The impact of neoadjuvant systemic therapy on the surgical management of soft tissue sarcoma

Burg, S.J.C. van der

Chapter 9

General discussion and future perspectives

Neoadjuvant systemic treatment (NAST) has shown efficacy in managing various cancer types by improving survival outcomes, reducing surgical extensiveness, and allowing response evaluation with prognostic value. However, in patients with soft tissue sarcomas (STS), evidence from randomized phase III trials directly comparing NAST followed by surgery to upfront surgery is lacking, resulting in an absence of conclusive evidence regarding the benefits of NAST in STS patients. This thesis seeks to expand current understanding of these benefits in STS patients, providing more insights into response evaluation, survival outcomes and tumor downsizing after NAST.

Response evaluation

With the introduction of neoadjuvant instead of adjuvant treatment, the possibility to utilize the response to treatment as prognostic biomarker has become available. Response can be evaluated either as clinical, radiological, metabolic, or pathological response. Where pathological response is normally determined after treatment, clinical, radiologic and metabolic response can be determined after treatment and during treatment. Response evaluation during treatment, in this thesis called early response evaluation, is often used to predict pathological response since there is a lack of other prognostic biomarkers. In clinical practice, early response evaluation can aid in detecting non-responsive tumors, and prevent additional cycles of toxic chemotherapy. The response after treatment can help in informing patients about disease prognosis and in deciding if additional treatments are necessary. Moreover, radiologic, metabolic, or pathologic response can potentially act as short term outcomes of neoadjuvant studies.

Prognostic value of pathological response

The evidence for an association between pathological response after neoadjuvant treatment and survival outcomes varies by cancer type. Where the association has been demonstrated for rectal cancer and bone sarcomas (1-3), there are mixed results for breast cancer and esophageal cancer (4-6). For STS, the prognostic value of pathological response remains undetermined. Studies investigating the relationship between pathological response and survival in STS utilized various criteria to define pathological response, including necrosis, stainable viable cells, and fibrosis/hyalinization, often with different cutoff thresholds. The three largest studies on this topic included patients treated with NACT, NART or both, and these found significant associations between overall survival and >90% or >95% necrosis (7-9). However, the proportion of patients only receiving NACT in these studies was low. Studies solely focusing on pathological response in patients receiving NACT, demonstrate conflicting results. The largest study, including 175 patients, did find an association between overall survival and <5% stainable cells (10), but smaller studies

did not confirm this finding (11, 12). The use of fibrosis/hyalinization as pathological response parameter has been used more often in recent studies, but its association with overall survival is mainly demonstrated in patients treated with NART (13-15). To conclude, a cutoff of >95% necrosis for defining pathological response after any form of neoadjuvant treatment is supported by the strongest evidence. However, evidence for a specific cutoff for response after NACT is lacking. This thesis provides additional data that aligns with the existing conflicting findings on this topic as chapter 3 demonstrated superior disease free survival in patients with pathological response, either defined as <10% viable cells or >15% fibrosis/hyalinization, while chapter 4 demonstrated no association between pathological response, defined as <10% viable cells or >20% fibrosis/hyalinization, and disease free or overall survival.

Prognostic value of radiological response

Similar to pathological response, there are associations between radiological response and survival after NAST for various cancer types (16, 17), though studies with STS patients have shown limited evidence for its prognostic value. Most often, no association was found (18, 19), but an association between progressive disease according to Response Evaluation Criteria in Solid Tumours (RECIST) 1.1 (20), which means an increase in tumor size of more than 20%, and poor survival outcomes is occasionally reported (21, 22). This finding was not confirmed for retroperitoneal sarcoma, but a linear trend between increased tumor size and death rate was observed. A similar result was found in chapter 6, which showed an association between absence of reduction in tumor size after neoadjuvant imatinib for gastrointestinal stromal tumors (GIST) and worse survival. In addition, the change in tumor size as continuous variable for survival has been described for extremity STS (23). These findings raise the question whether RECIST 1.1 is the most fitting outcome measure for response after NAST. Originally, RECIST 1.1 was developed for the metastatic setting, resulting in the current cutoff for progressive disease. Future research should explore if a new systematic radiological response assessment would be better suited for the neoadjuvant setting, instead of RECIST 1.1.

Early response evaluation

While the optimization of patient selection for NAST is still evolving, a non-response remains a significant challenge. It is crucial to identify non-responders in an early stage to avoid unnecessary exposure to toxic chemotherapy and to detect progressing tumors in time, not losing the opportunity of curative resection. Tumor size measured on early evaluation scans with MRI or CT lack predictive value for pathologic response (19, 24, 25). Conversely, chapter 3 demonstrates that reduction in metabolic activity measured on an early evaluation (18)F-FDG PET/CT is a promising predictor for pathologic response, which is supported by multiple other studies (26-28). Typically for STS, the studies on early evaluation with (18)F-FDG PET/CT have a low number of patients included with a wide variety of histological

tumor types. However, its clinical potential can be very valuable, as demonstrated in adenocarcinomas at the oesophagogastric junction (29), where the MUNICON trial demonstrated that stopping NACT based on predicted non-responsiveness on the (18)F-FDG PET/CT was safe and resulted in less cycles of chemotherapy in those patients (30). For GIST, the predictive value of (18)F-FDG PET/CT is already demonstrated as well (31), but larger cohorts are needed for other types of STS.

Future directions on response evaluation

When asked what the primary endpoint of future neoadjuvant trials should be in extremity STS, one third of the respondents of the survey described in chapter 2 answered pathological response. The same respondents stated that their institution reported the percentage of viable cells, necrosis and fibrosis/hyalinization in 75%, 86% and 55%, respectively. However, the lack of evidence supporting the association between pathological response after NAST and survival, combined with the variability in the reporting of pathological outcomes, undermines the use of pathologic response as outcome in neoadjuvant treatment studies. This issue becomes even more critical with the emerging role of neoadjuvant immunotherapy as a cancer treatment, highlighting the need for a universally accepted and standardized definition of pathological response as a short-term outcome in future neoadjuvant trials.

The absence of a standardized definition of pathologic response is partly caused by the rarity and heterogeneity of STS. The largest studies on this topic included 175 patients only. Collaborative efforts, such as the Transatlantic Australasian Retroperitoneal Sarcoma Working Group (chapter 4) or the Dutch GIST registry (chapters 6 and chapter 7), could potentially generate sufficient data to establish a standardized method for assessing pathological response. Machine learning may also play a role in developing this. For instance, Crombé et al. utilized machine learning to identify a cutoff of <5% viable cells as prognostically significant (10).

In the absence of evidence supporting the prognostic value of pathological response after NAST, the usefulness of early response evaluation as a predictor of pathological response remains limited. Nonetheless, significant efforts are being made to enhance early response assessment. The most promising advancements have emerged in the field of radiomics, which involves the extraction of quantitative features from medical imaging data derived from MRI, CT, or (18)F-FDG PET/CT (32). Examples of radiomic features include gray-level patterns and dynamic characteristics such as tracer uptake rates. Several studies have already demonstrated an association between changes in radiomic features observed on early evaluation scans and pathological response (24, 25, 33, 34).

It is likely that, in the future, machine learning will enable the development of models that integrate all available information gathered during neoadjuvant systemic treatment to predict patient prognosis. By combining patient details, treatment information, radiomics, and pathological outcomes, these models could provide highly specific prognostic insights.

Survival benefit

The survival benefit of adjuvant and neoadjuvant chemotherapy was demonstrated in a select group of patients with high-risk extremity and trunk wall STS only six and four years ago, respectively (35, 36). In these studies, high-risk classification was determined using a nomogram, which incorporates tumor histology, tumor size, deep tumor location, tumor grade, and patient age. These patients were hypothesized to have an elevated risk of micrometastases, making them more likely to benefit from additional chemotherapy. The neoadjuvant setting is nowadays often preferred over the adjuvant setting based on the non-inferiority trial published in 2016, combined with other potential advantages of neoadjuvant treatment (37). These advantages were response evaluation, as described before, tumor downsizing, and earlier treatment of potential micrometastases. Tumor downsizing could potentially lead to improved R0 rates, resulting in less local recurrences, or decreased morbidity, however, these effects have not yet been conclusively proven. A similar situation exists for GIST, where the survival benefit of adjuvant imatinib was established nine years ago (38), but the survival benefit of neoadjuvant imatinib is not yet shown in a prospective trial. However, neoadjuvant imatinib is given for the same reasons as NACT, but also without strong evidence.

The STRASS 2 trial, an ongoing randomized phase III trial comparing surgery following NACT to surgery alone for retroperitoneal leiomyosarcoma (LMS) and high-grade dedifferentiated liposarcoma (DDLPS), will provide the missing evidence for these specific subtypes (39). Meanwhile, the only evidence available for selecting patients for NAST are nomograms for extremity STS. Surprisingly, these nomograms are only used by 59% of the respondents described in chapter 2. Clearly, more data is necessary for selecting patients that will most likely benefit from NAST.

Histologic tumor type

The rarity and heterogeneity of STS pose significant challenges in establishing evidence for the survival benefit of NAST. Most studies on this topic include a variety of histologic tumor types, which complicates the interpretation of their findings. Chapter 5 is an example of a homogenous patient cohort, providing evidence for the efficacy of NACT in a specific subtype of STS, despite its rarity. It was shown that oncological outcomes significantly improve for patients with radiation associated

angiosarcoma (RAAS) of the breast when treated with taxane-based NACT. Future research should aim to elucidate the tumor characteristics responsible for this remarkable improvement in outcomes. Potential factors include the angiosarcoma being radiation associated, the presence of C-MYC amplification, its cutaneous location, or a combination of these features. Understanding this could lead to more tailored treatments for patients with angiosarcoma.

Mutational status

Besides studying specific subtypes of STS, the mutational status should be taken into account as well to select tumors for NAST. This is already well established in the treatment of gastrointestinal stromal tumors (GIST). In Chapter 6, we demonstrate that the presence of a KIT exon 11 mutation is associated with significant tumor reduction when treated with neoadjuvant imatinib, whereas the absence of a known mutation correlates with unresponsiveness to imatinib. Other examples of treatment decisions influenced by mutational status include the use of an increased imatinib dosage for GIST with a KIT exon 9 mutation (40) and the preference for avapritinib over imatinib for GIST with a PDGFRA D842V mutation (41). Ideally, such precision in drug selection would be extended to all types of STS.

Baseline metabolic activity

As mentioned before, the reduction in metabolic activity is able to predict pathological response in STS treated with NAST. In the same chapter (chapter 3), we also found that baseline PET parameters were associated with pathological response. Larger studies are necessary to confirm our findings, but baseline (18) F-FDG PET/CT could potentially help selecting patients who would benefit from NAST. In osteosarcoma, the predictive value of baseline (18)F-FDG PET/CT was already known (42, 43), but to the best of our knowledge, this was a new finding for STS.

Future perspectives on improving survival outcomes

Similar to the advancements in early response evaluation, radiomics is also emerging as a promising tool for predicting pathological outcomes even before the start of NAST. For gastric cancer and breast cancer, the association between radiomics measured before NAST and pathologic response has been demonstrated (44-47). Several small studies have explored this approach for STS as well (33, 48), with promising results. However, larger studies are needed to validate its clinical application.

Another emerging field in sarcoma is the application of neoadjuvant checkpoint inibitors in STS. In 2017 and 2018, the PEMBROSARC trial, the SARC028 trial, and the Alliance A091401 trial were published, all demonstrating limited activity of PD-1 inhibitors (49-51). The immunosuppressive tumor microenvironment of STS was

given as potential explanation for these disappointing results. On the bright side, these studies gave new insights for further studies on this topic. For instance, a sub-analysis of the PEMBROSARC trial found that the presence of tertiary lymphoid structures are a potential biomarker for response on PD-1 inhibitors (52). The SARC028 trial suggested that sarcoma NOS or DDLPS would potentially benefit the most from immunotherapy, which was further studied by Roland et al., who demonstrated significant efficacy of immunotherapy with concurrent radiotherapy in sarcoma NOS in the neoadjuvant setting (53). The combination of a PD-1 inhibitor with radiotherapy in the neoadjuvant setting has been confirmed to be effective for sarcoma NOS, DDLPS or pleiomorphic LPS of the extremity in the SU2C-SARC032 trial, which was published in 2024 (54). In addition to the combination of immunotherapy with radiotherapy, it was demonstrated by the ImmunoSarc trial that immunotherapy with targeted therapy is a promising combination as well. However, this trial was not in the neoadjuvant setting (55). Based on these studies, the future of immunotherapy for STS potentially lays in a multimodality treatment, and in finding specific subtypes and biomarkers for the selection of responsive tumors.

Surgical approach

The use of neoadjuvant chemotherapy was originally introduced in breast cancer to decrease the tumor size and allow for breast-conserving surgery (56, 57). In STS, it is also used to reduce the extensiveness of resection and consequently the morbidity (58). In addition, downsizing the tumor potentially increases the R0 resection rate, which was the second most important reason to give NACT in extremity STS according to the survey respondents in chapter 2. Interestingly enough, the improved R0 rates are only demonstrated after neoadjuvant radiotherapy (12, 13), and not in patients treated with NACT. Improved R0 rates after neoadjuvant imatinib for GIST have not been demonstrated in a trial either.

Clear resection margins

Although no trials proving the improved R0 resection margins after NAST are included in this thesis, additional information on this topic is presented. In chapter 4, surgeons were retrospectively asked if they thought NACT had an effect on the resection of RPS. In 5%, it was thought that a suspected R2 resection became an R0/R1 resection. Chapter 5 demonstrates that for RAAS of the breast, NACT increased the R0 rate from 82% to 100%. In chapter 6, the anticipated resection margin changed in 8% of all included GIST treated with neoadjuvant imatinib. All three studies have multiple limitations, so these percentages may not accurately reflect the actual change in resection margins. Nevertheless, the findings suggest that NAST may slightly improve R0 resection rates, though to a limited extent.

Surgical extensiveness

Another potential effect of downsizing the tumor with NAST is reducing the surgical extensiveness, which might result in less morbidity. In chapter 4, we found that 6% of the resections of RPS were less extensive after NACT, in terms of more organ preservation/less need for reconstructive surgery. However, the methodology in this chapter was of low quality, since surgeons were retrospectively asked if they thought NACT had an effect on the resection. The methodology in chapter 6 was of higher quality. The effect of neoadjuvant imatinib on the resection was objectified by asking surgeons to score anonymized scans before and after neoadjuvant imatinib in a randomized order. They had to determine which organs were involved and what surgical procedure was necessary (e.g. gastric wedge excision or partial gastrectomy). It was shown that neoadjuvant imatinib resulted in a decrease of anticipated surgical extensiveness in 51% of the patients. Future prospective studies should objectify the reduction in surgical extensiveness for other STS with the same methodology to help in decision making for the patients.

Surgical window

Besides improving our knowledge on the positive effects of neoadjuvant systemic treatment on the resection of STS, this thesis also gives more insight in the possibility of losing the surgical window due to tumor progression. Chapter 4 describes a decreased resectability in 1% of patients with a RPS, though this percentage is an underrepresentation since only operated patients were included. The surgical window was not lost for patients with RAAS of the breast and in only 2% of patients with a GIST this was the case, as discussed in chapter 5 and chapter 6, respectively. These findings do not support the concern of losing the surgical window during neoadjuvant systemic treatment.

Future directions of the surgical approach

Size reduction might improve as the development of drugs and proper patient selection continues. With the potential improved size reduction, new surgical challenges arise as well. Chapter 7 discussed an example of such a challenge, being the use of minimally invasive surgery (MIS) instead of open surgery for GIST. It was demonstrated that the use of MIS for gastric GIST increased over the past 13 years and that there was an association between smaller tumors and the use of MIS. Meanwhile, chapter 6 demonstrated a size reduction in 86% of the included tumors, so one might hypothesize that neoadjuvant imatinib influences the increased use of MIS for GIST.

While MIS is not an option for extremity or trunk wall STS, it is a topic of debate in RPS. The advantage might be a shorter length of hospital stay due to smaller incisions (59), but given that RPS typically present with large tumor sizes necessitating extensive incisions for removal, the benefit of smaller incisions often does not

hold in clinical practice. In addition, the decision-making process regarding which structures to sacrifice during surgery may be more challenging with MIS, although this has not been demonstrated by clinical trials. Given the rarity of RPS and the limited evidence supporting MIS, the likelihood of conducting a trial to compare MIS and open surgery for selected cases of RPS remains low (60).

In chapter 8, a solution to a potential future challenge is discussed. We demonstrated that magnetic seed localization (MSL) achieves a 100% success rate in localizing small melanoma, Merkel cell carcinoma, or soft tissue sarcoma lesions. As advances in drug development and improved patient selection are expected to lead to greater tumor size reductions, MSL offers a reliable method for localizing residual lesions following NAST.

In the ideal scenario, neoadjuvant treatment could achieve complete tumor eradication prior to surgery, sparing patients from the potential complications associated with surgical resection. While complete eradication remains uncommon in STS, chapter 5 demonstrates that it does occur, and the likelihood is expected to increase with advancing therapies. In colorectal cancer, complete tumor eradication has been observed following neoadjuvant chemoradiation, and the use of immunotherapy is expected to further increase its occurrence. This lead to the introduction of the watch-and-wait approach, where patients with complete radiological response did not undergo surgery. It was demonstrated that it was safe in terms of oncological outcomes, and that patients had a good quality of life (61). Angiosarcomas are a potential histologic tumor type were a watch-and-wait approach could be of interest, although currently we do not know how durable a CR is for these patients.

Future perspectives on study designs

As discussed in the introduction, initiating large randomized phase III trials for STS patients is challenging due to the rarity, heterogeneity, and ethical constraints associated with this patient population. Consequently, alternative study designs are essential to advance the topics explored in this thesis. Most studies reported in this thesis are retrospective, and while they do not answer the discussed research questions completely, they definitely point in certain directions and add to the knowledge of treatment of these diseases. Retrospective research is often considered to be of less quality than randomized phase III trials, but there are arguments contradicting this. First, hypothesis-generating studies are crucial, as they lay the groundwork for future research. Without retrospective analyses of previous treatment outcomes, new ideas for studies would not emerge. Second, observational data can be instrumental in quality assessment, ultimately improving

patient care. When specific research questions arise from retrospective analyses and conducting a phase III trial is not feasible, prospective non-randomized trials offer a viable alternative. Such trials reduce selection bias and enable more accurate answers to research questions, bridging the gap between observational studies and randomized controlled trials.

Researchers in the field of STS, and especially NAST, will have to accept that many questions will not be answered through a randomized phase III trial. Nevertheless, this should not discourage anybody from trying to find these answers. Both retrospective and prospective studies benefit significantly from larger patient cohorts, which enhance the quality and reliability of findings. While achieving large sample sizes is challenging due to the rarity and heterogeneity of sarcomas, international collaborations offer a promising solution. A notable example is the Transatlantic Australasian Retroperitoneal Sarcoma Working Group, which demonstrates the potential of collaborative efforts. Establishing similar registries for extremity and trunk wall sarcomas should be strongly encouraged to further advance research and improve patient outcomes.

With enhanced international collaboration, establishing a comprehensive registry could become a reality for more STS besides RPS. This registry could incorporate emerging advancements, including radiomics and biomarkers, and with the use of this extensive data and the growing capabilities of machine learning, the majority of research questions for a rare and heterogeneous disease like STS could be effectively addressed, paving the way for more personalized and precise treatment strategies.

Conclusion

Neoadjuvant systemic therapy for soft tissue sarcoma continues to present both challenges and promising opportunities. This thesis contributes to this field by identifying knowledge gaps, demonstrating methods to address them, and providing new insights into NAST for STS. Examples of these knowledge gaps are the missing consensus on pathological response and the lack of evidence on change in surgical approach after NAST. In this thesis, solutions were given on how to fill the knowledge gaps in the form of focusing on specific subtypes of sarcoma instead of sarcomas as a group, improving international collaborations, and objectifying change in extensiveness of surgery. The most important new insights were the efficacy of neoadjuvant chemotherapy in radiation associated angiosarcoma of the breast, the promising utility of (18)F-FDG PET/CT in response prediction, the lack of prognostic value of RECIST 1.1 in retroperitoneal sarcomas, and the objectified change in surgical approach after neoadjuvant imatinib for GIST.

References

1. Maas M, Nelemans PJ, Valentini V, Das P, Rödel C, Kuo LJ, et al. Long-term outcome in patients with a pathological complete response after chemoradiation for rectal cancer: a pooled analysis of individual patient data. Lancet Oncol. 2010;11(9):835-44.
2. Bielack SS, Kempf-Bielack B, Delling G, Exner GU, Flege S, Helmke K, et al. Prognostic factors in high-grade osteosarcoma of the extremities or trunk: an analysis of 1,702 patients treated on neoadjuvant cooperative osteosarcoma study group protocols. J Clin Oncol. 2002;20(3):776-90.
3. Lin PP, Jaffe N, Herzog CE, Costelloe CM, Deavers MT, Kelly JS, et al. Chemotherapy response is an important predictor of local recurrence in Ewing sarcoma. Cancer. 2007;109(3):603-11.
4. Conforti F, Pala L, Sala I, Oriecuia C, De Pas T, Specchia C, et al. Evaluation of pathological complete response as surrogate endpoint in neoadjuvant randomised clinical trials of early stage breast cancer: systematic review and meta-analysis. Bmj. 2021;375:e066381.
5. Su F, Yang X, Yin J, Shen Y, Tan L. Validity of Using Pathological Response as a Surrogate for Overall Survival in Neoadjuvant Studies for Esophageal Cancer: A Systematic Review and Meta-analysis. Ann Surg Oncol. 2023;30(12):7461-71.
6. Pennisi A, Kieber-Emmons T, Makhoul I, Hutchins L. Relevance of Pathological Complete Response after Neoadjuvant Therapy for Breast Cancer. Breast Cancer (Auckl). 2016;10:103-6.
7. Eilber FC, Rosen G, Eckardt J, Forscher C, Nelson SD, Selch M, et al. Treatment-induced pathologic necrosis: a predictor of local recurrence and survival in patients receiving neoadjuvant therapy for high-grade extremity soft tissue sarcomas. J Clin Oncol. 2001;19(13):3203-9.
8. Bonvalot S, Wunder J, Gronchi A, Broto JM, Turcotte R, Rastrelli M, et al. Complete pathological response to neoadjuvant treatment is associated with better survival outcomes in patients with soft tissue sarcoma: Results of a retrospective multicenter study. Eur J Surg Oncol. 2021;47(8):2166-72.
9. Salah S, Lewin J, Amir E, Abdul Razak A. Tumor necrosis and clinical outcomes following neoadjuvant therapy in soft tissue sarcoma: A systematic review and meta-analysis. Cancer Treat Rev. 2018;69:1-10.
10. Crombé A, Cousin S, Spalato-Ceruso M, Le Loarer F, Toulmonde M, Michot A, et al. Implementing a Machine Learning Strategy to Predict Pathologic Response in Patients With Soft Tissue Sarcomas Treated With Neoadjuvant Chemotherapy. JCO Clin Cancer Inform. 2021;5:958-72.
11. Lucas DR, Kshirsagar MP, Biermann JS, Hamre MR, Thomas DG, Schuetze SM, Baker LH. Histologic alterations from neoadjuvant chemotherapy in high-grade extremity soft tissue sarcoma: clinicopathological correlation. Oncologist. 2008;13(4):451-8.
12. Oda Y, Tanaka K, Hirose T, Hasegawa T, Hiruta N, Hisaoka M, et al. Standardization of evaluation method and prognostic significance of histological response to preoperative chemotherapy in high-grade non-round cell soft tissue sarcomas. BMC Cancer. 2022;22(1):94.
13. Schaefer IM, Hornick JL, Barysauskas CM, Raut CP, Patel SA, Royce TJ, et al. Histologic Appearance After Preoperative Radiation Therapy for Soft Tissue Sarcoma: Assessment of the European Organization for Research and Treatment of Cancer-Soft Tissue and Bone Sarcoma Group Response Score. Int J Radiat Oncol Biol Phys. 2017;98(2):375-83.

14. Rao SR, Lazarides AL, Leckey BL, Lane WO, Visgauss JD, Somarelli JA, et al. Extent of tumor fibrosis/hyalinization and infarction following neoadjuvant radiation therapy is associated with improved survival in patients with soft-tissue sarcoma. Cancer Med. 2022;11(1):194-206.
15. Boxberg M, Langer R, Woertler K, Knebel C, Rechl H, von Eisenhart-Rothe R, et al. Neoadjuvant Radiation in High-Grade Soft-Tissue Sarcomas: Histopathologic Features and Response Evaluation. Am J Surg Pathol. 2022;46(8):1060-70.
16. Fukui T, Matsui Y, Umeoka S, Inoue T, Kamba T, Togashi K, et al. Predictive value of radiological response rate for pathological response to neoadjuvant chemotherapy and post-cystectomy survival of bladder urothelial cancer. Jpn J Clin Oncol. 2016;46(6):560-7.
17. Bogani G, Matteucci L, Tamberi S, Ditto A, Sabatucci I, Murgia F, et al. RECIST 1.1 criteria predict recurrence-free survival in advanced ovarian cancer submitted to neoadjuvant chemotherapy. Eur J Obstet Gynecol Reprod Biol. 2019;237:93-9.
18. Reijers SJM, Gennaro N, Bruining A, van Boven H, Snaebjornsson P, Bekers EM, et al. Correlation of radiological and histopathological response after neoadjuvant radiotherapy in soft tissue sarcoma. Acta Oncol. 2023;62(1):25-32.
19. Gennaro N, Reijers S, Bruining A, Messiou C, Haas R, Colombo P, et al. Imaging response evaluation after neoadjuvant treatment in soft tissue sarcomas: Where do we stand? Crit Rev Oncol Hematol. 2021;160:103309.
20. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer. 2009;45(2):228-47.
21. Isaac C, Kavanagh J, Griffin AM, Dickie CI, Mohankumar R, Chung PW, et al. Radiological progression of extremity soft tissue sarcoma following pre-operative radiotherapy predicts for poor survival. Br J Radiol. 2022;95(1130):20210936.
22. Tseng WW, Barretta F, Conti L, Grignani G, Tolomeo F, Albertsmeier M, et al. Defining the role of neoadjuvant systemic therapy in high-risk retroperitoneal sarcoma: A multi-institutional study from the Transatlantic Australasian Retroperitoneal Sarcoma Working Group. Cancer. 2021;127(5):729-38.
23. Andrea Vanzulli RV, Ciriaco Buonomenna, Emanuela Palmerini, Vittorio Quagliuolo, Javier Martin Broto, Antonio L´opez Pousa, Giovanni Grignani, Antonella Brunello, Jean-Yves Blay, Robert D´ıaz-Beveridge, Virginia Ferraresi, Iwona A. Lugowska, Sara Pizzamiglio, Paolo Verderio, Valeria Duroni, Valeria Fontana, Carlo Morosi, Silvia Stacchiotti, Alessandro Gronchi; . Redefining radiologic responses (RR) in solid tumors: Shall we brace ourselves for a post-RECIST era? Results from a randomized clinical trial (RCT) on neoadjuvant chemotherapy in high-risk soft-tissue sarcomas (HR-STS) of the trunk or extremities. 2024.
24. Crombé A, Périer C, Kind M, De Senneville BD, Le Loarer F, Italiano A, et al. T(2) -based MRI Delta-radiomics improve response prediction in soft-tissue sarcomas treated by neoadjuvant chemotherapy. J Magn Reson Imaging. 2019;50(2):497-510.
25. Peeken JC, Asadpour R, Specht K, Chen EY, Klymenko O, Akinkuoroye V, et al. MRI-based delta-radiomics predicts pathologic complete response in high-grade soft-tissue sarcoma patients treated with neoadjuvant therapy. Radiother Oncol. 2021;164:73-82.
26. Benz MR, Czernin J, Allen-Auerbach MS, Tap WD, Dry SM, Elashoff D, et al. FDG-PET/CT imaging predicts histopathologic treatment responses after the initial cycle of neoadjuvant chemotherapy in high-grade soft-tissue sarcomas. Clin Cancer Res. 2009;15(8):2856-63.
27. Tateishi U, Kawai A, Chuman H, Nakatani F, Beppu Y, Seki K, et al. PET/CT allows stratification of responders to neoadjuvant chemotherapy for high-grade sarcoma: a prospective study. Clin Nucl Med. 2011;36(7):526-32.

28. Herrmann K, Benz MR, Czernin J, Allen-Auerbach MS, Tap WD, Dry SM, et al. 18F-FDG-PET/CT Imaging as an early survival predictor in patients with primary high-grade soft tissue sarcomas undergoing neoadjuvant therapy. Clin Cancer Res. 2012;18(7):2024-31.
29. Lordick F. Optimizing neoadjuvant chemotherapy through the use of early response evaluation by positron emission tomography. Recent Results Cancer Res. 2012;196:201-11.
30. Lordick F, Ott K, Krause BJ, Weber WA, Becker K, Stein HJ, et al. PET to assess early metabolic response and to guide treatment of adenocarcinoma of the oesophagogastric junction: the MUNICON phase II trial. Lancet Oncol. 2007;8(9):797-805.
31. Hassanzadeh-Rad A, Yousefifard M, Katal S, Asady H, Fard-Esfahani A, Moghadas Jafari A, Hosseini M. The value of (18) F-fluorodeoxyglucose positron emission tomography for prediction of treatment response in gastrointestinal stromal tumors: a systematic review and meta-analysis. J Gastroenterol Hepatol. 2016;31(5):929-35.
32. Lambin P, Rios-Velazquez E, Leijenaar R, Carvalho S, van Stiphout RG, Granton P, et al. Radiomics: extracting more information from medical images using advanced feature analysis. Eur J Cancer. 2012;48(4):441-6.
33. Fields BKK, Demirjian NL, Cen SY, Varghese BA, Hwang DH, Lei X, et al. Predicting Soft Tissue Sarcoma Response to Neoadjuvant Chemotherapy Using an MRI-Based Delta-Radiomics Approach. Mol Imaging Biol. 2023;25(4):776-87.
34. Dimitrakopoulou-Strauss A, Strauss LG, Egerer G, Vasamiliette J, Mechtersheimer G, Schmitt T, et al. Impact of dynamic 18F-FDG PET on the early prediction of therapy outcome in patients with high-risk soft-tissue sarcomas after neoadjuvant chemotherapy: a feasibility study. J Nucl Med. 2010;51(4):551-8.
35. Pasquali S, Colombo C, Pizzamiglio S, Verderio P, Callegaro D, Stacchiotti S, et al. High-risk soft tissue sarcomas treated with perioperative chemotherapy: Improving prognostic classification in a randomised clinical trial. Eur J Cancer. 2018;93:28-36.
36. Pasquali S, Palmerini E, Quagliuolo V, Martin-Broto J, Lopez-Pousa A, Grignani G, et al. Neoadjuvant chemotherapy in high-risk soft tissue sarcomas: A Sarculator-based risk stratification analysis of the ISG-STS 1001 randomized trial. Cancer. 2022;128(1):85-93.
37. Gronchi A, Stacchiotti S, Verderio P, Ferrari S, Martin Broto J, Lopez-Pousa A, et al. Short, full-dose adjuvant chemotherapy (CT) in high-risk adult soft tissue sarcomas (STS): long-term follow-up of a randomized clinical trial from the Italian Sarcoma Group and the Spanish Sarcoma Group. Ann Oncol. 2016;27(12):2283-8.
38. Joensuu H, Eriksson M, Sundby Hall K, Hartmann JT, Pink D, Schütte J, et al. One vs three years of adjuvant imatinib for operable gastrointestinal stromal tumor: a randomized trial. Jama. 2012;307(12):1265-72.
39. Lambdin J, Ryan C, Gregory S, Cardona K, Hernandez JM, van Houdt WJ, Gronchi A. A Randomized Phase III Study of Neoadjuvant Chemotherapy Followed by Surgery Versus Surgery Alone for Patients with High-Risk Retroperitoneal Sarcoma (STRASS2). Ann Surg Oncol. 2023;30(8):4573-5.
40. Comparison of two doses of imatinib for the treatment of unresectable or metastatic gastrointestinal stromal tumors: a meta-analysis of 1,640 patients. J Clin Oncol. 2010;28(7):1247-53.
41. Heinrich MC, Jones RL, von Mehren M, Schöffski P, Serrano C, Kang YK, et al. Avapritinib in advanced PDGFRA D842V-mutant gastrointestinal stromal tumour (NAVIGATOR): a multicentre, open-label, phase 1 trial. Lancet Oncol. 2020;21(7):935-46.
42. Bajpai J, Kumar R, Sreenivas V, Sharma MC, Khan SA, Rastogi S, et al. Prediction of chemotherapy response by PET-CT in osteosarcoma: correlation with histologic necrosis. J Pediatr Hematol Oncol. 2011;33(7):e271-8.

43. Byun BH, Kim SH, Lim SM, Lim I, Kong CB, Song WS, et al. Prediction of response to neoadjuvant chemotherapy in osteosarcoma using dual-phase (18)F-FDG PET/CT. Eur Radiol. 2015;25(7):2015-24.
44. Hu C, Chen W, Li F, Zhang Y, Yu P, Yang L, et al. Deep learning radio-clinical signatures for predicting neoadjuvant chemotherapy response and prognosis from pretreatment CT images of locally advanced gastric cancer patients. Int J Surg. 2023;109(7):1980-92.
45. Tan X, Yang X, Hu S, Ge Y, Wu Q, Wang J, Sun Z. Prediction of response to neoadjuvant chemotherapy in advanced gastric cancer: A radiomics nomogram analysis based on CT images and clinicopathological features. J Xray Sci Technol. 2023;31(1):49-61.
46. Lo Gullo R, Eskreis-Winkler S, Morris EA, Pinker K. Machine learning with multiparametric magnetic resonance imaging of the breast for early prediction of response to neoadjuvant chemotherapy. Breast. 2020;49:115-22.
47. Yang L, Chang J, He X, Peng M, Zhang Y, Wu T, et al. PET/CT-based radiomics analysis may help to predict neoadjuvant chemotherapy outcomes in breast cancer. Front Oncol. 2022;12:849626.
48. Crombé A, Spinnato P, Italiano A, Brisse HJ, Feydy A, Fadli D, Kind M. Radiomics and artificial intelligence for soft-tissue sarcomas: Current status and perspectives. Diagn Interv Imaging. 2023;104(12):567-83.
49. Toulmonde M, Penel N, Adam J, Chevreau C, Blay JY, Le Cesne A, et al. Use of PD-1 Targeting, Macrophage Infiltration, and IDO Pathway Activation in Sarcomas: A Phase 2 Clinical Trial. JAMA Oncol. 2018;4(1):93-7.
50. D'Angelo SP, Mahoney MR, Van Tine BA, Atkins J, Milhem MM, Jahagirdar BN, et al. Nivolumab with or without ipilimumab treatment for metastatic sarcoma (Alliance A091401): two open-label, non-comparative, randomised, phase 2 trials. Lancet Oncol. 2018;19(3):416-26.
51. Tawbi HA, Burgess M, Bolejack V, Van Tine BA, Schuetze SM, Hu J, et al. Pembrolizumab in advanced soft-tissue sarcoma and bone sarcoma (SARC028): a multicentre, two-cohort, single-arm, open-label, phase 2 trial. Lancet Oncol. 2017;18(11):1493-501.
52. Italiano A, Bessede A, Pulido M, Bompas E, Piperno-Neumann S, Chevreau C, et al. Pembrolizumab in soft-tissue sarcomas with tertiary lymphoid structures: a phase 2 PEMBROSARC trial cohort. Nat Med. 2022;28(6):1199-206.
53. Roland CL, Nassif Haddad EF, Keung EZ, Wang WL, Lazar AJ, Lin H, et al. A randomized, non-comparative phase 2 study of neoadjuvant immune-checkpoint blockade in retroperitoneal dedifferentiated liposarcoma and extremity/truncal undifferentiated pleomorphic sarcoma. Nat Cancer. 2024;5(4):625-41.
54. Mowery YM, Ballman KV, Hong AM, Schuetze SM, Wagner AJ, Monga V, et al. Safety and efficacy of pembrolizumab, radiation therapy, and surgery versus radiation therapy and surgery for stage III soft tissue sarcoma of the extremity (SU2C-SARC032): an open-label, randomised clinical trial. Lancet. 2024;404(10467):2053-64.
55. Martin-Broto J, Hindi N, Grignani G, Martinez-Trufero J, Redondo A, Valverde C, et al. Nivolumab and sunitinib combination in advanced soft tissue sarcomas: a multicenter, single-arm, phase Ib/II trial. J Immunother Cancer. 2020;8(2).
56. Clough KB, Acosta-Marín V, Nos C, Alran S, Rouanet P, Garbay JR, et al. Rates of Neoadjuvant Chemotherapy and Oncoplastic Surgery for Breast Cancer Surgery: A French National Survey. Ann Surg Oncol. 2015;22(11):3504-11.
57. Mougalian SS, Soulos PR, Killelea BK, Lannin DR, Abu-Khalaf MM, DiGiovanna MP, et al. Use of neoadjuvant chemotherapy for patients with stage I to III breast cancer in the United States. Cancer. 2015;121(15):2544-52.

58. Pasquali S, Gronchi A. Neoadjuvant chemotherapy in soft tissue sarcomas: latest evidence and clinical implications. Ther Adv Med Oncol. 2017;9(6):415-29.
59. Gani F, Goel U, Blair AB, Singh J, Overton HN, Meyer CF, et al. Minimally Invasive Versus Open Primary Resection for Retroperitoneal Soft Tissue Sarcoma: A Propensity-Matched Study From the National Cancer Database. Ann Surg Oncol. 2018;25(8):2209-17.
60. Gronchi A, Crago A, Raut CP. Minimally Invasive Surgery for Retroperitoneal Sarcoma: Just Because We Can Does Not Mean We Should. Ann Surg Oncol. 2018;25(8):2129-31.
61. Custers PA, van der Sande ME, Grotenhuis BA, Peters FP, van Kuijk SMJ, Beets GL, Breukink SO. Long-term Quality of Life and Functional Outcome of Patients With Rectal Cancer Following a Watch-and-Wait Approach. JAMA Surg. 2023;158(5):e230146.