (above or below S3 p=0.840, anterior p=0.209, posterior p=0.519, lateral p=0.232, central p=0.604). Similarly, for patients with IR1, re-resection margin status was not significantly associated with tumor location (anterior p=0.314, posterior p=0.208, lateral p=0.261, central p=0.693), although tumors located below S3 were more likely to have achieve an IR1-R0 re-resection compared to tumors located above (p=0.041. In the 95 patients who required re-

excision to achieve an R0 margin, 67 had no residual carcinoma in the resubmitted specimen and 18 had carcinoma present in the specimen but not at the new margin.

The probability of overall survival was significantly higher for patients with IR0 compared with those with IR1-R0 (p=0.02). Patients with IR1-R0 showed comparable survival outcomes to those with IR1-R1 (p=0.62) (Table 2, Fig. 2). Similarly, the probability of having no relapse in local or distant disease was significantly better for patients with IR0 compared with the IR1-R0 group ($p \leq 0.01$). When IR1-R0 patients were compared with IR1-R1, the chances of developing local or distal recurrence disease were however equivalent (p=0.14) (Table 2, Fig. 3). IR0 patients had the same probability of freedom from local re-recurrence as IR1-R0 patients (p=0.13). The IR1-R0 group also demonstrated similar freedom from local re-recurrence as IR1-R1 patients (p=0.15) (Table 2, Fig. 4).

Patients in the IR0 group had the best OS (5Y= 4.4) (Table 2). The IR1-R1 patients demonstrated equivalent survival to the IR1-R0 group (5Y OS of 2.9 and 2.7) (Table 2, Fig. 2). Similarly, IR0 (3.0 years) patients remained without local or distal recurrence for the longest period of time, followed by IR1-R1 (1.8 years) then, IR1-IR0 (1.8 years) patients (Table 2, Fig. 3).

DISCUSSION

This study aimed to determine whether re-resection of an IR1 margin to obtain R0 status conferred any oncologic benefit in a large cohort of patients undergoing surgery and IORT for LRRC. The key findings from our study were: 1) tumor location and whether or not the tumor was located above or below S3 did not impact initial resection margin status, 2) overall survival was significantly higher for patients with an IR0 resection compared with those who achieved R0 with re-resection (IR1-R0), 3) patients with IR1-R0 showed comparable survival outcomes to

those with IR1-R1, 4) the probability of having no relapse in local or distant disease was significantly better for patients with IR0 compared with the IR1-R0 group.

To our knowledge, there have been no studies evaluating whether or not re-resection of a positive margin in patients receiving IORT has a survival or local control benefit. IOFS analysis has been used in our practice for many years to assess tumor margin status in patients undergoing surgery for LRRC. The two ways this information is used at the time of surgery are 1) to plan re-resection of a positive margin, believing that a final R0 status would improve oncologic outcomes, and 2) to determine the role and dose of IORT, which is part of our standard multi-modality approach to patients with LRRC.

Our analysis showed that overall survival and recurrence-free survival was significantly better in the IR0 patients compared to those with an IR1-R0 resection. This finding has demonstrated that obtaining R0 on the first en-bloc resection attempt is critical to optimize oncologic outcomes and that surgeons cannot rely on re-resection to negative margins to achieve the same benefit obtained from IR0. Moreover, when the IR1-R0 patients were compared with IR1-R1 patients, the outcomes were equivalent for overall survival, recurrence free survival and freedom from local re-recurrence. These findings suggest that additional resection of IR1 margins to obtain R0 (in the presence of IORT) may not provide oncological beneficial and must be balanced with the risk of additional surgical resection.

Given a lack of comparable literature, these findings should be viewed in the context of IORT use. There is good data showing that the use of IORT benefits patients who have undergone R1 and R2 resections.[13] Although no randomized data is available, a previous Mayo Clinic series of palliative resection patients found that 3-year survival was 44% and local relapse 40% in R2 patients who received IORT compared to 15% 3-year survival and 93% local relapse in non-

IORT patients.[17] It is less clear whether or not patients undergoing an R0 resection benefit from IORT, as most series have similar outcomes for R0 patients whether IORT was given or not.[18–22] Given our results, we can speculate that the re-resection of an IR1 margin may not have impacted oncologic outcomes because the use of IORT in the persistent R1 patients had the same effect as re-resection due to low tumor volume being adequately treated by high doses of radiation. Moreover, the IR1 patients may represent a more complex group of patients with recurrence and are acting as a surrogate for worse outcomes due to other tumor and patient-related factors.

Given the results of this analysis, one might wonder if IOFS analysis adds any benefit in the setting of surgery for locally recurrent rectal cancer? Our view would be that it depends on whether IORT is being considered as part of the overall operative approach. The results of this analysis have not changed our protocol that includes the use of IOFS analysis. The reason is that in our practice, IOFS analysis determines whether there is a need for IORT, and if there is, what amount of radiation needs to be given to achieve a tumoricidal effect on any remaining tumor. Use and dosage of IORT are based on margin status – wide R0 (no IORT), R0 but close, R1, R2. Moreover, IOFS allows us to refine the IORT field by selecting the appropriate cone size for delivery. An additional benefit of IOFS analysis after face to face discussion and review of the specimen with the pathologist is that it avoids confusion that may come later when the pathologist reviews the specimen independently. We have heard from our pathologists that it can be very difficult for them to review a specimen without the input of the surgeon who removed it at the time of removal. Specimen orientation, review of regional anatomy and discussion of other factors may be lost with independent pathologist analysis. This project has made us wonder if delayed, permanent section analysis may be less accurate in terms of determining true margin

status for the reasons mentioned. If the pathologist is not oriented to the specimen by the surgeon, it can be very difficult to accurately analyze a specimen that has uneven surfaces, nooks, and ragged edges.

This study found that tumor location and relation to S3 were not significantly associated with initial resection margin status. This finding was interesting because although we don't have previous published data on location and R0 rates, our anecdotal experience, and those of others, is that pelvic sidewall tumors stand out as the most difficult group to achieve an R0 resection. This is our first look at our data related to IOFS analysis as it has not been analyzed it in this way previously and we admit that the *initial* R0 rate of 34% was concerning. There are many factors to consider when an R0 resection is not achieved (surgeon experience, patient goals of organ/nerve preservation, limitations of imaging, tumor factors, patient factors and many others). Following this project, we plan to further review our data/experience to determine what factors are significant and develop strategy around improving our initial R0 rates. Moreover, we intend to continue a prospective data collection to further define and clarify the roles for both IOFS and IORT. We have indeed changed our approach to lateral pelvic sidewall disease over the last decade which has been the most difficult area in the pelvis for our unit to achieve R0 resections. We now utilize a 2-stage posterior-first, then anterior approach, in most patients that have extensive sidewall disease. We have noted a higher rate of R0 resections using this modified approach. With 8 surgeons in the group doing these operations, we also need to better standardize our approach across the practice to imaging, operative planning, and intra-operative technique. We anticipate that this, combined with a focus on complete compartment resection, will lead to improved initial R0 rates similar to results described by Solomon and colleagues.[23]

When interpreting results of this study, the following limitations must be considered. First, the retrospective collection of data relies on several individuals for accurate records and thus we cannot exclude inherent bias. Second, factors aside from margin status may have influenced survival and recurrence outcomes in our cohort that are unaccounted for. Third, the impact of IORT on the results is unclear as there is no comparative non-IORT cohort. Finally, whether re-resection influences the risk of surgical complications is an important consideration, but was not specifically examined in this analysis.

In summary, IOFS analysis provides important information for surgeons and radiation oncologists when operating on patients with LRRC. One of the most significant findings is that IR0 is critical in optimizing oncologic outcomes and re-resection does not achieve the same results as IR0. Despite the limitations outlined above, we believe that the results of this retrospective review provide further perspective on the practice of re-resection of a tumor bed in patients undergoing surgery and IORT for LRRC that have an IR1 resection. Careful consideration should be made as to whether further re-resection of the tumor bed will improve oncologic outcomes. If R0 can be obtained by re-resection with minimal morbidity risk, it would seem reasonable to do so in attempt to maximize local control. However, re-resection could be omitted from the treatment paradigm of a patient that has an IR1 margin if it would lead to significant intraoperative risk or major permanent morbidity for the patient. Larger prospective studies or well conducted clinical trials are required to clarify the risks and benefits associated with re-resection of LRCC following IORT.

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LEGENDS

Figure 1. Multimodality neoadjuvant treatment regime.

Figure 2. Kaplan-Meier curve for overall survival including number at risk, red=R0, green=IR1-R0, blue= IR1.

Figure 3. Kaplan-Meier curve for recurrence-free survival including number at risk, red=R0, green=IR1-R0, blue= IR1.

Figure 4. Kaplan-Meier curve for local re-recurrence including number at risk, red=R0, green=IR1-R0, blue = IR1.

Demographics		R0 (N=94)	IR1 to R0 (N=95)	IR1 to R1 (N=78)
Mean age at original surgery (yrs.)		56.4	54.9	55.2
Gender (% F)		53.2	57.9	68.0
Primary Tumor				
Initial Staging of Primary Tumor (%)	T1	8.0	6.2	6.0
	T2	24.0	17.3	28.4
	T3	57.3	60.5	55.2
	T4	10.7	16.1	10.5
	N0	62.0	53.0	47.9
	N1	20.3	26.5	28.2
	N2	17.7	20.5	23.9
	M0	90.2	93.8	92.9
	M1	9.8	6.2	7.1
EBRT to primary tumor (%)		39.1	53.8	64.9
CT to primary tumor (%)		41.3	60.6	71.8
Recurrence				
Median age at 1st recurrence (yrs.)		44.7	46.3	50.0
Years from original surgery to 1st recurrence		2.0	2.2	2.4
Location (%)	Central	71.3	68.4	66.7
	Anterior	22.3	26.3	33.3
	Posterior	31.9	40.0	30.8
	Left lateral	19.2	22.1	28.2
	Right lateral	25.5	25.3	29.5
	Above S3	17.0	14.7	20.5
	S3 or below	91.5	93.7	85.9
Sites (%)	Central only	29.8	16.8	19.2
	1	45.7	55.8	43.6
	2	20.2	25.3	34.6
	3	4.3	1.0	1.3
	4	0.0	1.0	1.3

Table 1: Population demographics.

s, where, *Indicates significant values ($p<0.05$), EBRT test. NR represents data where ≤50% of patients have not reached the endpoint of interest and therefore, unable to calculate median value.

Table 2: Primary outcome and secondary outcome data presented as median values (95% CI), subgroup analysis presented using risk ratio (95% CI) and compared using Log Rank test. NR represents data where ≤50% of patients have not reached the endpoint of interest and therefore, unable to calculate median value.

Outcome		
Overall Survival	**Median Survival in years (95% CI)**	**P value**
All groups (R0, IR1-R0, IR1-R1)	R0 – 4.4 (3.1, 5.4) IR1-R0 – 2.7 (2.2, 3.3) IR1-R1 – 2.9 (2.3, 3.9)	0.0121
Overall Survival	**Risk Ratio (95% CIs)**	**P value**
R0 vs IR1-R0	0.7 (0.5, 0.9)	0.0227
R0 vs IR1-R1	0.6 (0.4, 0.9)	0.0052
IR1-R0 vs IR1-R1	0.9 (0.7, 1.3)	0.6203
Recurrence Free Survival	**Median Survival in years (95% CI)**	**P value**
All groups (R0, IR1-R0, IR1-R1)	R0 – 3.0 (2.2, 4.3) IR1-R0 – 1.8 (1.4, 2.2) IR1-R1 – 1.8 (1.5, 2.4)	0.0003
Recurrence Free Survival	**Risk Ratio (95% CIs)**	**P value**
R0 vs IR1-R0	0.6 (0.4, 0.8)	0.0015
R0 vs IR1-R1	0.5 (0.4, 0.7)	0.0002
IR1-R0 vs IR1-R1	0.9 (0.7, 1.3)	0.6001
Freedom from Local Re-recurrence	**Median Survival in years (95% CI)**	**P value**
All groups (R0, IR1-R0, IR1-R1)	R0 – NR (NR, NR) IR1-R0 – NR (NR, NR) IR1-R1 – NR (3.69, NR)	0.0100
Freedom from Local Re-recurrence	**Risk Ratio (95% CIs)**	**P value**
R0 vs IR1-R0	0.4 (0.2, 1.3)	0.1361
R0 vs IR1-R1	0.2 (0.1, 0.6)	0.0054
IR1-R0 vs IR1-R1	0.4 (0.2, 1.2)	0.1496

Figure 1

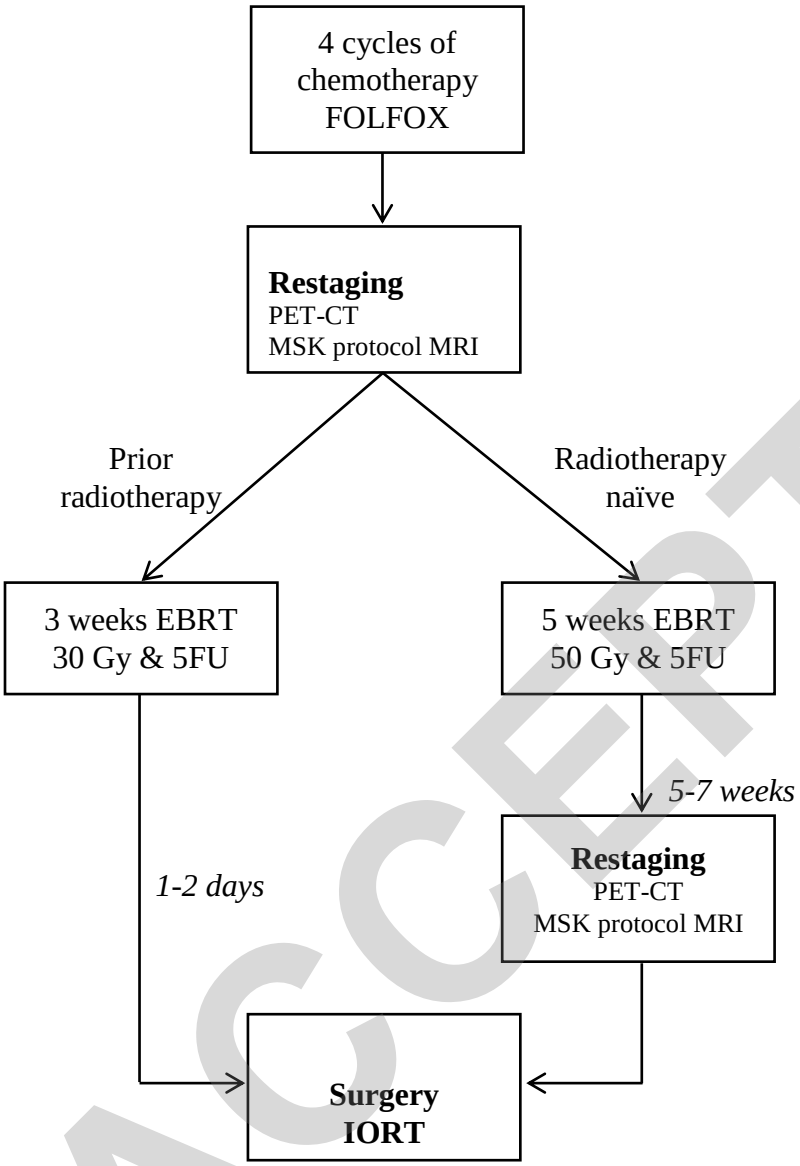

Figure 2

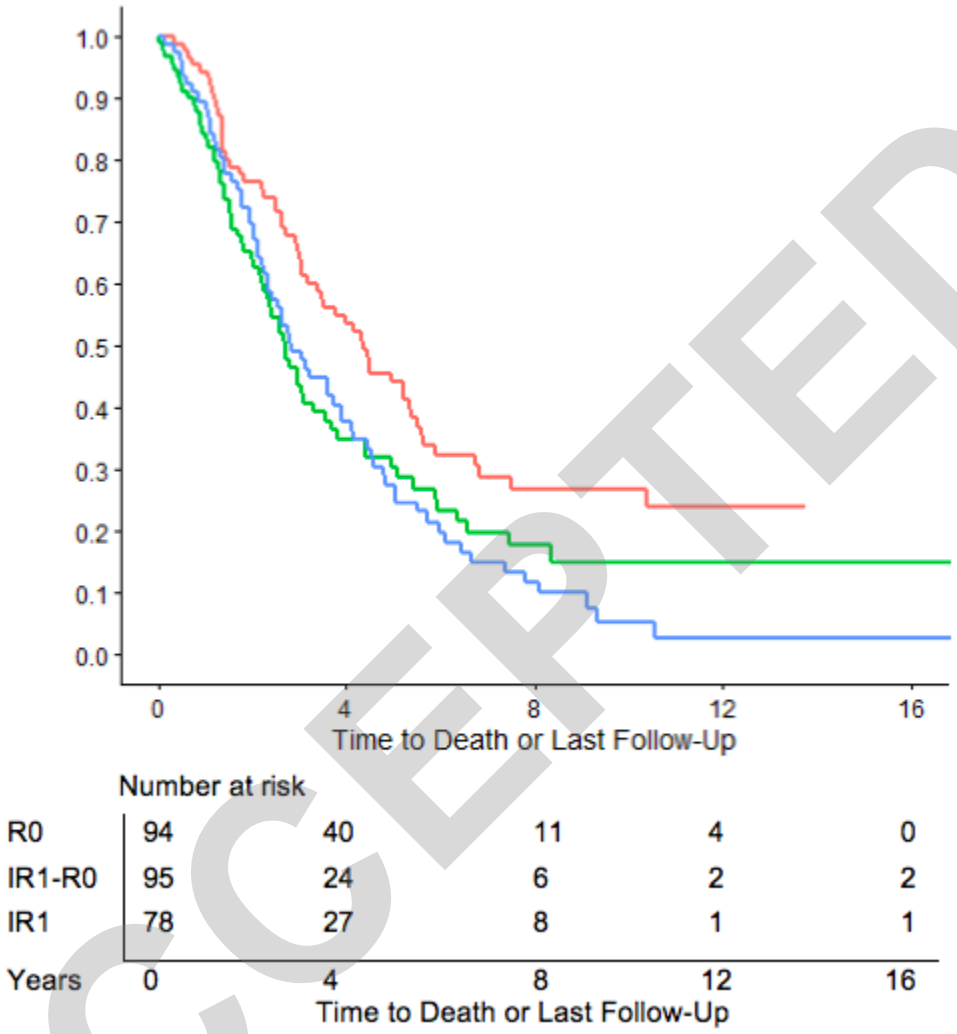

Figure 3

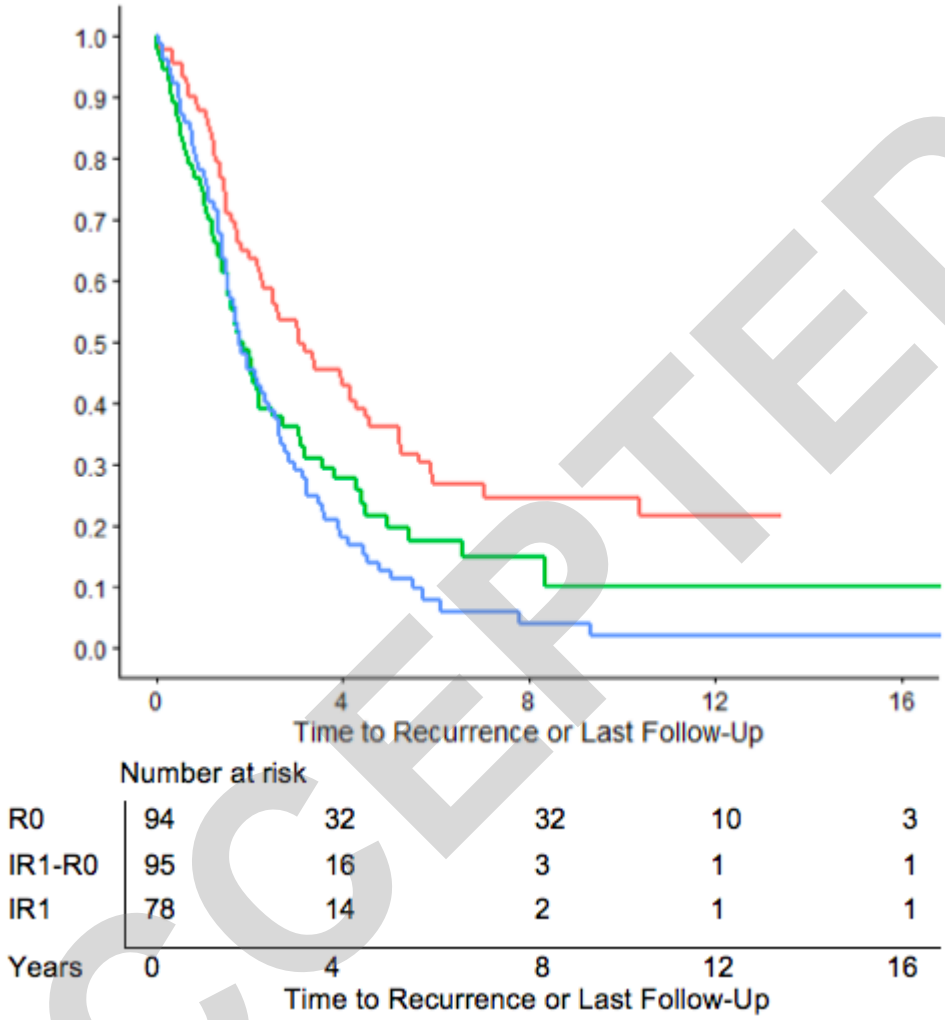

Figure 4