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Summary
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Epithelial ovarian cancer constitutes a great healthcare issue with a high mortality. Therapeutic options depend on the extensiveness of the disease. Surgical removal of all visible tumour sites is the treatment of choice whereas chemotherapy is used as alternative when resection is deemed not viable or impossible. Ultrasound and computed tomography (CT) are the backbone of ovarian cancer diagnosis and characterization. However, other techniques such as magnetic resonance imaging (MRI) and positron emission tomography (PET) are being investigated for diagnostic purposes.

In this thesis we evaluate how we can use existing and novel imaging strategies to optimally guide treatment decisions with the objective to improve long term outcome of patients with ovarian cancer. Chapter 1 provides a general introduction and introduces the research questions which form the outline of this thesis.

In part I of this thesis we have used information on skeletal muscle derived from standard CT scans as predictive factors in retrospective ovarian cancer survival analyses. In Chapter 2 we studied advanced ovarian cancer patients (n=123) treated with interval debulking surgery and investigated whether changes in skeletal muscle were related to overall survival. We measured surface areas of skeletal muscle on CT scans which were taken before and after treatment with neoadjuvant chemotherapy and compared patients that maintained or gained skeletal muscle with patients that lost skeletal muscle during chemotherapy. Patients with skeletal muscle gain had a significantly better median overall survival of 1431 days compared to patients with skeletal muscle loss who had a median overall survival of 916 days (p=0.004). The predictive influence of skeletal muscle loss was confirmed in multivariable Cox-regression analysis. In this patient group, a skeletal muscle index lower than the median skeletal muscle index at the baseline CT scan before treatment with chemotherapy was not predictive of prognosis. In Chapter 3 we studied our second patient cohort which consisted of 216 patients treated with primary debulking surgery. In this group only a single pre-treatment CT scan was available for analysis. Instead of using the median SMI at baseline we performed optimum stratification to find the optimal skeletal muscle index cut-off to define sarcopenia, severe skeletal muscle loss. The aims of the study were to investigate if sarcopenia was associated with overall survival and if sarcopenia was associated with surgical complications. We found that sarcopenia was neither predictive of overall survival nor of surgical complications in ovarian cancer patients undergoing primary debulking surgery. However a strong trend towards a survival disadvantage for patients with sarcopenia was seen but other predictors such as completeness of surgery, treatment in a specialized centre and the development of major surgical complications showed a stronger relationship with overall survival. The effect of sarcopenia on overall survival may be more prominent when studied in a larger cohort of patients. To conclude part I we investigated whether assessment of psoas muscle area reflects total muscle area in Chapter 4. If so, measuring the psoas muscle area alone instead of the total skeletal muscle area on CT could be a quick and easy method to identify sarcopenia. To answer this question we quantified the psoas muscle with two...
methods; firstly with imaging software and secondly manually by measuring the length and width of this muscle. We compared this to quantifications of total muscle area in 150 ovarian cancer patients treated with interval debulking surgery. The correlation between total skeletal muscle area and both psoas area measurement methods was poor. After categorizing patients into muscle loss or gain, kappa agreement was also poor for comparison between total skeletal muscle area and either methods of psoas area. We concluded that a change in psoas muscle area was not representative of a change in total muscle area. Measurement of psoas area should not be used to substitute measurement of total skeletal muscle area to predict sarcopenia and survival in patients with ovarian cancer.

In part II we explored how accurate CT-based prediction models are to predict outcome of primary debulking surgery and we considered two new imaging techniques for the prediction of resectability: diffusion-weighted magnetic resonance imaging (DW-MRI) and combined positron emission tomography magnetic resonance imaging (PET/MRI). In Chapter 5 three prospectively developed CT prediction models for incomplete surgery (any tumour residual > 1 cm in diameter) by Ferrandina (models A and B) and by Gerestein were applied to a validation cohort consisting of 151 patients with advanced epithelial ovarian cancer. All three models showed a limited discriminative ability and the reproducibility of the models was questionable. The models were not sufficiently reliable for clinical decision making. A radiologist's subjective assessment was as accurate as using a prediction model. The high importance of selecting patients who will benefit from primary debulking surgery in combination with the limited performance of CT encouraged us to investigate novel diagnostic modalities in the prediction of ovarian cancer resectability. In Chapter 6 we investigated the diagnostic accuracy of PET/MRI and DW-MRI in comparison with CT for the assessment of surgical resectability. In this prospective pilot study, six patients treated with primary debulking surgery and four patients treated with neoadjuvant chemotherapy and interval debulking surgery were subjected to standard CT scans and a combined PET/MRI scan with DW-MRI. The two novel methods showed a trend towards an improved sensitivity compared to CT in the detection of peritoneal tumour deposits. However, the results for PET/MRI were mainly a reflection of the contribution of MRI; FDG accumulation was not present in the majority of (small) intraperitoneal tumour sites and PET imaging could not be used reliably to predict negative tumour sites. The predictive value of DW-MRI regarding ovarian cancer resectability in comparison to CT has shown promise in recent studies and deserves further investigation in larger prospective trials. A higher diagnostic performance is expected with optimization of the DW-MRI scan protocol on dedicated MRI devices.

Part III of the thesis was dedicated to investigating the value of ultrasound and MRI techniques in the characterization of adnexal tumours. Correct differentiation is essential for further treatment decisions. In Chapter 7 we provide the results of our meta-analysis in which we evaluated the diagnostic performance of contrast-enhanced
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MRI and DW-MRI for differentiation between benign and malignant adnexal masses. Thirty-eight datasets were included which resulted in good diagnostic accuracy for contrast-enhanced MRI with a sensitivity of 91% and a specificity of 89%. A high pooled sensitivity and specificity was also found for DW-MRI with a trend towards an improved diagnostic accuracy compared to MRI. More prospective studies establishing the added value of DW-MRI are still desired. A different strategy towards improving the characterization of adnexal masses incorporating DW-MRI was therefore proposed in Chapter 8 in which we provide the protocol for the prospective multi-centre cohort study SUBSONiC. The International Ovarian Tumour Analysis (IOTA) group successfully developed ten ultrasound rules to characterize an adnexal mass: the Simple Rules. Subjective assessment of an expert sonographer is known to improve the accuracy of adnexal ultrasound further. Our aim was to test the value of a two-step triage test consisting of 1) the Simple Rules, supplemented with 2) subjective assessment by an expert sonographer or DW-MRI in the differentiation between benign and malignant adnexal masses. This triage test was compared with current clinical practice in which the Risk of Malignancy Index is applied. This index incorporates five ultrasound variables, the menopausal status and serum CA-125 to predict the likelihood that an adnexal mass is malignant but results in an incorrect diagnosis in around 20% of patients. We hypothesized that implementation of the two-step triage test would result in a better diagnostic accuracy than use of the Risk of Malignancy Index. In Chapter 9 we report the results of our interim analysis in which we analyzed one of the secondary objectives of the SUBSONiC study, the interobserver variability between the primary ultrasound executed by an untrained examiner and the subjective assessment of the expert ultrasound executed by an examiner trained in the interpretation of the Simple Rules. The interim analysis provided data for the first 50 consecutive women enrolled in the SUBSONiC study. Frequent misclassification of the tumour type and misinterpretation of the Simple Rules by untrained examiners resulted in a poor interobserver agreement and an incorrect diagnosis (benign, malignant or inconclusive) in 30% of the patients when compared to the diagnosis made by the expert examiner. Due to the high rates of mistakes found at the interim analysis in both the use of IOTA terminology and application of the Simple Rules, the SUBSONiC study has been halted until further notice. Training programmes for gynaecologists and gynaecological residents are necessary before the SUBSONiC study can be restarted and before assumptions can be made about the diagnostic performance of the model.