General discussion and future perspectives

Discussion

This thesis focused on several aspects to further improve locally advanced and recurrent rectal cancer management. During last decade, rectal cancer treatment has shifted increasingly towards a personalized treatment depending on the local tumor and the presence of distant metastases. A multimodality treatment can result in relatively good long-term outcomes for both LARC and LRRC. This thesis aimed to further improve the multimodality treatment in order to offer patients the best oncological care. Briefly, the first part of this thesis, focusing on staging, showed a beneficial effect of restaging by thoraco-abdominal CT-scan after (chemo-)radiotherapy. It resulted in newly discovered distant metastases altering treatment in a substantial number of patients. Unfortunately, the beneficial effect of adding DCE sequences to local restaging by MR imaging after (chemo-)radiotherapy was limited. The second part, which focused on LARC, suggested that applying IORT leads to improved local control in patients with a microscopically involved circumferential resection margin (CRM). Furthermore, the treatment of cT4 rectal cancer in high volume cT4 hospitals may lead to an improved overall survival, while the effect of the hospital volume in cT1-3 rectal cancer is limited. The third part, focusing on LRRC, demonstrated that patients with local recurrences after previous pelvic radiotherapy and TME surgery should also be considered candidates for curative surgery. Additionally, it showed that complete resections with close margins between 0-2mm have a poorer outcome than wider resection margins of >2mm and that the effect of systemic therapy on the local recurrence in previously irradiated area was limited.

The first part of this thesis focused particularly on restaging of patients with LARC after a long course of (chemo-)radiotherapy. Accurate staging is essential for high quality rectal cancer management. The accuracy of Magnetic Resonances (MR) imaging of tumor staging and CRM involvement is high in those who did not receive neo-adjuvant treatment. MR imaging can accurately differentiate between low tumor stage (T1-2) and high tumor stage (T3-4) with a high sensitivity of 87%.[1] Moreover, a specificity of 94% in CRM involvement shows that MR-imaging can accurately detect patients at risk for incomplete resections when performing a standard TME procedure. Given the knowledge that (chemo-)radiotherapy does not only leads to a reduced local recurrence rate, the fact that it leads to tumor downstaging made it interesting to reassess the local tumor extent after (chemo-)radiotherapy.[2,3] Potentially, these patients can be offered less radical resections in case of a good response to (chemo-)radiotherapy. Additionally, (chemo-)radiotherapy may lead to a complete pathological response (pCR). A pCR is seen in 11-19% of the patients after chemoradiotherapy.[4-7] Accurate determination of patients with a pCR may be valuable, because these patients can be offered a 'watch and wait' approach. In a 'watch and wait' approach, rectal cancer surgery is omitted and patients are closely surveilled. The results of close surveillance after a complete clinical

response are promising.[8-10] However, when considering applying a 'watch and wait' approach or performing less radical surgery, it is important to accurately stage rectal cancer after (chemo-)radiotherapy. For this reason patients, are increasingly restaged after neo-adjuvant (chemo-)radiotherapy. Unfortunately, the accuracy of restaging is poor. The sensitivity of differentiating between low tumor stage (T1-2) and high tumor stage (T3-4) tumor staging drops from 87% without neo-adjuvant therapy to 50% after (chemo-)radiotherapy.[1,11] Therefore, new techniques are necessary to accurately reassess the local stage or to predict a pCR. Dynamic Contrast Enhanced (DCE) sequences may improve the accuracy of MR restaging. Malignant tissue shows specific contrast-enhanced patterns due to the neoangiogenesis, resulting in elevated perfusion and permeability.[12] This may help in differentiating between malignant and non-malignant tissue. Unfortunately, adding DCE sequences did not improve accuracy of tumor restaging, CRM-involvement or predicting a pCR. The accuracy of Tumor staging (45%) was similar to other series without the addition of DCE sequences (34-60%).[13-18] Moreover, the accuracy of CRM-involvement was low and the radiologists were unable to detect a pCR. On the other hand, the accuracy of nodal staging was high. It is known that nodal staging after chemoradiotherapy is more accurate than at primary staging. This is caused by the lower prevalence of positive nodes, leading to a higher negative predictive value and thus a more accurate selection of the node negative patients after chemoradiotherapy.[19] Nonetheless, the accuracy of nodal staging in this study was high compared to other restaging studies. The fact early incomplete arterial phase enhancement was predictive for malignant nodes, makes DCE MR imaging promising for selecting patients for less radical surgery, such as Transanal Endoscopic Microsurgery (TEM) procedures. In TEM-procedures nodal staging is important to prevent local tumor regrowth due to positive lymph nodes, since a lymph node dissection is omitted in TEM procedures. Despite of the high accuracy of nodal staging, it is doubtful to carry out standard DCE MRI's in LARC restaging due to its poor accuracy of T- staging, CRM-involvement and predicting a pCR. MR imaging with extra DCE sequences is time-consuming and brings extra costs. The results of diffusion weighted (DW) MRI sequences are more promising. DW MRI has a sensitivity of 70% and a specificity of 98% in detecting a complete pathological response.[20] Future research should focus on the combining different MR techniques to increase restaging accuracy and on finding new tumor labeling agents to more accurately detect vital tumor. Furthermore, the optimal timing to perform restaging by MR imaging should be evaluated. It could be hypothesized that restaging shortly prior to surgery may improve diagnostic accuracy, because downstaging is an ongoing process after ending chemoradiotherapy.

Although the accuracy of local restaging after (chemo-)radiotherapy is generally poor, it is widely used as it seems to be a logical step in improving rectal cancer management. In line with local restaging, it also seems logical to restage by a thoraco-abdominal

CT-scan after chemoradiotherapy to detect distant metastases. Surprisingly, the number of studies concerning the effectiveness of local restaging are numerous, but studies assessing the usefulness of restaging by a thoraco-abdominal CT-scan after chemoradiotherapy are extremely rare. The chance of developing distant metastases is associated with the local tumor stage. LARC has the highest risk of developing distant metastases, since higher tumor and nodal stage are associated with distant metatases.[21-23] In LARC, the time interval between diagnosis and surgical resection is approximately 4 to 5 months. In this period occult metastases on primary imaging may become visible or new metastases may have evolved. Restaging could identify these patients. Our study found new metastases altering the treatment in 12% of the patients and surgery was cancelled in 8% of the patients. After publication of this study, other studies have reported their results of restaging to detect distant metastases during neo-adjuvant treatment. Even though new distant metastases were detected in all these studies, the reported percentages varied between 3 and 12%.[24-27] Some supported our findings concerning the usefulness of restaging to detect distant metastases[24]. However, others state that the yield was too low.[25,27] Davids et al.[25] found distant metastases in 5% of the restaged patients. Surprisingly, it did not lead to an alteration of the surgical plan. This is remarkable, as there are several options for patients with distant metastases opting for curation.[28] The fact that others studies did not find a beneficial effect of restaging by thoraco-abdominal CT-scan give room for a thought. Presumably, thoraco-abdominal restaging is only beneficial for patients with an advanced stage of disease. Our institute is a tertiary referral center for the Southwest region of Netherlands and this possibly explains the higher yield in our study compared to others studies with less advanced stage of disease. There are several well-known prognostic factors for developing distant metastases, such as T-, N-stage and extramural venous invasion.[21-23] These prognostic factors could identify patients at high risk for developing distant metastases during neo-adjuvant treatment. Future research should evaluate whether these prognostic factors are also applicable for the development of early distant metastases evolving during neo-adjuvant treatment. It would be interesting to develop a nomogram to select only those patients with a high chance of early metastases during neo-adjuvant therapy. This will save costs, radiation exposure and uncertainty concerning the curability of their disease.

Due to the fact that restaging is often common practice in most Western countries, it is important to critically appraise the benefit of local restaging. Theoretically, patients could be offered less radical surgery in case of tumor downstaging. However, as mentioned earlier, the accuracy of local restaging is poor.[1,11] Commonly, radiologists overstage rectal cancer after neo-adjuvant radiotherapy due to the difficulty to differentiate between viable tumor and fibrosis. However, 7-22% of the patients are understaged at restaging.[17,26,29] Surgeons should be cautious on performing less radical surgery based on

restaging imaging, as this could result in incomplete resections. Moreover, MR imaging is not able to detect microscopic remnants in radiotherapy induced fibrosis. Furthermore, it is important to realize that none of the Randomized Controlled Trials concerning the effect of chemoradiotherapy were able to demonstrate a significant increase in the rate of sphincter saving surgery.[30] This makes it even more doubtful to assume that restaging may contribute to less radical surgery when even chemoradiotherapy itself does not lead to less radical procedures. Momentarily, the 'watch and wait' is much debated as an option for patients with a complete clinical response. Unfortunately, MR imaging is unable to accurately identify patients with a complete clinical response.[31] However, when combining MR imaging with a digital examination and endoscopy, it leads to a probability of predicting a complete response of 98%.[32] This makes MR imaging an essential part of a set of examinations for a complete clinical response to be diagnosed. Restaging can be used as an early prognostic factor. Radiologically detected poor response is a strong prognostic factor for overall survival and disease free survival.[33] It should be evaluated whether these patients could benefit from a more intensified neo-adjuvant regime by adding an extra radiation boost or by adding induction chemotherapy after neo-adjuvant chemoradiotherapy. Furthermore, radiologically detected tumor response should be evaluated as a predictive factor for early distant metastases, since these patients may benefit from thoraco-abdominal restaging. Summarizing the current literature, there is limited evidence that local restaging is beneficial for patient or surgeon and there is conflicting literature that restaging by thoraco-abdominal CT-scan is useful to detect distant metastases. According to our data, restaging by thoraco-abdominal CT-scan is advisable.[34]

Even though rectal cancer management has improved drastically, patients remain with such advanced tumors, that complete resection is not possible. Incomplete resections are less common than 10 or 20 years ago due to the use of neo-adjuvant therapy and an improved surgical technique. However, CRM-involvement was still found in approximately 6% of the surgically treated patients in 2013 in The Netherlands.[35] Additionally, we are increasingly able to accurately select those patients at risk for incomplete resections. Intra-operative radiotherapy (IORT) may be beneficial when complete resection is not possible. IORT was first described in 1937.[36] Since the 1980s several institutes across the world published their experience with IORT.[37-39] The rationale behind IORT is that the biological equivalent of one single dose of IORT is two to three times higher than fractioned radiotherapy.[40] For example, an IORT dose of 10 Gy results in a biological equivalent of 20-30 Gy. This results in a total dose of 70-80 Gy when combined with a long course pre-operative radiotherapy of 50 Gy. This radiation dose cannot be achieved by external beam radiotherapy alone, since this would lead to extensive radiotherapy induced toxicity. The advantage of IORT is that an extra boost of radiotherapy can be administered at a specific area, while other radiotherapy sensitive structures, such as

small bowels, can be shielded from the radiotherapy. Previous studies have shown that IORT can be safely administered during surgery.[41,42] Although several studies suggested a beneficial effect of IORT on local control, comparative studies focusing on LARC and R1-resections are scarse. Our study suggests a beneficial effect on local control in patients with a microscopically involved CRM (tumor invading the resection planes on microscopic assessment), while no benefit was found in patients with a clear but narrow CRM (0.1-2mm). This finding is conform to previous studies from our institute.[43,44] The estimated 5-year local recurrence free survival of 84% in our study was higher than the local recurrence free survival rate of 65% reported in the previous study from our institute. This can be explained by the fact that our study only included R1-resections, while R2-resections were included in the previous studies as well. IORT is unlikely to be beneficial in R2-resections and these were therefore excluded from our analysis. Others studies have suggested a benefit of IORT on outcome, which is in line with our results,.[45,46] However, some did not find any evidence of a beneficial effect and skepticism about the effect of IORT remains.[47,48] Similar to our study, most published studies are retrospective with a relatively small amount of patients. This results in the lack of high level evidence of the benefit of IORT, making a future prospective randomized controlled trial necessary. Unfortunately, the accrual for such trial would be difficult. Since only R1-resections may benefit of IORT, solely 6% of all rectal cancer patients in the Netherlands would be candidates to participate in such trial. Moreover, results from retrospective studies indicate that it would be unethical to withhold IORT for patients with a R1-resection. Furthermore, incomplete resections are becoming less common due to the current high quality surgery.[35] Although our study focused on LARC, LRRC may also profit from IORT since incomplete resections are more frequent in LRRC surgery. Previously, others have found a benefit of adding IORT to the multimodality treatment compared to historical controls.[49]

Rectal cancer is a relatively common malignancy with approximately 3500 new patients in The Netherlands per year. However, there is a big difference between the treatment of the early stages of rectal cancer or the advanced stages of rectal cancer. Approximately 90% of the patients with rectal cancer are diagnoses with a cT1-3 stage.[50] These stages can be treated by a standard TME procedure. The treatment of the most advanced stage (cT4) is more difficult. Ingrowths into the surrounding structures are common in cT4 rectal cancer, such as prostate in men and vagina or uterus in women. In these cases exenterative 'beyond TME' surgery is often necessary to achieve complete resections.[51] These procedures are technically demanding and time consuming. Additionally, these procedures are accompanied by a high morbidity and a high post-operative complications rate.[52] Moreover, accurate high quality imaging is essential to determine the extent of the 'beyond TME-surgery'. These advanced stages may profit from a multidisciplinary team with experience in performing these radical surgical procedures. Our study

suggests a survival benefit for patients treated in high volume cT4 rectal cancer hospitals compared to low volume cT4 hospitals. This finding is in line with the results of studies of hospital volumes in other complex malignancies, such as pancreatic cancer and esophageal cancer.[53-55] However, in rectal cancer a survival difference according to the hospital volume has never been demonstrated. Although a recent study found a higher percentage of involved CRM's in low volume hospitals compared to high volume hospitals, a recent population based study for the Southern part of The Netherlands found no benefit of treatment of colorectal cancer in high volume hospitals.[50,56] The fact that we found a survival difference in contrast to other studies can be explained by that our study analyzed cT1-3 and cT4 separately. It is not naturally evident that experience in standard rectal cancer treatment also leads to sufficient experience for the treatment of the most advanced stages of rectal cancer. Our data suggests that cT4 rectal cancer should be considered as a separate entity within rectal cancer. Therefore, it would be more appropriate to apply a minimal number of cT4 rectal cancer patients treated per hospital annually than applying a minimal total number of rectal cancer patients per hospital.

The most appropriate approach for patients with stage IV colorectal with unresectable distant metastases is still under debate. It is clear that there is an indication for surgery in symptomatic patients. However, the indication is less clear in asymptomatic or mildly symptomatic patients. It could be hypothesized that surgery of the primary tumor will prevent future emergency surgery in case of obstruction or perforation during systemic therapy. Furthermore, some retrospective studies suggested a survival benefit when the primary tumor was resected.[57-59] However, these retrospective studies are limited due to selection bias. Patients in poor clinical condition were excluded for surgery, while relatively fit patients were selected for surgery. We assessed the current evidence for surgery of the primary tumor in patients with stage IV colorectal cancer. The lack of Randomized Controlled Trials, makes it difficult to conclude whether primary tumor resection leads to a survival benefit. Surgeons should take notice that systemic therapy will probably contribute the most to a prolonged survival in metastasized colorectal patients. Complications of primary tumor surgery will postpone the administering of systemic therapy.[60] For example, anastomotic leakage or surgical site infections will lead to a delay in the administering of systemic therapy. In addition, some patients will never be able to receive systemic therapy due to ongoing infectious complications. One of the most important goals of the treatment for incurable patients is to offer these patients the best possible quality of life. Surgery has a negative impact on quality of life up to 6 months after surgery.[61] The median survival of stage IV colorectal cancer patients in The Netherlands is only 12 months.[62] This median survival can be prolonged up to 22 months in patients who are in a good clinical condition due to the current systemic therapy.[63-65] Nevertheless, this means that these patients suffer a loss of quality of life caused by the surgical treatment during a substantial period of their life expectancy. Additionally,

complications after surgery have a long-term negative impact on the patients' quality of life.[66] Obstructive complications or tumor perforation during palliative systemic therapy are arguments to perform surgery. However, the chance of emergency surgery with the current systemic therapy is limited.[60,67,68] Nevertheless, high level of evidence is warranted to offer these patients the best treatment. Several Randomized Controlled Trials are recruiting patients, such as the SYNCHRONOUS trial[69], the CAIRO4 trial[70] and a Korean multicenter trial.[71] We are awaiting the results of these trials and hopefully, these studies will provide us the answer if we should perform primary tumor resection in case of unresectable distant metastases.

The introduction of TME and neo-adjuvant (chemo-)radiotherapy reduced the number of patients with a local recurrence after rectal cancer surgery. However, the introduction of these advancements also introduced the problem of treating LRRC after TME-surgery and radiotherapy. LRRC has a poor overall survival, a great impact on quality of life and often leads to severe pain with fistulating and bleeding tumors.[72,73] Surgical resection provides the greatest probability on durable overall survival and local control.[74] Unfortunately, TME surgery and neo-adjuvant radiotherapy makes surgical resection of the local recurrence more demanding. The dose of radiotherapy for the local recurrence is limited due to the previous pelvic radiotherapy and the use of TME surgery is causing that the local recurrences are no longer confined to an anatomic compartment. In agreement with most other studies, our results show that these local recurrences can be treated with acceptable overall survival and local re-recurrence rates. However, the complete resection rate seems to be lower in previously irradiated patients. Although this did not result in a higher re-recurrence rate in our series, others have reported higher re-recurrence rates in previously irradiated patients.[75,76] A recent study showed also a poorer overall survival and a higher complication rate in previously irradiated patients.[77] However, that study particularly did not administer re-irradiation to previously irradiated patients. This may explain the fact that our study did not find a survival difference while they did. The results of our study were in line with a previous study from our institute.[78] Although the local control rate in the previous study was poorer, the 3-year overall survival rate of the current and previous study were similar. Presumably, the results of the previous study led to a more thorough patient selection for LRRC surgery. Thorough patient selection is an important aspect of LRRC treatment, as morbidity and mortality rates of LRRC surgery are high.[77,79-81] However, if the selection of patients is too strict, an opportunity for curation for these patients may be suppressed. The selection of patients is one of the most important explanation of the overall survival differences of LRRC surgery reported in the literature. Re-irradiation might contribute to an improved outcome after LRRC surgery in a previously irradiated area.[75] The main goal is to induce tumor downstaging and to improve local control. However, it also provides an opportunity to restage these patients after the end of re-irradiation. Major abdominal surgery can be

spared in patients with a progressive local recurrence during re-irradiation or in patients who have developed distant metastases during re-irradiation. This could result in an improved patient selection for LRRC surgery. Future research in LRRC treatment should focus on achieving higher numbers of complete resections. For example, patients can be offered induction chemotherapy prior to neo-adjuvant therapy to maximize the chance of a complete resection. Others have demonstrated promising results of LRRC surgery after induction chemotherapy.[82]

In LRRC surgery, a complete resection is the most important prognostic factor. Generally, resections in LRRC surgery are classified as R0-resections (complete resections), R1-resection (microscopically involved margins) or R2-resections (macroscopically involved margins). In this thesis, we have demonstrated that the minimal tumor-free resection margin is of prognostic value. In line with primary rectal cancer, we found a superior oncological outcome after surgery with wide tumor-free resection margins of more than 2mm.[23,83,84] Sampling error may be a possible explanation for this phenomenon. For example, patients with close resection margins may actually have microscopically involved margins at another location. Another explanation may be that close margins are accompanied by a higher chance of tumor deposits outside the resected area. Nevertheless, the resection margin classification in our study could be used as an alternative for the currently used standard R0/R1/R2 classification of LRRC's. In the current study, more radical procedures were not associated with a survival benefit. Ideally, the surgical procedure should be as minimal as possible. To determine the optimal approach and extensiveness of the surgical procedure accurate staging is essential. Unfortunately, the accuraracy of staging of the local recurrence is limited due to the difficulty of differentiating between tumor and fibrosis. This is similar to the difficulties seen in the restaging of LARC after (chemo-)radiotherapy. In the future, fluorescence guided surgery may be helpful to achieve a higher number of complete resections in LRRC surgery. It may help to distinguish between viable tumor and scarring or fibrosis. In several other malignancies, fluorescence guided surgery has already been evaluated and has shown to a potential benefit in some cases.[85,86] Further investigation concerning the use of fluorescence guided surgery is needed in LARC and LRRC patients.

Unfortunately, approximately 60 to 70% of the diagnosed patients are not suitable candidates for surgical treatment due to distant metastasis or local recurrence that is too extended.[87,88] These patients should be offered palliative care. Pelvic radiotherapy can relief pain in a high number of symptomatic patients.[89] In case of metastasized disease, patients can be offered systemic therapy. However, the effect of palliative chemotherapy on local symptoms and overall survival is not well established. Furthermore, the widespread use of pelvic radiotherapy may have a negative impact on the effectiveness of systemic therapy on the local recurrence. Our results showed that the response of the local recurrence in previously irradiated area was less than the distant metastases

outside the irradiated area. This suggests that the effect of chemotherapy with palliative intent for symptomatic LRRC may be limited. However, the effect of chemotherapy on overall survival in LRRC remains unclear. The overall survival of the patients in this cohort treated with systemic therapy was 33 months, while the median survival of metastasized colorectal cancer is 22 months in trials with highly selected patients. [64] This suggests that systemic therapy in metastasized LRRC patients may be effective. However, the patients in our study were highly selected. It should also be realized that this study focused on LRRC in previously irradiated area, while the effectiveness of chemotherapy on the local recurrence in patients without previous radiotherapy is not fully established. Future research should focus on the potential benefit of systemic therapy on overall survival in LRRC patients and to evaluate the response of systemic therapy on the local recurrence without previous pelvic radiotherapy.

LRRC is a relatively uncommon and unknown disease for physicians worldwide and in the Netherlands.[2,90] As this thesis pointed out, there is a chance for cure in dedicated hospitals. Therefore, it is necessary to refer all LRRC patients to one of the dedicated referral centers in the Netherlands. By referring a higher number of LRRC patients to these centers, the experience of the surgeons will be extended, leading to improved results and this will provide the opportunity to perform high quality research for these patients suffering from this relative rare disease. Simultaneously, performing high quality research will provide us more necessary data on the quality of life of patients treated curatively by surgery and palliatively by radiotherapy or systemic therapy.

In summary, this thesis aimed to further improve the multimodality treatment of LARC and LRRC by focusing on several aspects of the treatment. Restaging by a thoraco-abdominal CT-scan after (chemo-)radiotherapy, applying IORT in R1-resections and performing cT4 rectal cancer surgery in high cT4 volume hospital seems to improve LARC treatment. In LRRC, applying a minimal tumor-free resection margin and considering patients with LRRC after previous radiotherapy and TME surgery candidates for LRRC surgery seem to improve LRRC treatment. The accurate selection of the most suitable treatment is the most important challenge in LARC and LRRC treatment. This means that imaging plays a key role in the multimodality treatment. Improving imaging quality will result in a more accurate selection of patients to administer neo-adjuvant treatment, applying IORT and more radical surgery.

References

1. Al-Sukhni E, Milot L, Fruitman M, et al. Diagnostic accuracy of MRI for assessment of T category, lymph node metastases, and circumferential resection margin involvement in patients with rectal cancer: a systematic review and meta-analysis. *Ann Surg Oncol* 2012; **19**(7): 2212-23.
2. Bosset JF, Collette L, Calais G, et al. Chemotherapy with preoperative radiotherapy in rectal cancer. *N Engl J Med* 2006; **355**(11): 1114-23.
3. Gerard JP, Conroy T, Bonnetain F, et al. Preoperative radiotherapy with or without concurrent fluorouracil and leucovorin in T3-4 rectal cancers: results of FFCD 9203. *J Clin Oncol* 2006; **24**(28): 4620-5.
4. Group MS. Diagnostic accuracy of preoperative magnetic resonance imaging in predicting curative resection of rectal cancer: prospective observational study. *BMJ* 2006; **333**(7572): 779.
5. Lim SB, Choi HS, Jeong SY, et al. Optimal surgery time after preoperative chemoradiotherapy for locally advanced rectal cancers. *Ann Surg* 2008; **248**(2): 243-51.
6. Theodoropoulos G, Wise WE, Padmanabhan A, et al. T-level downstaging and complete pathologic response after preoperative chemoradiation for advanced rectal cancer result in decreased recurrence and improved disease-free survival. *Dis Colon Rectum* 2002; **45**(7): 895-903.
7. Wheeler JM, Dodds E, Warren BF, et al. Preoperative chemoradiotherapy and total mesorectal excision surgery for locally advanced rectal cancer: correlation with rectal cancer regression grade. *Dis Colon Rectum* 2004; **47**(12): 2025-31.
8. 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. *Ann Surg* 2004; **240**(4): 711-7; discussion 7-8.
9. Maas M, Beets-Tan RG, Lambregts DM, et al. Wait-and-see policy for clinical complete responders after chemoradiation for rectal cancer. *J Clin Oncol* 2011; **29**(35): 4633-40.
10. Martens MH, Maas M, Heijnen LA, et al. Long-term Outcome of an Organ Preservation Program After Neoadjuvant Treatment for Rectal Cancer. *J Natl Cancer Inst* 2016; **108**(12).
11. van der Paardt MP, Zagers MB, Beets-Tan RG, Stoker J, Bipat S. Patients Who Undergo Preoperative Chemoradiotherapy for Locally Advanced Rectal Cancer Restaged by Using Diagnostic MR Imaging: A Systematic Review and Meta-Analysis. *Radiology* 2013.
12. Rudisch A, Kremser C, Judmaier W, Zunterer H, DeVries AF. Dynamic contrast-enhanced magnetic resonance imaging: a non-invasive method to evaluate significant differences between malignant and normal tissue. *Eur J Radiol* 2005; **53**(3): 514-9.
13. Allen SD, Padhani AR, Dzik-Jurasz AS, Glynne-Jones R. Rectal carcinoma: MRI with histologic correlation before and after chemoradiation therapy. *AJR Am J Roentgenol* 2007; **188**(2): 442-51.
14. Chen CC, Lee RC, Lin JK, Wang LW, Yang SH. How accurate is magnetic resonance imaging in restaging rectal cancer in patients receiving preoperative combined chemoradiotherapy? *Dis Colon Rectum* 2005; **48**(4): 722-8.
15. Kulkarni T, Gollins S, Maw A, Hobson P, Byrne R, Widdowson D. Magnetic resonance imaging in rectal cancer downstaged using neoadjuvant chemoradiation: accuracy of prediction of tumour stage and circumferential resection margin status. *Colorectal Dis* 2008; **10**(5): 479-89.

16. Pomerri F, Pucciarelli S, Maretto I, et al. Prospective assessment of imaging after preoperative chemoradiotherapy for rectal cancer. *Surgery* 2011; **149**(1): 56-64.
17. Suppiah A, Hunter IA, Cowley J, et al. Magnetic Resonance Imaging Accuracy in Assessing Tumour Down-staging Following Chemo-radiation in Rectal Cancer. *Colorectal Dis* 2008.
18. Suppiah A, Hunter IA, Cowley J, et al. Magnetic resonance imaging accuracy in assessing tumour down-staging following chemoradiation in rectal cancer. *Colorectal Dis* 2009; **11**(3): 249-53.
19. Heijnen LA, Maas M, Beets-Tan RG, et al. Nodal staging in rectal cancer: why is restaging after chemoradiation more accurate than primary nodal staging? *Int J Colorectal Dis* 2016; **31**(6): 1157-62.
20. Lambregts DM, Rao SX, Sassen S, et al. MRI and Diffusion-weighted MRI Volumetry for Identification of Complete Tumor Responders After Preoperative Chemoradiotherapy in Patients With Rectal Cancer: A Bi-institutional Validation Study. *Ann Surg* 2015; **262**(6): 1034-9.
21. Birbeck KF, Macklin CP, Tiffin NJ, et al. Rates of circumferential resection margin involvement vary between surgeons and predict outcomes in rectal cancer surgery. *Ann Surg* 2002; **235**(4): 449-57.
22. Chand M, Siddiqui MR, Swift I, Brown G. Systematic review of prognostic importance of extramural venous invasion in rectal cancer. *World J Gastroenterol* 2016; **22**(4): 1721-6.
23. Nagtegaal ID, Marijnen CA, Kranenbarg EK, et al. Circumferential margin involvement is still an important predictor of local recurrence in rectal carcinoma: not one millimeter but two millimeters is the limit. *Am J Surg Pathol* 2002; **26**(3): 350-7.
24. Bisschop C, Tjalma JJ, Hospers GA, et al. Consequence of restaging after neoadjuvant treatment for locally advanced rectal cancer. *Ann Surg Oncol* 2015; **22**(2): 552-6.
25. Davids JS, Alavi K, Andres Cervera-Servin J, et al. Routine preoperative restaging CTs after neoadjuvant chemoradiation for locally advanced rectal cancer are low yield: a retrospective case study. *Int J Surg* 2014; **12**(12): 1295-9.
26. Hanly AM, Ryan EM, Rogers AC, et al. Multicenter Evaluation of Rectal cancer ReImaging pOst Neoadjuvant (MERRION) Therapy. *Ann Surg* 2014; **259**(4): 723-7.
27. Liu GC, Zhang X, Xie E, et al. The Value of Restaging With Chest and Abdominal CT/MRI Scan After Neoadjuvant Chemoradiotherapy for Locally Advanced Rectal Cancer. *Medicine (Baltimore)* 2015; **94**(47): e2074.
28. van der Pool AE, de Wilt JH, Lalmahomed ZS, Eggermont AM, Ijzermans JN, Verhoef C. Optimizing the outcome of surgery in patients with rectal cancer and synchronous liver metastases. *Br J Surg* 2010; **97**(3): 383-90.
29. Alberda WJ, Dassen HP, Dwarkasing RS, et al. Prediction of tumor stage and lymph node involvement with dynamic contrast-enhanced MRI after chemoradiotherapy for locally advanced rectal cancer. *Int J Colorectal Dis* 2013; **28**(4): 573-80.
30. Gerard JP, Rostom Y, Gal J, et al. Can we increase the chance of sphincter saving surgery in rectal cancer with neoadjuvant treatments: lessons from a systematic review of recent randomized trials. *Crit Rev Oncol Hematol* 2012; **81**(1): 21-8.
31. de Jong EA, ten Berge JC, Dwarkasing RS, Rijkers AP, van Eijck CH. The accuracy of MRI, endorectal ultrasonography, and computed tomography in predicting the response of locally advanced rectal cancer after preoperative therapy: A metaanalysis. *Surgery* 2016; **159**(3): 688-99.

32. Maas M, Lambregts DM, Nelemans PJ, et al. Assessment of Clinical Complete Response After Chemoradiation for Rectal Cancer with Digital Rectal Examination, Endoscopy, and MRI: Selection for Organ-Saving Treatment. *Ann Surg Oncol* 2015; **22**(12): 3873-80.
33. Patel UB, Taylor F, Blomqvist L, et al. Magnetic resonance imaging-detected tumor response for locally advanced rectal cancer predicts survival outcomes: MERCURY experience. *J Clin Oncol* 2011; **29**(28): 3753-60.
34. Ayez N, Alberda WJ, Burger JW, et al. Is Restaging with Chest and Abdominal CT Scan after Neoadjuvant Chemoradiotherapy for Locally Advanced Rectal Cancer Necessary? *Ann Surg Oncol* 2012.
35. Gietelink L, Wouters MW, Tanis PJ, et al. Reduced Circumferential Resection Margin Involvement in Rectal Cancer Surgery: Results of the Dutch Surgical Colorectal Audit. *J Natl Compr Canc Netw* 2015; **13**(9): 1111-9.
36. Eloesser L. The Treatment of Some Abdominal Cancers by Irradiation through the Open Abdomen Combined with Cautery Excision. *Ann Surg* 1937; **106**(4): 645-52.
37. Kinsella TJ, Sindelar WF, DeLuca AM, et al. Tolerance of peripheral nerve to intraoperative radiotherapy (IORT): clinical and experimental studies. *Int J Radiat Oncol Biol Phys* 1985; **11**(9): 1579-85.
38. Tepper JE, Gunderson LL, Orlow E, et al. Complications of intraoperative radiation therapy. *Int J Radiat Oncol Biol Phys* 1984; **10**(10): 1831-9.
39. Willett CG, Shellito PC, Tepper JE, Eliseo R, Convery K, Wood WC. Intraoperative electron beam radiation therapy for primary locally advanced rectal and rectosigmoid carcinoma. *J Clin Oncol* 1991; **9**(5): 843-9.
40. P. Okunieff SS, S.W. Cheng. Biology of large dose perfraction radiation therapy. *Intraoperative Irradiation: Techniques and Results, New Jersey, Humana Press Inc* 2000.
41. Dubois JB, Bussieres E, Richaud P, et al. Intra-operative radiotherapy of rectal cancer: results of the French multi-institutional randomized study. *Radiother Oncol* 2011; **98**(3): 298-303.
42. Eble MJ, Lehnert T, Herfarth C, Wannenmacher M. Intraoperative radiotherapy as adjuvant treatment for stage II/III rectal carcinoma. *Recent Results Cancer Res* 1998; **146**: 152-60.
43. Ferenschild FT, Vermaas M, Nuyttens JJ, et al. Value of intraoperative radiotherapy in locally advanced rectal cancer. *Dis Colon Rectum* 2006; **49**(9): 1257-65.
44. Nuyttens JJ, Kolkman-Deurloo IK, Vermaas M, et al. High-dose-rate intraoperative radiotherapy for close or positive margins in patients with locally advanced or recurrent rectal cancer. *Int J Radiat Oncol Biol Phys* 2004; **58**(1): 106-12.
45. Hyngstrom JR, Tzeng CW, Beddar S, et al. Intraoperative radiation therapy for locally advanced primary and recurrent colorectal cancer: ten-year institutional experience. *J Surg Oncol* 2014; **109**(7): 652-8.
46. Mirnezami R, Chang GJ, Das P, et al. Intraoperative radiotherapy in colorectal cancer: systematic review and meta-analysis of techniques, long-term outcomes, and complications. *Surg Oncol* 2013; **22**(1): 22-35.
47. Wiig JN, Giercksky KE, Tveit KM. Intraoperative radiotherapy for locally advanced or locally recurrent rectal cancer: Does it work at all? *Acta Oncol* 2014; **53**(7): 865-76.
48. Wiig JN, Poulsen JP, Tveit KM, Olsen DR, Giercksky KE. Intra-operative irradiation (IORT) for primary advanced and recurrent rectal cancer. a need for randomised studies. *Eur J Cancer* 2000; **36**(7): 868-74.

49. Mannaerts GH, Rutten HJ, Martijn H, Hanssens PE, Wiggers T. Comparison of intraoperative radiation therapy-containing multimodality treatment with historical treatment modalities for locally recurrent rectal cancer. *Dis Colon Rectum* 2001; **44**(12): 1749-58.
50. Gietelink L, Henneman D, van Leersum NJ, et al. The Influence of Hospital Volume on Circumferential Resection Margin Involvement: Results of the Dutch Surgical Colorectal Audit. *Ann Surg* 2016; **263**(4): 745-50.
51. Beyond TMEC. Consensus statement on the multidisciplinary management of patients with recurrent and primary rectal cancer beyond total mesorectal excision planes. *Br J Surg* 2013; **100**(8): 1009-14.
52. Park S, Lee YS. Analysis of the prognostic effectiveness of a multivisceral resection for locally advanced colorectal cancer. *J Korean Soc Coloproctol* 2011; **27**(1): 21-6.
53. Brusselaers N, Mattsson F, Lagergren J. Hospital and surgeon volume in relation to long-term survival after oesophagectomy: systematic review and meta-analysis. *Gut* 2014; **63**(9): 1393-400.
54. Gooiker GA, van Gijn W, Wouters MW, et al. Systematic review and meta-analysis of the volume-outcome relationship in pancreatic surgery. *Br J Surg* 2011; **98**(4): 485-94.
55. Santos F, Zakaria AS, Kassouf W, Tanguay S, Aprikian A. High hospital and surgeon volume and its impact on overall survival after radical cystectomy among patients with bladder cancer in Quebec. *World J Urol* 2014.
56. Bos AC, van Erning FN, Elferink MA, et al. No Difference in Overall Survival Between Hospital Volumes for Patients With Colorectal Cancer in The Netherlands. *Dis Colon Rectum* 2016; **59**(10): 943-52.
57. Kaufman MS, Radhakrishnan N, Roy R, et al. Influence of palliative surgical resection on overall survival in patients with advanced colorectal cancer: a retrospective single institutional study. *Colorectal Dis* 2008; **10**(5): 498-502.
58. Ruo L, Gougoutas C, Paty PB, Guillem JG, Cohen AM, Wong WD. Elective bowel resection for incurable stage IV colorectal cancer: prognostic variables for asymptomatic patients. *J Am Coll Surg* 2003; **196**(5): 722-8.
59. Venderbosch S, de Wilt JH, Teerenstra S, et al. Prognostic value of resection of primary tumor in patients with stage IV colorectal cancer: retrospective analysis of two randomized studies and a review of the literature. *Ann Surg Oncol* 2011; **18**(12): 3252-60.
60. Poultsides GA, Servais EL, Saltz LB, et al. Outcome of primary tumor in patients with synchronous stage IV colorectal cancer receiving combination chemotherapy without surgery as initial treatment. *J Clin Oncol* 2009; **27**(20): 3379-84.
61. Cabilan CJ, Hines S. The short-term impact of colorectal cancer treatment on physical activity, functional status and quality of life: a systematic review. *JBI Database System Rev Implement Rep* 2017; **15**(2): 517-66.
62. Inegraal Kanker Instituut Nederland. https://wwwkankernl/bibliotheek/endeldarmkanker/wat-is/1503-overlevingscijfers-endeldarmkanker 2018.
63. Emmanouilides C, Sfakiotaki G, Androulakis N, et al. Front-line bevacizumab in combination with oxaliplatin, leucovorin and 5-fluorouracil (FOLFOX) in patients with metastatic colorectal cancer: a multicenter phase II study. *BMC Cancer* 2007; **7**: 91.
64. Van Cutsem E, Rivera F, Berry S, et al. Safety and efficacy of first-line bevacizumab with FOLFOX, XELOX, FOLFIRI and fluoropyrimidines in metastatic colorectal cancer: the BEAT study. *Ann Oncol* 2009; **20**(11): 1842-7.

65. Ychou M, Viret F, Kramar A, et al. Tritherapy with fluorouracil/leucovorin, irinotecan and oxaliplatin (FOLFIRINOX): a phase II study in colorectal cancer patients with non-resectable liver metastases. *Cancer Chemother Pharmacol* 2008; **62**(2): 195-201.
66. Brown SR, Mathew R, Keding A, Marshall HC, Brown JM, Jayne DG. The impact of postoperative complications on long-term quality of life after curative colorectal cancer surgery. *Ann Surg* 2014; **259**(5): 916-23.
67. Damjanov N, Weiss J, Haller DG. Resection of the primary colorectal cancer is not necessary in nonobstructed patients with metastatic disease. *Oncologist* 2009; **14**(10): 963-9.
68. Schmidt C. Metastatic colorectal cancer: is surgery necessary? *J Natl Cancer Inst* 2009; **101**(16): 1113-5.
69. Rahbari NN, Lordick F, Fink C, et al. Resection of the primary tumour versus no resection prior to systemic therapy in patients with colon cancer and synchronous unresectable metastases (UICC stage IV): SYNCHRONOUS--a randomised controlled multicentre trial (ISRCTN30964555). *BMC Cancer* 2012; **12**: 142.
70. t Lam-Boer J, Mol L, Verhoef C, et al. The CAIRO4 study: the role of surgery of the primary tumour with few or absent symptoms in patients with synchronous unresectable metastases of colorectal cancer--a randomized phase III study of the Dutch Colorectal Cancer Group (DCCG). *BMC Cancer* 2014; **14**: 741.
71. Kim CW, Baek JH, Choi GS, et al. The role of primary tumor resection in colorectal cancer patients with asymptomatic, synchronous unresectable metastasis: Study protocol for a randomized controlled trial. *Trials* 2016; **17**: 34.
72. Harji DP, Griffiths B, Velikova G, Sagar PM, Brown J. Systematic review of health-related quality of life issues in locally recurrent rectal cancer. *J Surg Oncol* 2015; **111**(4): 431-8.
73. Harji DP, Sagar PM. Advancing the surgical treatment of locally recurrent rectal cancer. *Br J Surg* 2012; **99**(9): 1169-71.
74. Bhangu A, Ali SM, Darzi A, Brown G, Tekkis P. Meta-analysis of survival based on resection margin status following surgery for recurrent rectal cancer. *Colorectal Dis* 2012; **14**(12): 1457-66.
75. Bosman SJ, Holman FA, Nieuwenhuijzen GA, Martijn H, Creemers GJ, Rutten HJ. Feasibility of reirradiation in the treatment of locally recurrent rectal cancer. *Br J Surg* 2014; **101**(10): 1280-9.
76. Holman FA, Bosman SJ, Haddock MG, et al. Results of a pooled analysis of IOERT containing multimodality treatment for locally recurrent rectal cancer: Results of 565 patients of two major treatment centres. *Eur J Surg Oncol* 2017; **43**(1): 107-17.
77. Rombouts AJ, Koh CE, Young JM, et al. Does radiotherapy of the primary rectal cancer affect prognosis after pelvic exenteration for recurrent rectal cancer? *Dis Colon Rectum* 2015; **58**(1): 65-73.
78. Vermaas M, Nuyttens JJ, Ferenschild FT, Verhoef C, Eggermont AM, de Wilt JH. Reirradiation, surgery and IORT for recurrent rectal cancer in previously irradiated patients. *Radiother Oncol* 2008; **87**(3): 357-60.
79. Alberda WJ, Verhoef C, Nuyttens JJ, et al. Outcome in Patients with Resectable Locally Recurrent Rectal Cancer After Total Mesorectal Excision with and Without Previous Neoadjuvant Radiotherapy for the Primary Rectal Tumor. *Ann Surg Oncol* 2013.
80. Bhangu A, Ali SM, Brown G, Nicholls RJ, Tekkis P. Indications and Outcome of Pelvic Exenteration for Locally Advanced Primary and Recurrent Rectal Cancer. *Ann Surg* 2013.

81. Rahbari NN, Ulrich AB, Bruckner T, et al. Surgery for locally recurrent rectal cancer in the era of total mesorectal excision: is there still a chance for cure? *Ann Surg* 2011; **253**(3): 522-33.
82. Kusters M, Bosman SJ, Van Zoggel DM, et al. Local Recurrence in the Lateral Lymph Node Compartment: Improved Outcomes with Induction Chemotherapy Combined with Multimodality Treatment. *Ann Surg Oncol* 2016; **23**(6): 1883-9.
83. Dent OF, Haboubi N, Chapuis PH, et al. Assessing the evidence for an association between circumferential tumour clearance and local recurrence after resection of rectal cancer. *Colorectal Dis* 2007; **9**(2): 112-21; discussion 21-2.
84. Trakarnsanga A, Gonen M, Shia J, et al. What is the Significance of the Circumferential Margin in Locally Advanced Rectal Cancer After Neoadjuvant Chemoradiotherapy? *Ann Surg Oncol* 2013.
85. Handgraaf HJM, Boonstra MC, Prevoo H, et al. Real-time near-infrared fluorescence imaging using cRGD-ZW800-1 for intraoperative visualization of multiple cancer types. *Oncotarget* 2017; **8**(13): 21054-66.
86. Harlaar NJ, Koller M, de Jongh SJ, et al. Molecular fluorescence-guided surgery of peritoneal carcinomatosis of colorectal origin: a single-centre feasibility study. *Lancet Gastroenterol Hepatol* 2016; **1**(4): 283-90.
87. Bakx R, Visser O, Josso J, Meijer S, Slors JF, van Lanschot JJ. Management of recurrent rectal cancer: a population based study in greater Amsterdam. *World J Gastroenterol* 2008; **14**(39): 6018-23.
88. Palmer G, Martling A, Cedermark B, Holm T. A population-based study on the management and outcome in patients with locally recurrent rectal cancer. *Ann Surg Oncol* 2007; **14**(2): 447-54.
89. Cameron MG, Kersten C, Vistad I, Fossa S, Guren MG. Palliative pelvic radiotherapy of symptomatic incurable rectal cancer - a systematic review. *Acta Oncol* 2014; **53**(2): 164-73.
90. Kapiteijn E, Marijnen CA, Nagtegaal ID, et al. Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer. *N Engl J Med* 2001; **345**(9): 638-46.