Today, with the high cure rates presented for disseminated testicular cancer (TC) after treatment with cisplatin-based combination chemotherapy, higher than for any other metastasized cancer treated with chemotherapy, it is hard to imagine how these results can be improved beyond the current results. This success comes at the price of late- and long-term toxicity caused by the initial treatment. The impact of the burden of these late- and long-term effects becomes increasingly clear. Hence, there is a noticeable shift in the focus of testicular cancer research aiming to reduce or prevent treatment-related morbidity. Reducing morbidity of treatment also starts with reducing patient and doctor delay when diagnosing testicular cancer. Today given the increasing incidence of TC, it is important to keep the focus on better education to the general public, e.g., adolescents (and their parents) and young adults, as well as physicians to increase awareness and knowledge about testicular cancer and subsequently decreasing delay. Research has shown that there is a trend in reduction of tumor size at presentation through the years and men presenting with TC are younger of age at first presentation. Therefore, promotion of regular periodic testicular self-examination and public education should remain important initiatives. Health care providers who aim to develop education programs to increase TC awareness in young men should take into account that men who feel embarrassed about scrotal changes and lower educated men may benefit most from their programs.

When evaluating retroperitoneal residual tumor masses after completion of cisplatin-based combination chemotherapy in patients with a biochemical complete remission, it is not possible to make the distinction between malignant and non-malignant disease. To date, resection of these masses is still seen as the most accurate staging method and treatment, since 40-45% of these masses contain teratoma and 10-15% viable germ cell tumor. About 40-50% of patients who have necrotic and/or fibrotic residual masses, are unnecessarily exposed to surgery and gain no benefit from resection of these masses. Diagnostic workup of patients with residual masses remains a clinical challenge and more research is needed to determine accurate markers to predict viable residual disease. There is no diagnostic imaging tool that can help discriminate between viable germ cell cancer, mature teratoma or fibrosis. In this thesis, one focus was on investigating and exploring a new modality, in specific volumetric analysis, which can be applied to monitor treatment response for advanced NSTGCT and help distinguish responders from non-responders. The future usage of volumetric analysis in retroperitoneal lymph
node masses in advanced NSTGCT can be promising, but more research is needed to define its merits in this specific patient category.

Advances made in molecular medicine, specifically in microRNA (miRNA) biology since the discovery in 1993 have been promising and have markedly benefited TGCT research. These miRNAs have gained importance because of specific characteristics, such as high stability in body fluids and easy detection, allowing miRNAs to act as novel biomarkers. In TGCT research the miRNA-371-3 cluster is of specific interest being overexpressed in malignant TGCTs. A first report of this important finding was published in 2011 with a decline of serum miRNA levels after treatment of a patient with paediatric TGCT. More recently Léaño and colleagues analyzed serum levels of three miRNAs (miR-371a-3p, miR-373-3p, and miR-367-3p) in patients who were treated for advanced TGCT. These measurements were evaluated in relation to clinical characteristics and serum tumor markers and also tumor histology after therapy. In this study it was concluded that miR-371a-3p serum level seemed to be a useful biomarker in TGCTs predicting the presence of viable residual disease after treatment. Although more research is needed, for example with regard to the specificity of miR-371a-3p as a biomarker, the potential of using miR-371a-3p as a new additive biomarker could have a positive influence on the management of advanced TGCTs. Currently such fundamental research is being performed at our center in a cohort of testicular cancer patients with recurrent or refractory disease after cisplatin based combination chemotherapy. This line of research could result in a lower frequency of routine follow up CT scans of chest and abdomen and therefore reduced radiation burden and more importantly a specific group of patients could be identified in which comfortably a wait-and-see policy can be executed and unnecessary surgery can be avoided.

In this thesis the main focus has been placed on minimally invasive procedures to resect retroperitoneal residual tumor masses. Morbidity associated with a conventional midline laparotomy is high and therefore even in advanced stages, laparoscopic procedures are continuously more performed. In the nearby future other minimally invasive procedures, such as the robot-assisted retroperitoneal lymph node dissection will also be more frequently used. With the availability of the Da Vinci Robot at the UMCG in 2018, this robotic technique to resect residual retroperitoneal tumor masses will be explored in the treatment of disseminated testicular cancer. Advantages for patients are thought to be equal to laparoscopic surgery with less morbidity compared to a laparotomy. Also there are indications that improved visualization and dexterity over conventional laparoscopy, can lead to significantly reduced morbidity for the TC patient. In times where surgeons are facing an ergonomic crisis, where increasingly complex laparoscopic procedures are executed, another important advantage is that robotic surgery also offers optimal ergonomics for the operating surgical oncologist.

Over the last decades significant strides have been made in testicular cancer research, and small steps but equally important steps will follow. Fine tuning management regarding the treatment in testicular cancer should always continue since although rare, testicular cancer overwhelmingly occurs in young men and is the most common cancer in young men. Even in the future, treatment in testicular cancer should serve as an example for the treatment of other cancers. Another important part of the current and future research at the UMCG is to improve insight in the pathogenesis of short- and long-term treatment related side effects and how to manage them. Several projects concern the identification of TC patients who are more susceptible to treatment related morbidity. This treatment related morbidity in TC survivors resemble the accelerated aging phenotype. TC patients at a high risk for late effects might benefit from intervention strategies such as lifestyle and physical activity programs. Intervention trials to address these issues are currently performed at the UMCG. Another important issue is how to take care of the increasing number of TC survivors. Just recently a shared care survivorship program for testicular cancer survivors, in which follow-up was done by the oncologist together with the patient and his primary care physician, was completed and appeared to be safe. For the nearby future such developments are of importance for the increasing number of testicular cancer survivors. The ultimate goal remains to improve the short and long-term outcome of patients with testicular cancer.

References


