Tampere University

RIIKKA-LIISA VUORINEN

Costs of Cancer Treatment

Focus on Robotic Surgery and Anti-Angiogenetic Agents

Tampere University Dissertations 257

Tampere University Dissertations 257

RIIKKA-LIISA VUORINEN

Costs of Cancer Treatment

Focus on Robotic Surgery and Anti-Angiogenetic Agents

ACADEMIC DISSERTATION
To be presented, with the permission of
the Faculty of Medicine and Health Technology
of Tampere University,
for public discussion at Tampere University,
on 5th of June 2020, at 12 o'clock.

ACADEMIC DISSERTATION
Tampere University, Faculty of Medicine and Health Technology
Tampere University Hospital, Department of Obstetrics and Gynecology
Finland

Responsible supervisor and Custos
Professor Emerita
Johanna Mäenpää
Tampere University
Finland

Supervisor
Professor Emerita
Pirkko-Liisa Kellokumpu-Lehtinen
Tampere University
Finland

Pre-examiners
Associate Professor
Paulus Torkki
University of Helsinki
Finland

Docent
Katriina Peltola
University of Helsinki
Finland

Opponent
Docent
Johanna Hynninen
University of Turku
Finland

Cover design: Roihu Inc.

ISBN 978-952-03-1570-2 (print)
ISBN 978-952-03-1571-9 (pdf)
ISSN 2489-9860 (print)
ISSN 2490-0028 (pdf)
http://urn.fi/URN:ISBN:978-952-03-1571-9

PunaMusta Oy – Yliopistopaino
Tampere 2020

Rakkaimmilleni, Eetulle, Ollille ja Paulille

"Smile though your heart is aching

Smile, even though it's breaking

When there are clouds in the sky, you'll get by

If you smile through your fear and sorrow

Smile and may be tomorrow

You'll see the sun come shining through, for you."

Charlie Chaplin, John Turner, Geoffrey Parsons

ACKNOWLEDGEMENTS

The research work was carried out at the Department of Gynecology and Obstetrics of Tampere University hospital, Departments of Oncology in Tampere, Turku, Kuopio and Oulu University hospitals and Vaasa Central hospital and also in collaboration with the Universities of Tampere, Turku and Kuopio. A research grant from Tampere University and the Competitive State Financing of the Expert Responsibility Area of Tampere University Hospital supported the work financially.

To start from the beginning…

I want to express my warm and deep gratitude to my responsible supervisor Professor Emerita Johanna Mäenpää. I truly value her strong expertise and I am grateful for all the time and energy she has invested in me and this project. A thesis is kind of an obtacle course and her support and counsel kept me going, for which I will be forever grateful. Thank you.

Since life sometimes has a strange sense of humor, my second supervisor was Professor Emerita Pirkko-Liisa Kellokumpu-Lehtinen, also known as my mom. My mother is one of the strongest women I know, therefore life outside work might be interesting with two strong willed women. Yet, I could not have hoped for a better guide for this journey. Her firm expertise and guidance gave me the strenght I needed to finally reach this goal. Thank you, love you mom.

Research is always somewhat of a group project and I have been very lucky to have been surrouded by talented people throughout these project years. I would like to express my warm gratitude to all of them. PhD Timo Purmonen has been the co-author and the financial expert in two of these projects and I have had the priviledge to work with him even before these studies. Professor Emeritus Seppo Pyrhönen initially supervised my medical licenciate master's thesis, I am grateful for his guidance since then. Warm thank you to M.D. Päivi Nuttunen, Docent Vesa Kataja, Professor Taina Turpeenniemi-Hujanen, M.D. Taina Reunamo, Docent Antti Jekunen, Professor Emeritus Harri Sintonen for your valuable contribution on these projects and the publications. To M.D. Ph.D. Niina Paunu also a thank you for your happy emails, I could always picture your smile in them. These people have given a lot for this project, especially on the oncology side of it. Closer to my own expertise,

I had a priviledge to work in a top research project concerning robotic-assisted surgery. Thank you M.D., Ph.D. Minna Mäenpää, for trusting me with this part of your own work. To Docent Kari Nieminen and Docent Eija Tomás, thank you for your support and advice. And also a thank you to Professor Anssi Auvinen for stairway consultations and for his advice concerning my project.

M.Sc. Tiina Luukkaala, deserves a special thank you for research statistic help and work. I could have not survived through those reefs without you.

I am in gratitude to all my co-authors for their expert contribution and kind, yet insightful comments.

I truly appreciate the work of my official pre-examiners, assistant Professor Paulus Torkki and Docent Katariina Peltola. Your kind, yet critical and intuitive comments gave a valuable final contribution to my manuscript. Thank you Docent Annika Auranen and Docent Minna Tanner for being my follow-up group.

The financial side of the first and the second study could not have been executed without the help of Mikko Hannola, Katriina Hepokari and Sonja Petäjäjärvi concerning Ecomed and Tableau data. Without you it would have been much harder to decide what to do with all that money.

My colleagues and other co-workers at the Department of Gynecology and Obstetrics in Tampere University hospital deserve my gratitude for fruitfull working atmosphere. You make me smile and hopefully sometimes I can return the favour.

I would also like to express my deep gratitutude to the teaching team of Gynecology and obstetrics, Professor Hannele Laivuori, clinical teachers Jutta Sikkinen and Eeva Pohjonen, teaching coordinators Kristiina Kujanpää and Sanna-Kaisa Kukko. Your support during these last one and a half years has been priceless. It is a priviledge to work as a part of such an amazing teaching team.

My teacher colleague, co-worker and friend Laura Kotaniemi-Talonen, I cannot give you a big enough hug for all your support, advice and friendship. Especially thank you for tolerating my craziness.

I would also like to place a warm thank you to Ronja, our summer nanny 2019 summer. It was important for me to have a person like you to entertain and take care the boys while ”äiti tekee taas väitöskirjaa…”. Trust is a crucial thing in all kinds of relationships, especially in these kinds.

All my friends, thank you! There are so many of you, who have supported me through these years, I feel priviledged. Especially during these final years towards becoming a specialist in gynecology and obstetrics, I have found such a group of amazing people, I cannot appreciate you enough. Particularly F… Allstars, you know who you are, hugs.

The extracurricular activities kept me sane during this entire project. Therefore I would like to give a warm hug to my Tennis Ladies Suvi, Johanna and Noora. Stress can truly be released through upper extremities. However, the best place in the world to escape a project this magnitude is the stables. For the best counter balance ever, I will eternally be in gratitude to Reija, Lotta, Ritu, Ave, Saija, my Wednesday Chaos -group and all the rest of my friends in Sappeen Ratsutila. Most of all a huge bag of carrots with cuddlings to my furry friends, early on Vennu and now my own precious, one in a million, Uljas U. Also cuddlings to Roope, your paw print in my heart is eternal. 🐾

To my best friend since forever, Juusi, I am forever grateful. You have always believed in me, even when I have doubted myself, thank you. Hopefully I can show you mutual support. Growing up with you has been a priviledge, LYLAS.

Thank you to my family through marriage, Annukka, Heikki, Sanna, Thomas, Matti and Suvi. You have made my life again more rich and full. And hugs to all the kids.

Dad, I love you, you are my stability, hug. My brothers Sampsa and Ilari, I love you, you drive me crazy. Hanna and Heidi also deserve a huge hug as well as all the kids in Helsinki.

And finally I would like to apologize to my children Olli and Eetu for this time consuming project. It's over now, so hopefully you don't have to hear the word "väitöskirja" from my part ever again. You are truly my world, my everything, my sunshine, I love you so much. Thank you for being so patient. My husband Pauli, you are my rock, my shoulder to cry on, a warm cuddle in the cold world. Your support through this journey has been irreplaceable. As I leave this project behind, I look forward to the next chapter with you. I love you.

While writing these words the world is struggling with the COVID-19 pandemic. It has changed many things, yet this project shows that there was life before the pandemic and life goes on after the pandemic, in some form.

April 2020,

Riikka-Liisa Vuorinen

ABSTRACT

Cancer creates a significant burden to society in many ways, and as the population is aging, this burden will profoundly increase in the future. The costs of cancer treatment influence the economical approach of different treatment modalities and affect the decisions regarding the treatment choices provided to patients. This thesis collects our findings of the treatment costs related to the operative treatment of endometrial cancer, the bevacizumab and chemotherapy treatment of epithelial ovarian cancer, and the interferon-α and sunitinib treatment of metastatic renal cell cancer.

The primary treatment for endometrial cancer is surgery, which can be executed as an open approach by laparotomy or by using minimally invasive techniques, including traditional laparoscopy or robotic-assisted laparoscopy. In the framework of a randomized prospective trial, the cost differences were calculated between these two minimally invasive techniques (traditional group n=51, robotic-assisted group n=50) retrospectively. The surgeries included the removal of the gynecological organs and the pelvic lymph nodes. The robotic-assisted laparoscopy was found to be approximately 2,000 € more expensive than the traditional approach. The main difference in the cost was due to the robotic instrumentation and the amortization of the robot console. Even though the original trial results presented a shorter operative time with the robotic-assisted approach, the time difference was not enough to compensate for the cost differences.

In epithelial ovarian cancer angiogenesis plays a significant role in the advancement of the disease. Bevacizumab is a vascular endothelial growth factor inhibitor and has therefore been used in the treatment of ovarian cancer. The treatment has been directed to patients with advanced disease or to patients with recurrent disease who have not received bevacizumab as primary treatment. The study population consisted of 75 ovarian cancer patients who were diagnosed between 2011 and 2012 at Tampere University Hospital, and who were followed-up until the end of 2017. Of the patients, 66 were given chemotherapy, and they formed the focus of the analysis. The costs were calculated during medical treatment (bevacizumab and/or chemotherapy) while the surgical costs were not included in the analysis. Bevacizumab was used in 24 patients, of whom 16 received this drug as

part of their first-line therapy and eight received it as a later treatment. The medical treatment and all the related variables (follow-up, on-call visits, imaging, laboratory samples, inpatient stay, granulocyte colony stimulating factors) for the 66 patients cost a total of 2,404,521 €, and bevacizumab accounted for 47.1%. The median cost of treatment per patient was 22,115 €; in the non-bevacizumab group (n=42) 7,700 € and in the bevacizumab group (n=24) 82,542 €. In the non-bevacizumab group the cost of inpatient stay accounted for 40% of the costs and was the main cost driver.

Interferon-α was the primary treatment choice for metastatic renal cell cancer for a couple of decades. Data on 83 patients treated with first-line interferon-α for metastatic renal cell carcinoma was retrospectively collected: medication, inpatient stay, outpatient visits, radiotherapy, surgical procedures, nursing home stays and diagnostics. An estimation of future burden was conducted based on the epidemiological data and incidence of renal cell cancer, and projections for population change. Medication costs, including those for interferon-α comprised 60% of the total treatment costs during interferon-α treatment and accounted for only 6% after the treatment was discontinued. The median cost of interferon-α medication per patient was 7,130 €. However, during the entire follow-up period factors other than medical treatment accounted for 73% of the total costs and 79% of these costs were associated with inpatient stays. Future estimation yielded an increase in renal cell cancer burden and therefore an increase in the treatment costs. Sunitinib was at the time a promising new approach and was therefore also included in future estimations on the burden of cancer costs. In Finland, the cost burden of an estimated 227 new annual patients with metastatic disease was 15,600,000 € in five years and assuming that half of these patients would receive sunitinib, the annual treatment costs would increase by an average of 2,700,000 €. These estimations only include first-line treatment. The cost analysis and future estimations indicate an increase in the economic burden of metastatic renal cell cancer.

Even though new treatment modalities are emerging, sunitinib is still a valid treatment for advanced renal cell cancer. The final part of this study evaluated the costs and effects of sunitinib treatment in patients with metastatic renal cell cancer. A total of 81 patients receiving first-line sunitinib were recruited for this prospective study. Information was collected during the follow-up period regarding drug doses, laboratory and imaging studies, outpatient visits and inpatient stays. The health-related quality of life was measured with the 15D- and EQ-5D-3L questionnaires. Sunitinib treatment itself accounted for the largest proportion of the treatment cost at 73%, and the mean was 22,268 € per patient, while the total treatment cost was 30,530 € per patient. A decrease in quality of life during the treatment was found;

however, it remained rather constant during the treatment period. Notably, quality of life was already poorer among these patients at baseline than in the age- and gender- standardized general population.

As new treatments emerge it is crucial to evaluate treatment costs and the cost effectiveness. Treatment costs arise from different variables, and all of these variables need to be taken into account when detailed and specific information is required. It is also important to consider the differences in treatment modalities and in healthcare systems between nationalities when calculating treatment costs. A detailed cost analysis helps to identify the main drivers of cost during treatment and to direct the resources in use in a more sustainable way.

TIIVISTELMÄ

Syövän yhteiskunnalliset vaikutukset ovat lukemattomat ja väestön ikääntyessä taakka tulee lisääntymään. Syövänhoidon kustannukset vaikuttavat eri hoitojen valintaan ja myös siihen, millaisia hoitoja on tarjolla. Tähän väitöskirjaan on koottu hoitojen kustannuksiin liittyviä havaintoja ja tuloksia. Aihepiireinä ovat leikkaushoito kohtusyövässä, bevasitsumabihoito epiteliaalisessa munasarjasyövässä ja interferoni-α sekä sunitinibi -hoidot levinneessä munuaissyövässä.

Kohtusyövän ensisijainen hoito on leikkaus. Leikkaushoito voidaan toteuttaa avoimesti laparotomiana tai mini-invasiivisella lähestymistavalla, perinteisenä tähystysleikkauksena tai robottiavusteisena tähystysleikkauksena. Ryhmämme toteutti satunnaistetun prospektiivisen tutkimuksen vertaillen kahta viimeksi mainittua tekniikkaa (perinteinen n=51, robottiavusteinen n=50) ja kustannukset laskettiin molemmille lähestymistavoille retrospektiivisesti. Toteutettuun leikkaukseen sisältyi gynekologisten elimien ja lantion imusolmukkeiden poisto. Robottiavusteinen tekniikka oli noin 2 000 € kalliimpi kuin perinteinen tähystyskirurgia. Suurin osa kustannuserosta johtui robottikonsoliin liittyvistä kuoletuskustannuksista ja robotti-instrumentaation hinnasta. Vaikka alkuperäisessä tutkimusasetelmassa robottiavusteinen tähystysleikkaus oli nopeampi toteuttaa, ajallinen ero toimenpiteiden välillä ei ollut riittävä kompensoimaan kustannuksista syntyvää eroa.

Angiogeneesi eli verisuonten uudismuodostus on tunnistettu tekijä epiteliaalisen munasarjasyövän synnyssä ja leviämisessä. Bevasitsumabi estää verisuonten kasvutekijän vaikutusta ja sen myötä bevasitsumabia on käytetty munasarjasyövän hoitoon. Hoito on kohdistettu potilaille, joilla on jo diagnoosivaiheessa edennyt tauti tai potilaille, joilla tauti uusii eikä bevasitsumabia ole käytetty ensilinjan hoidossa. Otoksemme kattoi 75 potilasta, joiden epiteliaalinen munasarjasyöpä diagnosoitiin 2011-2012 Tampereen yliopistollisessa sairaalassa. Seurannan päätepäivä oli 31.12.2017. Kustannukset laskettiin niiden 66 potilaan osalta, jotka olivat saaneet syövän lääkehoitoja. Potilaat, jotka eivät saaneet lääkkeellistä hoitoa, jätettiin pois kustannusanalyysistä. Kustannukset laskettiin lääkehoidon ajalta ja mahdollisia operatiiviseen hoitoon liittyviä kustannuksia ei otettu huomioon. Kaiken kaikkiaan 24 potilasta sai bevasitsumabihoitoa, heistä 16 osana ensilinjan hoitoa ja kahdeksan

myöhemmissä hoidon vaiheissa. Lääkehoito ja siihen liittyvät tekijät (seurantakäynnit, päivystyskäynnit, kuvantaminen, verikokeet, osastohoito ja valkosolukasvutekijät) 66 potilaan osalta maksoivat yhteensä 2 404 521 €, josta bevasitsumabin osuus oli 47,1 %. Potilaskohtainen mediaani kustannus oli 22 115 € koko otannassa; ei-bevasitsumabiryhmässä (n=42) 7 700 € ja bevasitsumabiryhmässä (n=24) 82 542 €. Osastohoito selitti suurimman osan (40 %) ei-bevasitsumabiryhmän hoidon kustannuksista ja oli näin ollen suurin yksittäinen kustannustekijä.

Interferoni-α on ollut aiemmin parin vuosikymmenen ajan levinneen munuaissyövän ensilinjan hoito. Keräsimme retrospektiivisesti tiedot 83 metastaattista munuaissyöpää sairastavasta ensilinjan interferoni-α -hoidetusta potilaasta: lääkitys, osastohoito, poliklinikkakäynnit, sädehoito, leikkaustoimenpiteet, hoitokotijaksot ja diagnostiikkaan liittyvät asiat. Lisäksi toteutettiin tulevaisuuden syöpäkuormitusarvio perustuen epidemiologisiin tietoihin, munuaissyövän insidenssiin ja väestömuutoksen ennusteisiin. Lääkekustannukset, jotka sisälsivät interferoni-α-hoidon, muodostivat 60 % kokonaishoidon kustannuksista interferoni-α-hoidon aikana ja vain 6 % interferoni-α-hoidon jälkeen. Potilaskohtainen interferoni-α-lääkityksen mediaanikustannus oli 7 130 €. Kuitenkin huomioidessa koko seuranta-aika, muun kuin lääkehoidon kustannusten osuus oli 73 %, joista 79 % muodostui osastohoidosta. Tulevaisuusarvio osoitti munuaissyöpäpotilaiden määrän kasvavan ja sen myötä myös hoidon kustannusten lisääntyvän. Arvioon sisällytettiin myös lupaavan hoidon, sunitinibin, osuuden kasvu. Suomessa 227 vuotuisen uuden levinneen munuaissyöpäpotilaan kustannukset olivat noin 15 600 000 € viiden vuoden ajalta. Jos puolet näistä tulisi saamaan sunitinibihoitoa, vuotuinen kokonaiskustannus nousisi keskimäärin 2 700 000 €. Näihin arvioihin sisällytettiin vain ensilinjan hoito. Kustannusanalyysi ja tulevaisuusarvio osoittavat levinneen munuaissyövän taloudellisen taakan merkittävän kasvun.

Vaikka uusia kohdennettuja hoitoja kehitetään jatkuvasti, sunitinibi on puolustanut asemaansa hoito-ohjeissa. Viimeisessä osatyössä keskityttiin sunitinibihoidon kustannuksiin ja hoidon elämänlaadullisiin vaikutuksiin. Kaiken kaikkiaan 81 potilasta rekrytoitiin mukaan tähän prospektiiviseen tutkimukseen. Tutkimuksen seuranta-aikana kerätyt tiedot sisälsivät lääkeannokset, verikokeet, kuvantamistutkimukset, poliklinikkakäynnit ja osastohoidot. Elämänlaatua kartoitettiin 15D- ja EQ-5D-3L- kyselyillä. Itse sunitinibihoito kattoi suurimman osan kustannuksista, 73 %, tarkoittaen keskiarvona potilaskohtaisesti 22 268 €, kun koko hoitojakson potilaskohtainen kustannus oli 30 530 €. Elämänlaatu laski hoidon aloituksen myötä, mutta säilyi varsin vakaana hoidon ajan. Huomattavaa oli kuitenkin

se, että elämänlaatu oli jo hoidon aloituksessa sunitinibipotilailla huonompi kuin ikä- ja sukupuolivakioidulla normaaliväestöllä.

Uusia syöpähoitoja kehitetään jatkuvasti, minkä vuoksi on erittäin tärkeää arvioida ja laskea myös hoitojen kustannuksia sekä kustannusvaikuttavuutta. Kokonaiskustannukset muodostuvat useista eri tekijöistä ja nämä kaikki tulee ottaa huomioon, kun halutaan todellista tietoa hoidon kustannuksista. Lisäksi tulee ottaa huomioon kansalliset erot hoitojen toteutuksessa ja terveydenhuoltojärjestelmissä kustannuksia kartoitettaessa. Yksityiskohtainen kustannusanalyysi auttaa myös määrittämään eniten kustannuksiin vaikuttavat tekijät ja näin ollen ohjaamaan resursseja hoidossa oikealla tavalla.

TABLE OF CONTENTS

ABBREVIATIONS

CA12-5	Cancer antigen 125
CEA	Carcinoembryonic antigen
CI	Confidence interval
CRP	C-reactive protein
CT	Computed tomography
CTLA-4	Cytotoxic T-lymphocyte-associated antigen 4
DFS	Disease free survival
EC	Endometrial cancer
EGF	Epidermal growth factor
FIGO	International Federation of Gynecology and Obstetrics
FIMEA	Finnish Medicines Agency
G-CSF	Granulocyte colony stimulating factor
HE4	Human epididymal secretory protein
HGSC	High grade serous carcinoma
HNPCC	Hereditary non-polyposis colon cancer
HR	Hazard ratio
HRQoL	Health-related quality of life
HRT	Hormone replacement therapy
ICER	Incremental cost-effectiveness ratio
IFN-α	Interferon-α
IGF	Insulin-like growth factor
IL-2	Interleukin-2
IMDC	International Metastatic RCC Database Consortium
IQR	Interquartile range
ISUP	The International Society of Urological Pathology
LVSI	Lymphovascular space invasion
mRCC	Metastatic renal cell cancer
Md	Median
MRI	Magnetic resonance imaging
MSKCC	The Memorial Sloan Kettering Cancer Center

mTOR	Mechanistic target of rapamycin
NICE	National Institute for Health and Care Excellence
OC	Ovarian cancer
OR	Operating room
OS	Overall survival
PACU	Postanesthesia care unit
PALKO	Terveydenhuollon palveluvalikoimaneuvosto
PARP	Poly(ADP-ribose) polymerase
PD-1	Programmed cell death 1
PDGF	Platelet-derived growth factor
PDL-1	Programmed cell death-ligand 1
PFS	Progression free survival
PET-CT	Positron emission tomography-computed tomography
PLD	Pegylated liposomal doxorubicin
POLE	Polymerase epsilon
pTNM	pathological tumor, node and metastasis
QALY	Quality-adjusted life year
QoL	Quality of life
RCC	Renal cell cancer
RT	Radiotherapy
TAP	Doxorubicin, cisplatin, paclitaxel combination treatment
TCGA	The Cancer Genome Research Atlas Network
TKI	Tyrosine kinase inhibitor
TNM	Tumor, node and metastasis
UICC	The Union for International Cancer Control
VAS	Visual analog scale
VEGF	Vascular endothelial growth factor
WHO	World Health Organization

ORIGINAL PUBLICATIONS

This thesis is based on the following original publications. In the text, these are referred to by their Roman numerals (I-IV).

I Vuorinen R-L, Mäenpää M, Nieminen K, Tomas E, Luukkaala T, Mäenpää J. Costs of robotic surgery vs traditional laparoscopy in endometrial cancer. *International Journal of Gynecological Cancer 2017,;27(8):1788-1793.*

II Vuorinen R-L, Luukkaala T, Mäenpää J. The Influence of bevacizumab on the costs of ovarian cancer treatment in routine clinical practice. *Acta Oncologica 2020;59(4):453-457.*

III Purmonen T, Nuttunen P, Vuorinen R, Pyrhönen S, Kataja V, Kellokumpu-Lehtinen P-L. Current and predicted cost of metastatic renal cell carcinoma in Finland. *Acta Oncologica 2010;49(6):837-843.*

IV Vuorinen R-L, Paunu N, Turpeenniemi-Hujanen T, Reunamo T, Jekunen A, Kataja V, Sintonen H, Purmonen T, Kellokumpu-Lehtinen P-L. Sunitinib first-line treatment in metastatic renal cell carcinoma: costs and effects. *Anticancer Research 2019;39(10):5559-5564.*

The original publications are presented with the permission of the copyright holders. In addition, there are some unpublished data included in this thesis.

1 INTRODUCTION

In 2018, there were over 18,000,000 new cancer cases in the world. Over 9.5 million cancer-related deaths occurred during that same year, and cancer is currently the leading cause of death worldwide. (WHO statistics; Torre et al. 2015) The incidence of cancer is increasing because of the growth and aging of the population. People are also adopting more cancer risk-related behaviors and lifestyles, such as smoking, reduced activity, obesity, delayed childbirth and fewer childbirths, which all lead to an increase in cancer incidence. This increased incidence is already evident in both high-income countries and low- and middle-income countries. (Torre et al. 2015; Torre et al. 2016)

During the past several decades, cancer has had a significant financial impact both at individual and societal levels. The direct costs of cancer treatments are associated with surgical operations, radiotherapy, cancer drugs, cancer follow-up visits, emergency visits, inpatient stays, laboratory tests, imaging studies and other medications related to the treatment and the disease itself. The additional societal costs include indirect costs, such as loss of productivity (work absences, permanent disability, death before age 65), and costs related to prevention, screening and rehabilitation. Treatments are chosen according to treatment guidelines and are dependent on the stage of cancer and the patient's performance status and comorbidities at the time of diagnosis. (Jönsson, Wilking 2007; Luengo-Fernandez et al. 2013; Torre et al. 2017)

The increase in cancer incidence influences the expenditures and the burden it creates. The costs of diagnostics and treatment have increased due to new imaging methods and cancer screening programs. Another change, to patients' benefit, is that improvements in cancer treatment have led to better outcomes. Overall cancer mortality has been shown to be declining, and cancer survival has generally improved; however, there is a vast variability between different cancer types. This positive change is due to improvements in the possibility of early detection and cancer treatments. Decreased mortality, however, means that there is a growing number of working-age patients living with cancer. In terms of cost, this decreased mortality increases the expenditures of continued cancer care and rehabilitation as

well as increases loss of productivity in working-age patients, even though loss of productivity is obviously also evident if the patient dies. (Jönsson et al. 2016; Kang et al. 2016)

New cancer treatments are often expensive, which also contributes to the international burden of increasing cancer costs (Dolgin 2018). This expense has led to the discussion of equal distribution and accessibility of treatment options and new treatments. More careful cost effectiveness analyses are needed to determine the true benefit of treatments. (Hillner and Smith 2009; Bernard et al. 2011; Smith 2011; Mazzucato 2016; Dolgin 2018; Voda et al. 2018; Chien et al. 2019).

The WHO has presented willingness-to-pay thresholds of 100,000 USD, but 100,000 USD-150,000 USD is also used. However, the WHO also suggests that these types of thresholds should be created nationally related to the nations' per-capita gross domestic product. To compare the cost effectiveness of new treatments, incremental cost-effectiveness ratio (ICER) presented as USD/Quality-adjusted life year (QALY), has been developed. (Bertram et al. 2016; Torkki et al. 2018; Chien et al. 2019)

This thesis examines the costs of four known cancer treatments. All the studied treatments have been considered during their time, or still are considered, to be expensive. The cancers evaluated in these studies include endometrial cancer (cancer of corpus uteri, EC), ovarian cancer (focus on epithelial ovarian cancer, OC) and renal cell cancer (RCC). The focus has been mainly on the direct costs related to the treatments and non-healthcare related societal costs have been excluded from the studies. The number of new cases, incidence, number of deaths and ordinal number in these categories of EC, OC and RCC are presented in **Table 1**.

Table 1. Incidence and Mortality in 2018. (WHO statistics)

2018	New cases/Incidence (#all/#gyn.)	Deaths (#all/#gyn.)
All cancers	18,078,957/236.9:100,000	9,555,027
Endometrial (females)	382,069/10.1:100,000 (6./2.)	89,929 (14./3.)
Ovarian (females)	295,414/7.8:100,000 (8./3.)	184,799 (8./2.)
Kidney (males and females)	403,262/5.3:100,000 (14.)	175,098 (16.)

2 REVIEW OF THE LITERATURE

2.1 Endometrial cancer

Endometrial cancer is a gynecological cancer originating from the endometrium of the uterus. EC is the most common gynecological cancer in developed countries, and its prevalence is increasing. (Morice et al. 2016; Colombo et al. 2016) EC was responsible for 0.9% of cancer-related deaths in 2018. (WHO statistics).

In Finland, there were 911 new cases of uterine cancers, of which most were ECs, in 2017, and 202 patients died of the disease. The patients with EC had good relative survival rates; the one-year survival rate was 92%, and the five-year survival rate was 81%, in patients who received a cancer diagnosis between 2015 and 2017. Compared to all female cancers diagnosed in Finland during those years, with a one-year survival rate of 82% and a five-year survival rate of 70%, the prognosis of uterine cancers is rather good. The five-year survival rate has increased from 38% during the years 1955-1957 to the previously mentioned 81%; however, this is a few percentage points lower than the rate from the best years or 84% in 2006-2008. (Finnish Cancer Registry) EC is commonly diagnosed in the later years of life, and over 90% of patients are diagnosed at an age >50 years (median age 63 years); the main patient group is postmenopausal women, and only 14% of ECs are diagnosed in premenopausal women. (Morice et al. 2016; Colombo et al. 2016) In Finland, the greatest incidence of uterine cancers has been among patients aged 60-69 years since the 1980s (Finnish Cancer Registry).

Exposure to unopposed estrogen is the main known risk factor, along with obesity, early menarche, late menopause, nulliparity, age ≥55 years and tamoxifen treatment. The greatest incidence of EC geographically is in the USA, Canada and Northern and Western Europe. This increased incidence is considered to be related to the high number of obese women and those with metabolic syndrome, combined with an aging population. In the USA, the role of hormone replacement therapy (HRT) due to the ever-increasing incidence of EC during the last decade is also being studied. The independent role of diabetes mellitus type II is debatable, since these patients are likely to be obese. (Amant et al. 2005; Colombo et al. 2016; Morice et al. 2016; Amant et al. 2018)

2.1.1 Diagnostics and characteristics

EC often causes symptoms and is therefore usually found during a relatively early stage of the disease. Therefore, there is no gain achieved by screening for EC, except in patients with a hereditary risk. Abnormal uterine bleeding is the most common symptom, occurring in up to 90% of EC patients, and is a reason for further investigation. Especially in postmenopausal women, 10% of abnormal bleeding is caused by EC. In the rare case of advanced disease, there can also be symptoms such as abdominal or pelvic pain or abdominal distension. Other types of persistent vaginal discharge in postmenopausal women are also possible if the disease has created a pyometra. In premenopausal women, a change in menstrual pattern can be a symptom of endometrial cancer. (Amant et al. 2005; May, Mehasseb 2013; Morice et al. 2016; Colombo et al. 2016)

If a patient has symptoms, such as postmenopausal bleeding, she needs further assessment. A pelvic examination, an endometrial biopsy and a vaginal ultrasound examination are the first diagnostic steps. Risk factors and comorbidities should be assessed. An endometrial thickness of less than 5 mm has a good negative predictive value, while the observation of an endometrial polyp on vaginal ultrasound is related to an increased risk of endometrial cancer. Currently, outpatient hysteroscopy is also a common first-line diagnostic method, as well as endometrial sampling. Hysteroscopy enables the better detection of endometrial polyps and leiomyomas responsible for abnormal bleeding. However, endometrial sampling via e.g., Pipelle® is safe, easily accessible and provides sufficient diagnostic information, although cervical stenosis in postmenopausal women sometimes makes sampling more difficult. Vaginal ultrasound combined with endometrial biopsy has a negative predictive value of 96%. Hysteroscopy is helpful in situations of diagnostic uncertainty. (Amant et al. 2005; May, Mehasseb 2013; Morice et al. 2016; Amant et al. 2018)

If a diagnosis of EC is confirmed by endometrial biopsy, the next phase is to evaluate the size of the uterine tumor and to determine if there are metastatic sites and/or perioperative risks. Computed tomography (CT) or magnetic resonance imaging (MRI) is generally used to estimate the spread of the cancer and to assist in planning of the surgical approach. MRI or positron emission tomography-computed tomography (PET-CT) are more sensitive than pure CT for identifying lymph node infiltration. Three-dimensional ultrasound may also be used to estimate myometrial invasion. The most common metastatic sites of EC are the vagina, ovaries and lungs. (Saarelainen et al. 2012; Gupta 2017; Amant et al. 2018)

The WHO classifies endometrial cancer into two main histological types, namely, endometrioid adenocarcinoma (type I) and other adenocarcinomas (type II). Endometrioid adenocarcinoma represents 80-90% of endometrial cancers. The subtypes of endometrioid adenocarcinoma include villoglandular, secretory, with squamous differentiation and with ciliated cells. The other adenocarcinomas (type II) include serous carcinoma, clear cell carcinoma, mucinous carcinoma, mixed carcinoma, squamous-cell carcinoma, transitional cell carcinoma, small-cell carcinoma and undifferentiated carcinoma. Type I tumors are usually low-grade and are preceded by endometrial hyperplasia. Type II tumors are generally high grade. Histopathological grading defines endometrial carcinomas according to the solidness of the tumor. In grade 1 tumors, 5% or less of the tumor is solid, in grade 2 tumors, 6-50% of the tumor is solid, and in grade 3 tumors, over 50% of the tumor is solid. (Amant et al. 2005; Arora et al. 2012; Sorosky 2012)

The Cancer Genome Research Atlas Network (TCGA) classifies type I EC into four groups. Group 1 is associated with a good prognosis but very high mutation rates and somatic inactivating mutations in polymerase epsilon (POLE) exonuclease. Group 2 presents microsatellite instability with frequent MLH-1 promoter hypermethylation and high mutation rates. Group 3 has low copy number alterations. Group 4 shows a low mutation rate but frequent TP53 mutations and a worse prognosis. This classification is recommended in addition to pathologic classification to improve prognostic assessment, especially in high-grade endometrial carcinomas. (Piulats et al. 2017)

In 1971, FIGO created a clinical staging classification, which was changed to a surgical staging classification in 1988, to be used in EC to standardize therapeutic approaches (Amant et al. 2018). According to the most recent classification (Table 2) Stage I disease is limited to the uterine corpus and is divided, depending on the depth of the myometrial invasion, into substage A (no invasion or less than half) and B (equal or more than half). Stage II disease invades the cervical stroma. Stage III presents a locally spread tumor divided into substage A, which invades the uterine serosa and/or adnexa, substage B, which involves the vagina and/or parametrium, and substage C, which involves metastasis in the pelvic (C1) and/or para-aortic (C2) lymph nodes. Stage IV disease has spread outside the gynecological organs in the pelvis to the bladder and/or bowel mucosa (IVA) or to distant metastatic sites (IVB). (Amant et al. 2018)

Table 2. FIGO classification and percentage of EC patients in these stages

Stage	Definition	% of EC
I	No invasion or myometrial invasion only	70
II	Invades to cervical stroma	12
III	Invades/spreads locally	13
IV	Invades/spreads outside gynecological organs	3

The risk of future recurrence is assessed based on prognostic factors. These factors include the disease stage, histological type and grade, age at diagnosis, tumor size, lymphovascular space invasion (LVSI) status and hormone receptor status. The survival of a given patient also depends on comorbidities and peri- and postoperative complications. Poor prognostic factors are age >65 years, tumor size >2 cm, LVSI, grade 3, serous type, clear cell type, malignant mixed Müllerian type (carcinosarcoma), deep myometrial invasion ≥50%, tumor in the lower uterine segment, no estrogen or progesterone receptors, involvement of the adnexa and/or lymph nodes, and high stage disease. (Amant et al. 2018)

The hereditary nonpolyposis colon cancer (HNPCC) family of mismatch repair gene mutations is known to predispose to a form of EC that develops at a younger age. This form of EC is sometimes considered type III EC. (Arora et al. 2012) HNPCC increases also the risk of colon cancer, ovarian cancer and other cancers. This feature, an autosomal-dominant condition, is also called Lynch syndrome. (Arora et al. 2012) Lynch syndrome increases the risk of EC by 32-60%, and these patients represent 5% of EC patients. With this patient group, annual screening beginning at age 35 years, with endometrial biopsy and vaginal ultrasound, is recommended by the International Federation of Gynecology and Obstetrics (FIGO). Furthermore, prophylactic removal of the ovaries and uterus (hysterectomy and bilateral salpingo-oophorectomy) is considered when fertility no longer needs to be preserved. Lynch syndrome should be kept in mind if a patient has abnormal vaginal bleeding and has a first-degree relative with EC. (Amant et al. 2005; Renkonen-Sinisalo et al. 2007; Arora et al. 2012; Sorosky 2012; Morice et al. 2016; Colombo et al. 2016)

2.1.2 Treatment

The selection of treatment options is based on staging, which is accomplished surgically and by preoperative assessment of myometrial invasion and local and

distant metastasis. In particular, myometrial invasion and histology are important to assess even before surgery, since they determine the need for lymphadenectomy. It is also possible to obtain an intraoperative frozen section to assess for myometrial invasion. (Amant et al. 2018)

If the patient is diagnosed with stage IV disease preoperatively or has stage III disease that is inoperable at the time, neoadjuvant treatment is an option. The purpose of neoadjuvant treatment is to reduce tumor volume by radiotherapy and/or chemotherapy. After completing neoadjuvant therapy, a new assessment can be performed to determine operative treatment. (Morice et al. 2016; Amant et al. 2018)

Preoperative assessment, operative staging, histopathological diagnosis and evaluation of the patient's condition allow determination of the need for a suitable postoperative adjuvant treatment for each patient. A well-designed adjuvant therapy reduces the risk of recurrence in high-risk patients and prevents overtreatment of low-risk patients. High/intermediate-risk factors include age >60 years, deep myometrial invasion, grade III, serous or clear cell histology. (Sorosky 2012; Morice et al. 2016; Gupta 2017; Lee et al. 2017; Amant et al. 2018)

2.1.2.1 Surgery

Surgery is the principal treatment method, and surgery alone is sufficient for most patients with EC. Hysterectomy and bilateral salpingo-oophorectomy are adequate treatments for low-grade stage IA cancer. A complete staging operation includes pelvic and para-aortic lymphadenectomy, obtaining a sample for peritoneal cytology, and removal of the uterus and adnexa. During the operation, the abdominal status is also explored; the omentum, liver, bowel and peritoneal surfaces are evaluated. A complete staging operation should be performed for patients with stage IB and II disease. Patients with stage III disease benefit from maximal debulking surgery, which involves the removal of all visual disease. Patients with stage IV disease should be assessed individually to determine whether they will benefit from cytoreductive or palliative surgery. (Colombo et al. 2016; Morice et al. 2016; Amant et al. 2018; Gupta 2017; Lee et al. 2017)

Surgery can be executed with a minimally invasive technique, traditional laparoscopy or robotic-assisted laparoscopy, or with traditional laparotomy. Minimally invasive techniques offer a shorter postoperative inpatient stay (2-3 days vs. 6 days), reduced perioperative blood loss and fewer postoperative complications (0-1% vs. 2%) than laparotomy, with similar operative results. These advantages

support a faster recovery from surgery. Obesity creates challenges for traditional laparoscopy and laparotomy that can be avoided with robotic-assisted laparoscopy. A robotic-assisted technique also offers the advantage of fewer conversions than traditional laparoscopy. However, if surgery with a minimally invasive technique might require morcellation (slicing) of the uterus or if the cancer is already in stage III (or IV), laparotomy may be the only option for optimal results. (Diaz-Arrastia et al. 2002; Kuoppala et al. 2004; Corrado et al. 2015; Chiou et al. 2015; Rabinovich et al. 2015; Colombo et al. 2016; Morice et al. 2016; Gupta 2017; Lee et al. 2017; Amant et al. 2018; Galaal et al. 2018)

2.1.2.2 Radiotherapy

Radiotherapy (RT) can be given as neoadjuvant therapy or adjuvant therapy and can be administered with or without chemotherapy. RT is recommended for patients with a high-risk for recurrence and is discouraged in low-risk patients. RT can be given as vaginal brachytherapy or as external radiation.

Neoadjuvant radiotherapy can be used, as previously mentioned in chapter 2.1.2. If the patient has risk factors, such as age >60 years, deep myometrial invasion, LVSI and/or grade 2 disease, adjuvant brachytherapy is more efficient and has less impact on quality of life (QoL) than external radiation. For higher risk patients with stage I-II disease, adjuvant pelvic external radiotherapy is recommended. In these patients, pelvic irradiation is as effective as and better tolerated than vaginal brachytherapy combined with chemotherapy. Patients with stage III disease may benefit from a combination of external radiotherapy and chemotherapy, but the use of this combination should be decided individually. The main advantage of RT is the reduction in pelvic and vaginal recurrence, but this treatment does not offer an overall survival benefit. RT can also be used as palliative care in patients with progressive disease. (Sorosky 2012; Colombo et al. 2016; Amant et al. 2018; De Boer 2018; Randall et al. 2019)

2.1.2.3 Chemotherapy

Adjuvant chemotherapy can be considered in patients with adverse prognostic factors and in those with stage IA grade 3 or IB grade 1 and 2 disease instead of RT. In patients with stage IB grade 3 cancer with adverse prognostic factors, a combination of RT and chemotherapy is recommended. In stage II disease,

chemotherapy is recommended with or without RT if there are poor prognostic factors. In stage III disease, a combination of chemotherapy and RT benefits the patients in terms of recurrence-free survival. Patients with stage IV disease should be considered individually to determine whether they can benefit from neoadjuvant treatment or adjuvant therapy. (Amant et al. 2018)

Current practice is a platinum-based chemotherapy. Single-agent therapy can be used to reduce side effects; however, a better effect is gained with combination chemotherapy, including double or triple treatments. Several combinations have been tested: carboplatin and paclitaxel; ifosfamide with cisplatin; doxorubicin, cisplatin and paclitaxel (TAP); cisplatin and paclitaxel; doxorubicin and cisplatin; and doxorubicin and paclitaxel. A combination of carboplatin and paclitaxel has shown similar efficacy with fewer side effects (PFS up to 14 months) and less toxicity than triple treatment (TAP) and is currently the recommended adjuvant therapy for stage 3 and 4 disease. (Fleming et al. 2004; Thigpen et al. 2004; Leslie et al. 2012; Colombo et al. 2016; Amant et al. 2018)

2.1.2.4 Other treatment options

If the patient cannot undergo surgery due to difficulties concerning the operation and spread of the disease or due to the patient's condition, a progesterone-based treatment can be given. This treatment does not offer a survival benefit, but in estrogen and progesterone receptor positive disease, this treatment may slow down advancement of the disease in patients with metastatic disease. (Colombo et al. 2016; Amant et al. 2018)

In younger patients with low-risk (grade 1) early-stage EC, fertility can be preserved by using oral or intrauterine progestin therapy (medroxyprogesterone acetate or megestrol or a levonorgestrel-releasing intrauterine device). After the need to preserve fertility has passed or if there is no response to treatment, a hysterectomy should be performed. In premenopausal patients, the ovaries can be preserved to prevent surgical menopause in patients with low-grade early-stage disease. (Colombo et al. 2016; Amant et al. 2018)

Immunotherapy and targeted therapies are being studied in the treatment of metastatic, unresectable, persistent or recurrent EC. These treatments target different pathways, such as angiogenesis, genomic instability, proliferative signaling, endogenous immune response and hormonal therapy. The combination of lenvatinib and pembrolizumab has shown promising results in a phase 2 study, the treatment reduced tumor activity. However, a significant number of adverse-events

was recorded during the treatment. The topic of immunotherapy for endometrial cancer obviously still needs further investigation before it is adopted as a standard treatment. (Charo and Plaxe 2019; Di Tucci et al. 2019; Makker et al. 2020)

2.1.2.5 Follow-up

In previous years, follow-up has been recommended for up to five years: 3-4 times a year for the first three years and twice a year up to 5 years after the initial treatment. (Colombo et al. 2016) This follow-up practice has been questioned, and recommendations seem to be moving towards symptom-based follow-up. Symptom-based follow-up has shown equal sensitivity in identifying recurrent disease and reduces routine visits and imaging studies. Weight loss and vaginal bleeding may be symptoms of recurrent disease. If the patient has suspicious symptoms, a thorough gynecological examination and imaging are performed. (Amant et al. 2005; Amant et al. 2018)

2.1.3 Recurrent disease

Even though EC is a cancer with a good prognosis, in approximately 13% of cases, recurrence occurs. Most recurrences are discovered during the first three years of follow-up. Treatment response depends on the disease-free interval and the location and degree of extrapelvic metastases. The treatment choices include surgery (for a local or isolated recurrence), RT, hormonal therapy and chemotherapy. For local vaginal recurrence, RT has proven to be effective. Hormonal therapies, such as progestins, tamoxifen or aromatase inhibitors, are recommended for patients with endometrioid histology. If the patient has estrogen and/or progesterone receptor positive grade 1 disease, they may benefit from progestin treatment in the form of prolonged remission of metastatic disease. (Amant et al. 2018) If chemotherapy has not been previously used in the treatment, platinum-based drugs (cisplatin, carboplatin), anthracyclines (doxorubicin) and taxanes (paclitaxel) can be used alone or in combination. If recurrence occurs in a patient originally treated with chemotherapy, chemoresistance is common. Only paclitaxel has shown response rates of >20%. New treatment options are continuously being studied; for instance, the antiangiogenic agent bevacizumab combined with chemotherapy has shown efficacy. In addition, the preliminary results in early clinical trials have shown that immune checkpoint inhibitors may be beneficial in patients with POLE-

ultramutated disease. (Sorosky 2012; Huijgens et al. 2013; Colombo et al. 2016; Morice et al. 2016; Rose et al. 2017; Mittica et al. 2017; Amant et al. 2018)

2.1.4 Costs

Many studies on the costs of EC treatment are based on comparing the expenses of surgery, as it is the primary form of treatment and therefore the largest contributor to treatment cost. The approved adjuvant therapy used for EC in routine clinical practice does not yet include new, expensive drugs. Moreover, as there are already generic and biosimilar products available for standard treatment choices, chemotherapy for EC is relatively inexpensive. RT offers rather standard prices as well, since there have been no radical innovations in that area. RT treatment planning and delivering systems are in constant development but are used for a large number of patients and thus inexpensive per patient. (Barnett et al. 2010; Venkat et al. 2012; Leitao et al. 2014; Marino et al. 2015; Mäenpää et al. 2016)

Surgical treatment costs include surgeon costs, operating room costs (equipment, supplies, staff), hospital accommodations, medications, laboratory costs and if necessary, imaging and blood products. In terms of surgical treatment, many studies have compared the three previously mentioned treatment options, namely, traditional laparoscopy, robotic-assisted laparoscopy and laparotomy, in different settings. In all of these analyses, traditional laparoscopy was determined to be the most inexpensive approach. This method offers the advantage of minimally invasive surgery, and the shortened postoperative hospital stay is a significant contributor to total operative expenses compared to laparotomy. Traditional laparoscopy also has advantages over robotic-assisted laparoscopy in terms of the amortization costs of the robot console and the costs of the specific instrumentation required. (Barnett et al. 2010; Venkat et al. 2011; Leitao et al. 2014; Marino et al. 2015; Mäenpää et al. 2016)

Laparotomy and robotic-assisted laparoscopy expenses have been alternatively in the first and second place being more expensive than traditional laparoscopy, depending on the study design. In most cases, laparotomy is more expensive than robotic-assisted laparoscopy, since the longer postoperative stay among laparotomy patients compensates for the costs of robot console amortization and robot instrumentation expenses. (Barnett et al. 2010; Venkat et al. 2011; Reynisson et al. 2013; Leitao et al. 2014; Marino et al. 2015; Herling et al. 2016; Mäenpää et al. 2016)

Leitao et al. published a study that included the cost calculations for all of these three approaches. These authors also included a follow-up period of six months after initial discharge and compared the costs with and without the amortization of the robotic platforms (excluding capital costs in all approaches). When amortization was included, the results for traditional laparoscopy, robotic-assisted laparoscopy and laparotomy were 20,489 USD, 23,646 USD and 24,642 USD, respectively. The non-amortized costs for traditional laparoscopy, robotic-assisted laparoscopy and laparotomy were 20,289 USD, 20,467 USD and 24,433 USD, respectively. This study demonstrated the significance of primary investment expenses related to robotic surgery. (Leitao et al. 2014)

However, according to most studies, robotic-assisted laparoscopy takes a longer time to perform than traditional laparoscopy. Mäenpää et al. prospectively randomized EC patients to traditional laparoscopy or robotic-assisted laparoscopy. In this study, surprisingly, robotic-assisted laparoscopy was faster when the operations were otherwise identical (hysterectomy, salpingo-oophorectomy and pelvic lymphadenectomy). However, the cost difference between these two surgical approaches is approximately 1,000-2,000 € when the operational and postoperative stay expenses are taken into account. Therefore, the magnitude of the time difference needed between these approaches to balance the costs per operation has to be quite remarkable. (Barnett et al. 2010; Venkat et al. 2011; Leitao et al. 2014; Wrigth et al. 2014; Marino et al. 2015; Mäenpää et al. 2015; Mäenpää et al. 2016)

The average Finnish health care unit costs of 2011 were published in 2014. The expenses concerning gynecologic oncology are presented in Table 3. These data confirm that for the standard care of EC, surgery is the most expensive component. (Kapiainen et al. 2014)

Other costs of EC also include follow-up costs. If control routine visits were executed as the original guidelines suggest, routine follow-up visits calculated with Finnish health care units would cost 3,480 € (4 visits in the 1st year, 3 visits in the 2nd and 3rd years, and 2 visits in the 4th and 5th years; a total of 14 visits and a unit price of 248.6 €/visit). If the number of visits can be halved in low-risk patients, the reduction in follow-up costs is significant. (Colombo et al.2016; Kapiainen et al. 2014)

Table 3. Finnish health care unit costs of 2011 concerning gynecologic oncology. (Kapiainen et al. 2014)

Treatment	Cost €/treatment period	# treatment days included/treatment period
Gynecological radical surgery	7,612	7.5
Other operation	5,063	5.3
Other operation, short stay	2,225	1.0
Local radiotherapy	2,045	3.7
External radiotherapy	3,853	5.6
Regular chemotherapy protocol	2,418	2.9

2.2 Ovarian cancer

Table 1 shows the worldwide incidence of ovarian cancer (OC); in 2017, the incidence of OC in Finland was 13.5:100 000. OC was ranked the 8th cancer in terms of female mortality rates, accounting for 1.9% of all cancer-related deaths worldwide in 2018. In Finland in 2017, OC was the most lethal gynecological malignancy, causing 315 deaths. OC also has the lowest survival rates in this cancer category; the one-year survival rate is 74%, and the five-year survival rate is 42%. The five-year survival rate has improved over time since 1958-1960 when it was only 23% to the 21st century rate of over 40%. The greatest incidence occurs between ages 60-69 years. (WHO statistics; Finnish Cancer Registry)

Epithelial ovarian cancer is the most common form of OC (greater than 90% of ovarian malignancies) and thus the focus in this thesis. Of epithelial OCs, high-grade serous carcinoma (HGSC) is by far the most common type, accounting for approximately 70% of all cases. Furthermore, the origin of HGSC is the epithelium of the fallopian tube rather than the ovary. (Permuth-Way and Sellers 2009; Hennessy et al. 2009)

There are a few theories regarding the tumorigenesis of OC. The most popular theory is related to incessant ovulation and the resulting increased proliferation required to repair the epithelium of the ovary throughout a woman's fertile life. It is thought that this proliferation is vulnerable to spontaneous mutations and thereby prone to creating cancer cells. A second theory suggests that gonadotropins overstimulate proliferation in the epithelium yielding similar consequences. However, the recent discovery of the fallopian tube being the origin of HGSC has made these theories less attractive at least for high-grade tumors. (Permuth-Way and Sellers 2009; Hennessy et al. 2009)

The most significant risk factor for OC is family history. Other risk factors include early menarche, late menopause, nulliparity, and increasing age. On the other hand, oral contraceptives, multiparity, lactation, tubal ligation, hysterectomy and salpingectomy decrease the risk of OC. (Permuth-Way and Sellers 2009; Hennessy et al. 2009; Falconer et al. 2015)

2.2.1 Diagnostics and characteristics

Ovarian cancer causes rather nonspecific symptoms or is asymptomatic; therefore, it is often found, in approximately 70% of patients, at an advanced stage. The symptoms may include abdominal or pelvic pain, loss of appetite, abdominal distension or "bloating", changes in urination and menstrual changes. When suspected, a physical examination may reveal a palpable mass in the ovarian region, ascites or pleural effusion. (Permuth-Way and Sellers 2009; Hennessy 2009; Capriglione et al. 2017)

Pelvic examination, vaginal ultrasound and breast and rectal palpation are the principal diagnostic tools for OC. Vaginal ultrasound is sensitive for identifying ovarian masses, which usually appear as a complex ovarian cyst with possible ascites, indicating the malignant nature of the tumor. Three-dimensional power Doppler ultrasound can be useful in expert hands as a reliable method for assessing the nature of an ovarian tumor (Niemi et al. 2017). Cancer antigen 125 (CA12-5) levels can be used, together with physical examination and vaginal ultrasound, to determine the character of an ovarian mass; in OC, these levels are elevated. CA 12-5 levels can be elevated by malignancies other than OC and by some benign conditions, such as endometriosis; therefore, this should not be used as an isolated diagnostic tool. Even though the FDA has approved human epididymal secretory protein 4 (HE4) as a diagnostic marker for OC, neither is this biomarker is also completely specific for

this cancer. However, when these two markers (CA 12-5 and HE4) are measured simultaneously, the diagnostic accuracy increases, and this combination can help to distinguish malignant and nonmalignant lesions. Carcinoembryonic antigen (CEA) levels can be used to differentiate OC from gastric or colon cancer that has metastasized to the ovaries. CT can be used to assess for metastatic disease, and thorax radiographs can be used to identify pleural effusion. (Hennessy 2009; Huhtinen et al. 2009; Capriglione et al. 2017; Berek et al. 2018)

Histologically, epithelial ovarian tumors are classified as serous, endometrioid, clear cell, mucinous, Brenner, undifferentiated carcinomas, carcinosarcomas and mixed epithelial tumors. Grading of the epithelial tumors is categorized by the differentiation of the existing cells; grade X cannot be assessed, grade 1 is well differentiated, grade 2 is moderately differentiated, and grade 3 is poorly differentiated. Serous carcinoma is the most common histological type of epithelial OC and is divided into high-grade and low-grade based on its biology. HGSCs of the ovary, fallopian tube and peritoneum actually represent the same disease (see above) and are treated according to the same principles. (Berek et al. 2018)

FIGO has a staging classification for OC to standardize treatment of different types of disease, and the latest edition was published in 2014. Stage I disease is limited to the ovaries and the fallopian tubes; substage IA disease involves only one ovary or fallopian tube, and substage IB disease involves either both ovaries or fallopian tubes. Both substage IA and IB tumors have intact capsules. Substage IC disease is limited to both ovaries or fallopian tubes and is also dependent on the following: substage IC1 disease has surgical spillage, substage IC2 disease involves tumors in which the capsule is ruptured before surgery or tumors on the ovarian or fallopian tubal surface, and substage IC3 disease has malignant cells in the ascites or peritoneal washing. Stage II disease involves both ovaries or fallopian tubes and has pelvic extensions or peritoneal infiltrates; substage IIA disease has spread to the uterus, substage IIB disease has spread to other pelvic intraperitoneal tissues. Stage III disease, in addition to involving both ovaries/fallopian tubes or presenting with peritoneal cancer, has spread outside the pelvis into the peritoneum and/or has metastasized to the retroperitoneal lymph nodes. Substage IIIA1 disease has spread only to the retroperitoneal lymph nodes [substage IIIA1(i) disease has metastasis measuring up to 10 mm, and substage IIIA1(ii) disease has metastasis measuring more than 10 mm], substage IIIA2 disease has microscopic extrapelvic peritoneal spread, substage IIIB disease has macroscopic extrapelvic peritoneal metastasis measuring up to 2 cm in the largest measurement, and substage IIIC disease is similar to substage IIIB disease except the largest measurement of metastasis is more than

2 cm. Substages IIIB and IIIC disease can also present with metastasis to the retroperitoneal lymph nodes. Substage IIIC disease may also extend to the liver or splenic capsule without penetrating it. Stage IV disease has distant metastasis; for example, in substage IVA disease, there is pleural effusion with malignant cytology, and in substage IVB disease, there are parenchymal metastases and/or metastases to extra-abdominal organs, including inguinal and extra-abdominal lymph node infiltration. (Berek et al FIGO 2018)

Inherited factors are found in up to 20% of patients with ovarian cancer. The breast cancer associated genes BRCA 1 and 2 are known to cause most cases of hereditary OC. Approximately 10-15% of cases of OC can be explained by these mutations, and BRCA1 is in general twice as common as BRCA2. However, in the Finnish population, BRCA2 is more common. BRCA mutations usually lead to HGSC, and even without a family history of OC and/or breast cancer, patients with HGSC should be tested for these mutations. HNPCC is also known to cause ovarian cancer, in addition to endometrial cancer, in approximately 2% of cases. Usually, OC associated with Lynch syndrome is endometrioid or clear cell according to histology and is stage I disease. There are also a number of other mutations that are responsible for a small proportion of OC cases. Mutations generally prevent the normal function of genome repair genes and allow cancerous mutations to survive. (Sarantaus et al. 2001; Hennessy et al. 2009; Webb et al. 2017)

Poor prognostic factors enable the identification of patients who are likely to develop recurrent or treatment-resistant disease. These factors include age >65 years, clear cell or mucinous histology, advanced stage disease, large residual tumor volume, lower global QoL score and high-grade disease. (Permuth-Way and Sellers 2009; Hennessy et al. 2009; Webb et al. 2016; Capriglione et al. 2017; Berek et al. 2018; NICE ovarian cancer overview 2019)

2.2.2 Treatment

Along with the histology, grade and stage of the disease, residual disease after cytoreductive surgery is an important predictor of a patient's prognosis. These factors also determine a patient's treatment options. Therefore, a staging operation in apparent Stage I disease is important, as 20-25% of the patients have occult metastases. For patients with advanced Stage III-IV disease, open primary debulking surgery aiming at zero residual disease is essential. In cases where according to the preoperative assessment, primary debulking surgery is not possible, neoadjuvant

chemotherapy followed by interval debulking surgery should be considered. Since most OCs are found at an advanced stage, adjuvant chemotherapy follows the surgical treatment, and chemotherapy is the only choice of treatment in patients with inoperable disease. Although even advanced stage HGSC responds to chemotherapy in approximately 80% of patients, recurrence occurs in 70%. (Capriglione et al. 2017; Berek et al. 2018).

2.2.2.1 Surgery

As stated above, a proper staging operation is crucial even in apparent early-stage disease to minimize the risk of neglecting the presence of unnoticed and subclinical metastases. However, careful preoperative assessment must be performed for each individual, since complete cytoreductive laparotomy is prone to present risks for complications. Comorbidities, everyday life activities, nutritional status and general physical condition should be taken into account. (Trimbos 2017; Hacker, Rao 2017; Berek et al. 2018)

In general, in patients with suspected malignant disease, staging is performed via laparotomy. The standard operation should proceed through the following steps: cytological sampling of the ascites or peritoneal washing, evaluation of all peritoneal surfaces, infracolic omentectomy, selective lymphadenectomy (pelvic and para-aortic), biopsies of any suspicious lesions, peritoneal biopsies of normal surfaces from selected locations, appendectomy for mucinous tumors, total hysterectomy and bilateral salpingo-oophorectomy. (Trimbos 2017; Hacker, Rao 2017; Berek et al. 2018)

Even in early-stage disease, proper laparotomy staging has long been the primary treatment option. A laparoscopic approach has been purported to present the risks of capsule rupture, surgical spillage and port-site metastases and cannot be recommended. In addition, inspection of the bowel and peritoneal surfaces is more difficult, and peritoneal and bowel palpation cannot be performed. However, laparoscopic staging in apparent early-stage disease is gaining popularity, especially following primary surgery for tumors originally interpreted as benign. Thorough surgical staging is an independent factor that improves the patient's prognosis in terms of both PFS and OS and may also eliminate the need for adjuvant therapy in true Stage IA disease. (Trimbos 2017; Hacker, Rao 2017; Berek et al. 2018)

In advanced stage disease (III and IV), maximal cytoreduction is pursued, namely, debulking surgery. In primary or interval debulking, the aim is to remove all macroscopic disease. This approach may include bowel or liver resections,

splenectomy, peritonectomy and even removal of the cardiophrenic lymph nodes (ultraradical surgery) in addition to the procedures included in the standard surgery listed above. (Trimbos 2017; Hacker, Rao 2017; Berek et al. 2018)

2.2.2.2 Medical treatment

Patients who are adequately staged and have stage IA or IB grade 1-2 disease do not benefit from adjuvant chemotherapy. Beginning from stage IC and for higher-grade stage IA/B tumors, adjuvant chemotherapy is recommended for all patients. However, the patient's condition, comorbidities and performance status are important to evaluate when adjuvant treatment is considered.

The first-line chemotherapy is platinum-based (carboplatin or cisplatin) combined with a taxane (paclitaxel or docetaxel). In stage I disease, the number of cycles is usually 3 to 6, and for the more advanced stages, 6 cycles are used. In patients who have allergic reactions to paclitaxel, docetaxel may be used used instead. If a patient cannot tolerate a combination chemotherapy because of comorbidities or old age, a single-agent chemotherapy with carboplatin can be used. In any case, chemotherapy at an advanced stage is adjusted individually, making dose and drug modifications according to toxicity and tolerability.

Bevacizumab is an antiangiogenic agent. Vascular endothelial growth factor (VEGF) induces pathological angiogenesis, which is the formation of new vessels and enables a tumor to grow without limitations. Bevacizumab, an anti-VEGF monoclonal antibody, blocks tumor growth by preventing angiogenesis. This drug is used for advanced-stage disease, started during chemotherapy and continued as a maintenance therapy. The main advantage has been an increase in PFS of approximately four months, both during the primary treatment of advanced-stage disease and in a recurrence setting. Yet, a subgroup analysis in patients with suboptimal stage III and IV disease and a poor prognosis has shown an almost 5-month benefit in the mean OS and a 9-month benefit in the median OS. (Burger et al. 2011; Perren et al. 2011; Oza et al. 2015)

In a recent report on the final OS of GOG-0218 by Tewari et al., no overall survival differences were found for patients who received bevacizumab compared with those who received chemotherapy alone. However, a significant difference in the median OS in the subgroup of patients with stage IV OC was found between those treated with concurrent plus maintenance bevacizumab and those treated with chemotherapy alone [42.8 vs 32.6 months, HR 0.75, (CI 95%, 0.59 to 0.95)] (Tewari et al. 2019)

In advanced-stage disease, neoadjuvant treatment with three to four cycles of chemotherapy followed by interval debulking surgery and postoperative chemotherapy decreases postoperative morbidity in patients with a poor performance status. (Ferrara et al. 2002; Oza et al. 2015; Hacker et al. 2017; Berek et al. 2018)

Especially in patients with BRCA mutations, poly(ADP-ribose) polymerase (PARP)-inhibitors have shown promising efficacy as a first-line treatment. According to the SOLO-1 trial, olaparib decreased the risk of progression or death by 70% compared to placebo (HR 0.30; 95% CI 0.23 to 0.41). However, not only patients with BRCA mutations get benefit from PARP inhibitors. The PRIMA trial that recruited ovarian cancer patients in general reported that niraparib decreased the risk by 40% (HR 0.62; 95%CI 0.49 to 0.72). At least similar outcome was reported in PAOLA-1 trial for olaparib (HR 0.59; 95%CI 0.50 to 0.76). (Naumann et al. 2018; Gonzalez-Martin et al. 2019; Moore et al. 2018; Ray-Coquard et al. 2019)

2.2.2.3 Other treatment options

Intraperitoneal chemotherapy has also been used, mainly in the USA. However, the toxicity- and catheter-related problems of this approach have raised questions, and its advantages compared with regular chemotherapy are still controversial. Consequently, this treatment has never gained popularity in Europe.

In young patients with stage I OC, fertility-preserving operative treatment can be considered after careful discussion with the patient. In this approach, the healthy ovary, fallopian tube and uterus are spared. (Trimbos 2017; Berek et al. 2018)

2.2.2.4 Follow-up

The purpose of follow-up is to detect recurrence; however, no evidence shows that frequent clinic visits improve QoL or OS. After follow-up every three months during the first year, follow-up visit intervals can be increased in the 2nd and 3rd years to every 4-6 months and finally annually after the 5th year. The likelihood of death due to OC decreases with time. (Dinklespiel et al. 2015; Berek et al. 2018)

It is important to detect recurrence-related symptoms, treatment-related complications and supervise performance status. Follow-up includes clinical examination and radiological imaging. The measurement of CA 12-5 levels may provide an early warning of recurrence; however, in asymptomatic patients, this

biomarker should not be used alone to determine the next treatment steps. In a randomized study, there was no benefit in starting treatment for recurrence based only on increasing CA 12-5 values. The decision to continue chemotherapy or consider operative treatment should be based on all different factors, including symptoms, clinical and radiological findings, disease-free interval, overall condition, applied treatments and primary surgery results. (Rustin et al. 2010; Berek et al. 2018)

2.2.3 Recurrent disease

As mentioned previously, relapses occur in 70% of patients with OC. Clinical follow-up visits are therefore recommended, and further investigations should be symptom-based, not solely based on increasing CA 12-5 levels. Recurrence can present with symptoms or patient can be asymptomatic; sometimes recurrence is only detected with radiological imaging. If the disease-free interval from chemotherapy is less than six months, the OC in considered platinum resistant. If the treatment interval is more than 6 months, the disease is usually platinum sensitive. Diseases that progress during initial chemotherapy are thought to be platinum refractory. Continuing treatment for recurrent OC should be carefully assessed according to the extent of the disease, and the patient's symptoms, condition and wishes should also be considered. Attention should also be paid to maintaining as good quality of life as possible. (Rustin et al. 2010; Mirza et al. 2016; Giornelli 2016; Tew 2016; Capriglione et al. 2017; Taylor and Eskander 2017; Berek et al. 2018; Moore et al. 2018)

In platinum-sensitive recurrence, a combination of carboplatin and paclitaxel can be used. This combination has been shown to benefit PFS compared with carboplatin treatment alone. If paclitaxel has caused neurotoxicity, gemcitabine or pegylated liposomal doxorubicin (PLD) should preferably be used instead. (Berek et al. 2018)

For platinum-resistant OC, there is no single recommendation for further treatment. The options include taking part in a clinical study; however, weekly paclitaxel produced a meaningful median OS of approximately 12 months according to a subgroup analysis of the Aurelia trial (Pujade-Lauraine et al. 2014). PLD, topotecan, etoposide and gemcitabine may also be used, albeit with a very modest response. New agents are continuously being studied. (Berek et al. 2018)

If bevacizumab has not been used in the primary treatment, this agent can be used for recurrent disease. In addition, with this second-line treatment, an approximately four month PFS benefit has been shown. The greatest benefit is

gained in platinum resistant disease by combining bevacizumab with weekly paclitaxel, which doubles the OS gained with weekly paclitaxel alone. In terms of overall survival, a benefit of almost five months has been shown in platinum-sensitive recurrence. (Aghajanian et al. 2012; Pujade-Lauraine et al. 2014; Coleman et al. 2017; Berek et al. 2018)

PARP inhibitors have been studied also in recurrent, high-grade serous OC. A significantly prolonged disease-free interval has been reported. The evidence supports the use of PARP inhibitors in patients with platinum-sensitive recurrence as maintenance therapy following chemotherapy or as monotherapy in recurrent OC in some patients. Patients with BRCA mutations have been proven to derive the greatest benefit from PARP inhibitors. However, the benefit is almost as good in patients with non-BRCA disease with homologous recombination defects (the so-called BRCAness phenotype). (Mirza et al. 2016; Taylor and Eskander 2017)

A minority of selected patients, mainly patients with localized solitary recurrence, benefit from secondary surgical debulking. Patients benefit at least in terms of PFS if there are only 1-2 sites of disease and their condition allows surgery that results in a complete removal of the tumor foci. If a patient undergoes secondary cytoreductive surgery, chemotherapy is recommended postoperatively. (Berek et al. 2018)

Immunotherapeutic aspects have also been studied in OC, as in EC. Selected patient groups may benefit from these treatments, but it has not yet been clearly demonstrated which patient group benefits most from these approaches. The field therefore needs further clinical investigation. (Ventriglia et al. 2017)

Recurrent disease is basically not curable. Sometimes good symptom-based care, namely, palliative care, is the best option for the patient. In particular, in older patients, chemotherapy may create worse toxicity than in younger patients and lead to poorer outcomes. Quality of life should be valued in these situations. (Giornelli 2016; Mirza et al. 2016; Tew 2016; Taylor and Eskander 2017; Capriglione et al. 2017; Berek et al. 2018; Moore et al. 2018)

2.2.4 Costs

OC is one of the most expensive cancers to treat in women. The costs of active OC treatment include costs associated with surgery, chemotherapy, targeted drugs and follow-up visits. During the first year after diagnosis, the first six months account for significant portion of the expenses. (Kwon et al. 2017; Bercow et al. 2017)

As previously discussed in the chapter about EC costs, standard first-line chemotherapy is relatively inexpensive in Finland, and platinum-taxane treatments are also considered cost-effective internationally (Kapiainen et al. 2014; Poonawalla et al. 2015). However, as OC is often diagnosed at an advanced stage, most women require second- and further-lines of chemotherapy. A longer treatment period increases all costs related to treatment (laboratory tests, imaging studies, clinic visits, treatment of complications, et cetera) and costs related to more expensive chemotherapeutic agents. In the review by Poonawalla et al., most chemotherapies were still found to be cost-effective. (Poonawalla et al. 2015)

Bevacizumab is relatively expensive and its cost effectiveness has been widely debated. The drug itself, not its administration or complications, presents the most significant costs. (Cohn et al. 2011; Poonawalla et al. 2015; Chappell et al. 2016; Hinde et al. 2016; Neyt et al. 2018; Suidan et al. 2019) Biosimilars have been created for bevacizumab, and some have already been approved for marketing. The original patent for bevacizumab has not yet expired in Europe, but it expired in the United States in July 2019. This expiration is likely to mean a future reduction in bevacizumab prices. (Serna-Gallegos et al. 2018; www.gabionline update 2019)

In the FDA approval of bevacizumab for platinum-resistant recurrent OC, bevacizumab dosing at 10 mg/kg biweekly presented an ICER of 160,000 USD. When dosing was elevated to 15 mg/kg and the cycle prolonged to every three weeks, the ICER was 100,000 USD. The benefit gained with bevacizumab was approximately three months in the analysis by Chappell et al. (Chappell et al. 2015)

PARP inhibitors, including niraparib and olaparib, have shown efficacy, especially in patients with BRCA mutations. However, these treatments are new, and as mentioned previously, new cancer treatments present higher costs. A study by Zhong et al. presented a cost-effectiveness analysis of niraparib and olaparib as maintenance therapy in patients with a platinum-sensitive ovarian cancer recurrence. Both therapies exceeded the willingness-to-pay threshold of 100,000 USD, presenting an ICER of approximately 250,000 USD, when compared to placebo. The use in patients with BRCA mutations provides a better cost-effectiveness status, yet the ICER of approximately 200,000 USD still significantly exceeds the willingness-to-pay threshold. However, Guy et al. demonstrated a cost-effectiveness analysis in which niraparib treatment fell below the willingness-to-pay threshold when compared to routine surveillance in the United States or an ICER of 69,000 USD in patients with BRCA mutations. In this study, niraparib was also the most cost-effective choice compared with olaparib and rucaparib. However, the presented treatment costs were still rather high when not compared with QALY: for

routine surveillance, the cost was 95,600 USD; for niraparib, the cost was 396,800 USD; for olaparib, the cost was 405,600 USD; and for rucaparib, the cost was 595,500 USD. These results might differ internationally considering that the active treatments were compared with rather costly routine surveillance. (Zhong et al. 2018; Guy et al. 2019)

Because of the high cost of the treatments, different methods have been tested to reduce the cost burden of OC. Diagnostic laparoscopy before cytoreductive surgery to help to avoid futile laparotomy has been shown to benefit patients in terms of QoL while not increasing treatment costs (van de Vrie et al. 2017). Neoadjuvant therapy and subsequent surgery compared with primary debulking has been debated from both sides and may either be cost-effective or not in patients with advanced epithelial OC; Forde et al. found support for primary debulking in 2016, and Cole et al. found support for neoadjuvant treatment in 2018 (Forde et a.l 2016; Cole et al. 2018). Testing for the presence of BRCA mutations in all patients with epithelial OC has been considered to be cost-effective in the UK. This treatment has been calculated to result in lower breast and ovarian cancer incidence rates in first-degree relatives of patients with BRCA-positive OC, as well as lower treatment costs, lower cancer related mortality and higher QoL in patients themselves. (Eccleston et al. 2017) Screening for ovarian cancer by vaginal ultrasound and CA 12-5 tests has not been proven to be worth the expense. On the other hand, the reduction in OC incidence related to opportunistic salpingectomy, salpingectomy concomitant to hysterectomy and salpingectomy as a means of surgical sterilization has been considered cost-effective. (Falconer et al. 2015; Dilley et al. 2017; Kwon et al. 2017)

Preventive strategies may help to reduce the societal costs of OC in the future (Eccleston et al. 2017; Kwon et al. 2017, Dilley et al. 2017). However, new therapeutic agents have been introduced, but generic or biosimilar drugs for these new inventions are not yet available; thus, until the original patents expire, the treatment costs may not decrease. (Poonawalla et al. 2015; Neyt et al. 2018)

2.3 Renal cell cancer

In 2018, 403,262 new kidney cancers were diagnosed (Table 1), and kidney cancer ranked 16th in terms of mortality statistics and was responsible for 1.8% of cancer-related deaths (WHO statistics). Cancer of the kidney parenchyma, which is the focus in this thesis, represents 80-90% of the renal cell cancers (RCCs), and it originates from the renal parenchyma and its tubules. The remaining portion of kidney cancers

are cancers of the renal pelvis, which are histologically transitional cell carcinomas. (Chow et al. 2010; Escudier et al 2019)

The highest incidence of RCC globally is in the U.S. and in Scandinavia. An increase has been seen in the incidence of RCC; however, the five-year survival rate has improved significantly. (Johansson, Axelson 2013; Capitanio, Montorsi 2016).

In Finland, there were 981 new kidney cancers and 328 RCC-related deaths in 2017. The death rate has varied between 300 and 400 since 1993, while the incidence has increased more rapidly from the 1980s and again from 2007. The one-year and five-year survival rates have been 81% and 67%, respectively. The five-year survival rate has been increasing steadily to this level. Most new cases are diagnosed in patients older than 60 years, with the greatest incidence in the age group 65-69 years. (Finnish Cancer Registry)

Cigarette smoking, including active and passive smoking, is the number one risk factor for RCC. Other known risk factors include obesity and hypertension. The male to female ratio is 2:1, and heritage accounts for 2-3% of RCC cases, mainly due to von Hippel-Lindau syndrome. Patients with end-stage renal disease also have an increased risk of RCC. Fruit and vegetable consumption is considered to be a protective factor, while red meat consumption is another risk factor. Exposure to carcinogens has also been thought to be a risk factor, but the roles of this factor and dietary components are debatable. However, the connection between trichloroethylene, which is used to decaffeinate coffee, and an increased risk of RCC has been proven. (Motzer et al. 1996; Rini et al. 2009; Capitanio, Montorsi 2016; Escudier et al. 2019)

2.3.1 Diagnostics and characteristics

A few decades ago, RCC was most often diagnosed at an advanced state, since this disease caused very few symptoms. However, the increased use of CT and ultrasound for abdominal imaging has led to more incidental discoveries of RCC; these modalities are currently the major method of diagnosing RCC, resulting in 65% of cases identified at a localized stage. Nevertheless, approximately 17% of RCCs are diagnosed as metastatic disease. (Motzer et al. 1996; Rini et al. 2009; Sunela et al. 2009; Escudier et al. 2019)

If findings occur or symptoms are present, they include hematuria, pain in the kidney region and a palpable mass. These three previously mentioned are called the classical triad and are not as frequently found as in the past because of the increase

in incidental identification. Paraneoplastic disorders, such as hypertension, hypercalcemia, anemia and weight loss, are rather common, since this cancer can sometimes produce hormone-like and/or cytokine-like biological substances. (Motzer et al. 1996; Rini et al. 2009; Sunela et al. 2009; Escudier et al. 2019)

Physical examination only plays a small diagnostic role, but when a patient presents with a palpable abdominal mass, subjective symptoms, and a varicocele or edema in the lower extremities as new findings, CT or MRI should be considered to rule out RCC. These imaging techniques are more accurate and specific RCC diagnostics than ultrasound. CT or MRI can reveal possible metastatic disease and allow estimation of local invasion and lymph node involvement. If RCC is suspected, serum creatinine, hemoglobin and blood cell counts, lactate dehydrogenase, C-reactive protein (CRP) and calcium levels should also be measured. (Rini et al. 2009; Escudier et al. 2019

The diagnosis is currently based on a histological specimen. A biopsy from an occult renal lesion is recommended to discriminate RCC from renal metastasis, lymphoma, abscesses and benign cysts, especially if ablation is considered. Histological verification enables choosing the proper treatment, particularly in a metastatic setting. (Motzer et al. 1996; Rini et al. 2009; Capitanio, Montorsi 2016; Shingarev, Jaimes 2017; Escudier et al. 2019)

RCC is classified by its morphology, genetic characteristics and molecular pathways. The WHO lists the following sixteen subtypes of renal cell tumors: 1. clear cell adenocarcinoma, 2. multilocular cystic, 3. papillary, 4. hereditary leiomyomatosis and renal cell carcinoma-associated, 5. chromophobe, 6. collecting duct carcinoma, 7. renal medullary carcinoma, 8. MiT family translocation carcinoma, 9. succinate dehydrogenase-deficient, 10. mucinous tubular and spindle cell carcinoma, 11. tubulocystic, 12. acquired cystic disease-associated, 13. clear cell papillary, 14. unclassified, 15. papillary adenoma and 16. oncocytoma. Clear cell RCC accounts for 80% of these subtypes, and together with papillary and chromophobe types, these classes include up to 85-95% of renal cancers. (Moch 2013; Johansson, Axelson 2013; Capitanio, Montorsi 2016; Escudier et al. 2019)

Because RCC is characterized by hematogenous dissemination, it metastasizes early in the course of disease. Disseminated disease is usually found in the lungs, bone and brain. The adrenal glands, the other kidney and the liver may also be sites of metastasis. (Capitanio, Montorsi 2016)

Gene mutations account for 2-3% of RCCs. Von Hippel-Lindau syndrome is the most common of these genetic disorders and is known to increase the risk of clear cell RCC. In a study by Nickerson et al., the majority of clear cell RCCs were

considered to be derived from von Hippel-Lindau gene alterations. Mutations in this area cause the tumor suppressor gene to inactivate, leading to overexpression of VEGF and platelet-derived growth factor (PDGF); this enables excessive angiogenesis and can result in tumor growth. (Maynard, Ohh. 2004; Nickerson et al. 2008; Escudier et al. 2019)

According to the International Society of Urological Pathology (ISUP) and WHO consensus, the prognostic factors include histologic subtype, nucleolar grade in clear cell and papillary RCC, sarcoimatoid and/or rhabdoid differentiation, presence of necrosis and microvascular invasion, pathological tumor, node and metastasis (pTNM) stage and description of nonneoplastic renal tissue. All these evaluations are necessary, since the prognosis of RCC is unpredictable based on histology alone.

Because of this unpredictability, different types of risk assessment models have been created to evaluate the prognosis and risk of an individual patient. For localized disease, no model is better than another. However, in advanced disease, the Memorial Sloan Kettering Cancer Center (MSKCC) system is commonly preferred, and this system used to be the golden standard for risk assessment in metastatic RCC (mRCC). The International Metastatic RCC Database Consortium (IMDC) created a modified model, which is nowadays standard in risk evaluation and treatment selection for advanced disease (Table 4). (Molina, Motzer 2011; Moch 2013; Escudier et al. 2019)

The Union of International Cancer Control (UICC) has created a tumor, node and metastasis (TNM) staging system, of which system 8 is recommended for use in the staging of RCC. Generally, this system introduces the size and invasion of the tumor (from TX = cannot be assessed to T4 = tumor invades beyond Gerota's fascia), regional lymph node invasion (NX = cannot be assessed, N0 = no regional lymph node metastasis, N1 = metastasis in regional lymph nodes) and the presence of distant metastasis (M0 = no distant metastasis, M1 = distant metastasis). Stage I disease is a tumor measuring less than 7 cm (T1: T1a ≤4 cm, T1b >4 cm/ <7 cm) in diameter that is limited to the kidney without lymph node involvement or distant metastasis. Stage II disease is also limited to the kidney, but the tumor is 7-10 cm (T2a) or >10 cm in size (T2b), and the NM status is similar to stage I. Stage III disease involves either a tumor extending to the major veins or peripheral tissue (T3), but no disease is present in the lymph nodes, nor are metastases present, or these disease is N1 with a smaller tumor up to a T3 tumor. In stage IV disease, the tumor invades beyond Gerota fascia and might include the ipsilateral adrenal gland (T4, with any N but M0), or there is a metastatic site (M1 with any T or N). (Escudier et al. 2019)

In addition to staging, different risk models are used to divide the patients into good/favorable risk, intermediate risk and poor risk survival groups. (Moran et al. 2019; Escudier et al. 2019)

Table 4. IMDC risk model for mRCC (also available at mdcalc.com)

< 1 year from time of diagnosis to systemic therapy	
Karnofsky performance status < 80%	
Hemoglobin < lower limit of normal (~120 g/l)	
Corrected calcium > upper limit of normal (~8.5-10.2 mg/dl)	
Neutrophils > upper limit of normal (~2.0-7.0x10^9/l)	
Platelets > upper limit of normal (~150 000 – 400 000 cells/µl)	
Interpretation: Yes = 1 point/no = 0 points	
0 points	Good/favorable risk
1-2 points	Intermediate risk
≥ 3 points	Poor risk

2.3.2 Treatment

The main primary treatment of RCC is surgery. Drug therapy is used in mRCC and radiotherapy is mainly used as a palliative symptom-based option. Selection of treatment/treatments used is mainly dependent on the patient's condition and the stage of the disease. In metastasized disease, based on the extent of the disease and clinical factors (Table 4), patients are divided into good risk, intermediate risk and poor risk groups. This risk guides also the selection of drug therapies. Active surveillance is also an option in elderly people with comorbidities or in patients with a short life expectancy and small solid tumors. Palliative care should also be kept in mind when a patient has a poor risk disease and the condition may be combined with a low performance status. (Escudier et al. 2019)

2.3.2.1 Surgery or localized treatments

The operative approach is dependent on the tumor size. For localized disease, operative treatment can be curative. T1 tumors measuring less than 7 cm can be operated by partial nephrectomy via open surgery or with traditional or robotic-assisted laparoscopy. This approach preserves the patient's kidney function and is

also recommended when the patient has poor renal function, only one kidney or bilateral tumors. Laparoscopic radical nephrectomy is an option if partial nephrectomy cannot be performed. (Escudier et al. 2019)

For T2 tumors, radical nephrectomy is recommended. If the disease has reached a T3 or T4 size but is still local, open radical nephrectomy is the treatment of choice; however, in some cases, a laparoscopic approach can be considered. (Escudier et al. 2019)

Surgery is not the only option in patients with localized disease. If the patient has a small tumor measuring ≤3 cm in the renal cortex and has high surgical risk or has kidney function that is jeopardized, local treatments, such as radiofrequency ablation, microwave ablation and cryoablation, can be used. (Escudier et al. 2019)

In mRCC, cytoreductive surgery can be considered in patients with a good performance status and low volume of metastatic disease who are initially eligible for observation. A meta-analysis by Flanigan et al. in which nephrectomy was compared with no nephrectomy during the IFN era at the beginning of the millennium, the median OS was 13.6 months in patients who received the combination of IFN plus nephrectomy compared with 7.8 months in patients who received IFN alone (HR 0.69; p=0.002) (Flanigan et al. 2003). CARMENA study, however, showed that nowadays during tyrosine kinase inhibitor (TKI) era nephrectomy is no longer necessary (Mejean et al. 2018). Metastasectomy or other local treatments for metastasis can be used, and no systemic treatment is recommended after metastasectomy. Nevertheless, operative treatment for mRCC is rarely used currently, and the treatment is mainly TKIs- and/or immunotherapy. (Lyon et al. 2019; Escudier et al 2019)

2.3.2.2 Medical treatment

Treatment for RCC is dependent on whether the disease is local or metastatic, and in metastatic disease, treatment is determined by a risk group analysis (Table 4). For local disease, adjuvant therapy with VEGF and PDGF-targeted therapies, sunitinib, sorafenib and pazopanib has been approved in the U.S. but not in Europe. (NCCN guidelines, Kidney Cancer, 2019) Adjuvant therapy in patients with localized disease has not shown any benefits in terms of OS. Therefore adjuvant therapy is not commonly used as the primary treatment of RCC. Before starting therapy for metastatic disease, an observation period may be recommended. This is especially the case in patients who have limited tumors and only few symptoms. (Escudier et al. 2019)

In most studies of mRCC, patients with clear cell cancer with a low tumor burden are the primary observed population; therefore, the recommendations may not be as straightforward for patients with other histological types of mRCC. Originally, mRCC showed high resistance to traditional chemotherapy, and since the 1990s, mRCC was treated with interferon-α (IFN-α) or interleukin-2 (IL-2). Response to these cytokines was poor (5-20%), and the median OS was low (approximately 12 months). (Pyrhönen et al. 1999) The understanding of angiogenesis and the role of tyrosine kinase, VEGF and PDGF pathways in the beginning of the 21st century, has led to targeted therapies directed at these pathways, yielding improved PFS and OS in mRCC patients. Bevacizumab (an anti-VEGF antibody) has been found to prolong PFS in patients with mRCC patients, which has led to further discoveries in this treatment direction. A tyrosine kinase inhibitor (TKI) and VEGF and PDGF receptor inhibitor sunitinib (and sorafenib) were introduced shortly afterwards for mRCC treatment. Initially, these drugs yielded a 30-40% response rate, benefiting patients in terms of PFS and OS. Numerous other TKIs have also been developed, such as pazopanib, axitinib, dovitinib and cabozantinib. Tivozanib, a selective VEGF inhibitor, has been compared with sorafenib, and it has shown improved PFS. (Yang et al. 2003; Motzer et al. 2007; Molina, Motzer 2011; Funakoshi et al. 2014; Ruiz-Morales et al. 2016; Moran et al. 2019)

Immunotherapies offer another approach for treating mRCC. The targets for these therapies include the programmed cell death 1 (PD-1) pathway, a cytotoxic T – lymphocyte – associated antigen 4 (CTLA – 4) and the programmed cell death-ligand 1 (PD – L1) pathway. The PD – 1 checkpoint inhibitor nivolumab (35% response rate), combined with ipilimumab to yield a 40% overall response rate, CTLA – 4 checkpoint inhibitor ipilimumab (12,5% response rate) and PD – L1 inhibitor atezolizumab have been studied alone, as combinations and in combination with sunitinib in the treatment of mRCC. (Motzer et al. 2018; Atkins, Tannir 2018) In a recent publication by Motzer et al., the combination of nivolumab plus ipilimumab was compared with sunitinib in patients with intermediate- and poor-risk advanced RCC. The benefit of the combination was significant in terms of OS (HR 0.66, CI0.54-0.80, $p<0.0001$) at 26.6 months in the sunitinib group, while the OS of the combined group was not reached within the follow-up period of 32.4 months. In addition complete response rate with the combination was significantly higher (9% vs 1%). (Motzer et al. 2019)

Mechanistic target of rapamycin (mTOR) is a protein kinase. The activation of mTOR promotes tumor growth and creates metastases. Therefore, mTOR inhibitors, such as everolimus and temsirolimus, have also been investigated

individually and compared with immunotherapies. These inhibitors were found to offer some OS benefit, but they are also associated with the development of resistance. (Motzer et al. 2015; Hua et al. 2019; Escudier et al 2019)

The ESMO guidelines approach treatment suggestions for first-line treatment of clear cell mRCC through risk evaluations. For good-risk patients, sunitinib, pazopanib, bevacizumab combined with IFN-α or tivozanib are standard treatment choices. Optional treatments include high-dose IL-2 or bevacizumab combined with IFN-α. For patients with intermediate-risk, the standard care is a combination of nivolumab and ipilimumab. The options include cabozantinib, sunitinib, pazopanib, tivozanib or bevacizumab combined with IFN-α. For poor-risk patients, nivolumab and ipilimumab are combined in standard care, while the optional treatments include cabozantinib, sunitinib, pazopanib and temsirolimus. (Escudier et al. 2019)

Second-line treatment is based on the applied first-line treatment. If any TKI is the initial choice, treatment can proceed with the TKI cabozantinib or the checkpoint inhibitor nivolumab. The TOR inhibitor everolimus, as are the TKI axitinib or the TKI lenvatinib combined with everolimus, are optional. If first-line treatment has included combination immunotherapy, any TKIs, as well as a combination of lenvatinib and everolimus, can be used. The choice of first- and second-line treatments is primarily the standard option but is also dependent on what is available. (Escudier et al. 2019)

If a patient needs further lines of treatment, each treatment should be individually planned and based on the first- and second-line treatment choices. The models for recommended treatments mainly include the previously mentioned second-line treatments, as shown in a recent study by Auvray et al. This study found that even after a combination of nivolumab-ipilimumab, patients may still significantly benefit from TKIs. (Auvray et al. 2019; Escudier et al. 2019)

Evaluations of mRCCs other than clear cell carcinoma are very limited based mainly on phase two trials or retrospective data. Therefore, the ESMO guidelines recommend that patients be enrolled in clinical trials. Sunitinib has been shown to be favorable in subgroup analyses from larger studies; however, all other treatments have also shown benefit in clinical studies. Papillary histology-type cancer is the only one in which standard care including sunitinib or pazopanib should be provided according to the guidelines. Additionally, cancers with collecting duct histology might benefit from cisplatin-based treatment. (Escudier et al. 2019)

2.3.2.3 Follow-up

No follow-up protocol has proven to be better than any others in clinical studies, but follow-up is recommended for the first two years after treatment, which is when most recurrences occur. The ESMO guidelines suggest that high-risk patients have a thoracic and abdominal CT scan every 3 – 6 months for the first two years, whereas the recommendation for low-risk patients is annual CT scans for the first two years. When a patient is undergoing systemic therapy, a CT scan is recommended every 2-4 months as a follow-up. As in the case of EC, there is no tumor marker for RCC. For localized disease, after operative treatment, the follow-up plan is based on the treatment options to be used if recurrence occurs. (Escudier et al. 2019; NCCN guidelines, Kidney Cancer, 2019)

2.3.3 Costs

The treatment costs for localized disease consist of surgery and a two-year follow-up period mainly involving CT imaging. If calculated using the follow-up tests presented in the previous chapter (not including visits) and the average Finnish health care unit costs in 2011 (CT scan cost of 150-200 €), the cost of treatment for local RCC in Finland would be approximately 9,500 € for a high-risk patient (surgery + CT every 4 months for 2 years) and 8,900 € for a low-risk patient (surgery + CT annually for 2 years). The average Finnish health care unit costs for the treatment of RCC are presented in Table 4. The chemotherapy treatment costs include the necessary personnel, clinic setting, necessary basic tools and basic medication but do not include the treatment costs of new expensive drugs. (Kapiainen et al. 2014; Chien et al. 2018).

Internationally, cost comparisons between open surgery, robotic-assisted laparoscopy and traditional laparoscopy in patients with local RCC are incoherent. However, in partial nephrectomy, minimally invasive techniques have shown a cost benefit over open surgery. (Chien et al. 2018)

The burden of costs in the treatment of mRCC is related to expensive drugs, and it seems to be increasing, since mRCC does not respond well to traditional chemotherapies. Therefore, there are relatively few "old" inexpensive or biosimilar treatment options available. Cost-effectiveness analyses have been increasingly reported with clinical studies and mainly include modeled approaches. Comparing cost analyses is not easy, since studies approach the expense setting slightly differently and use different thresholds for acceptable results. In addition, a drug

may yield a different response in different population, as reviewed by Deng et al., who reported that sorafenib may be more suitable for Asian patients, and sunitinib may be more suitable for European patients. These differences also influence the cost-effectiveness ratio. However, in the latest analyses of first-line treatment of mRCC, some conclusions have been made; pazopanib has been found to be the most cost-effective, and sunitinib was found to be the second-most cost-effective, over a combination of bevacizumab and IFN-α as well as over sorafenib. Nivolumab combined with ipilimumab had an ICER of 108,363 USD/QALY and was considered cost effective by Wan et al. when using the threshold of 100,000-150,000 USD in unselected mRCC patients. However, in another study by Reinhorn et al. of intermediate- and poor-risk patients, the ICER was 125,739 USD/QALY. (Chien et al. 2018; Shih et al. 2019; Deng et al. 2019; Wan et al. 2019; Vargas et al. 2019; Reinhorn et al. 2019)

For second-line treatments, similar conclusions are more difficult to draw. Some cost-effectiveness analyses have been performed for the second-line treatment of mRCC; however, different styles were used. Nivolumab (ICER 146,532 USD/QALY) has been shown to be more cost-effective than everolimus (ICER 226,197 USD/QALY) (Sarfaty et al. 2018). A Swedish group compared the costs of treatment of patients diagnosed with mRCC before targeted therapies, early in the introduction of targeted therapies and when targeted therapies were well-established treatments. These authors found that targeted therapies were cost-effective over time. (Redig et al. 2019)

Table 5. Finnish health care unit costs of 2011, concerning RCC (Kapiainen et al. 2014)

Treatment	Cost €/treatment period	# treatment days included
Operation	8,596	9.3
Radiotherapy	4,220	8.3
Regular chemotherapy protocol	1,386	2.8
Demanding chemotherapy	3,491	3.0

3 AIMS OF THE STUDY

The aim of this study was to evaluate the costs related to relatively expensive treatment modalities in endometrial cancer, ovarian cancer and metastatic renal cell cancer. The specific aims were the following:

- Are there differences between traditional laparoscopy and robotic assisted laparoscopy regarding operative costs in patients with endometrial cancer?
- How much does bevacizumab influence the costs of ovarian cancer treatment?
- What are the costs of first-line interferon-α treatment and what is the change in cost burden compared to the new targeted therapy era of patients with metastatic renal cell cancer?
- What is the role of sunitinib in the treatment costs and quality of life in patients with metastatic renal cell cancer?

4 PATIENTS, MATERIALS AND METHODS

4.1 Patients and original study designs

Table 6. Patients and the original study designs. All of the cost calculations were performed retrospectively.

Study no.	Patients	Treatments	Study design
I	101 EC patients	Traditional laparoscopy (n=51) Robotic-assisted laparoscopy (n=50)	Prospective randomized
II	75 OC patients	Focus on bevacizumab	Retrospective observational
III	83 mRCC patients	Focus on interferon-α	Retrospective observational
IV	81 mRCC patients	Focus on sunitinib	Prospective observational

4.2 Methods

4.2.1 Study I: Robotic-assisted vs. traditional laparoscopy

The original study design randomized 101 EC patients into two arms: traditional laparoscopy and robotic-assisted laparoscopy. All data on the operations and postoperative period of up to six months were recorded. The costs of these treatments were retrospectively calculated based on the hospital's internal accounting and billing system, hospital purchase costs and yearly expense data of 2012. In addition, the amortization of the robot console and traditional laparoscopy towers were included in the calculations. In the final calculations, costs concerning operative personnel, operation room (OR), equipment related to the operating room, instrumentation, operation medication, post-anesthesia care unit (PACU), inpatient stay, laboratory tests, blood products, imaging studies and general hospital costs were taken into account. Complications were defined as unscheduled contacts with health services, related imaging studies, readmissions and operative treatment. These costs were calculated separately from the costs of the initial operative treatment.

4.2.2 Study II: Bevacizumab in ovarian cancer

A cohort of patients diagnosed with epithelial ovarian cancer during the years 2011 and 2012 was chosen as the study population, and this cohort included a total of 75 patients. The endpoint for follow-up was 31.12.2017. The data were retrospectively collected from the patient files during 2017 and 2018 on a structured form. The data collected included information about the diagnosis, original operative treatment, chemotherapy, other medication concerning treatment, bevacizumab treatment and all follow-up visits. The cost calculations included chemotherapy, bevacizumab, follow-up visits, laboratory and imaging studies, on-call visits, inpatient stay and use of granulocyte-colony stimulating factors (G-CSF). For cost calculations, data derived from internal management accounting systems used yearly expense data and national market prices from Pharmaca Fennica for G-CSF. Only the costs during chemotherapy and bevacizumab treatment, and the costs concerning the Department of Obstetrics and Gynecology, were calculated and included in the final analysis; the operative treatment was omitted. The aim was to analyze the costs of the treatment and to determine the main variable influencing the costs.

4.2.3 Study III: Interferon-α in mRCC

As the basis and background, the information about treatment and survival and the cost of treatment, concerning mRCC patients receiving first-line IFN-α treatment, were retrospectively collected. Models of the future burden of mRCC were constructed based on the collected information regarding 83 locally studied patients, epidemiological data and a forecast of population growth. The impact of sunitinib was also included to predict the cost burden. The implemented costs were regionally adjusted Finnish unit costs and real-valued amounts using the official health care price indexed to the year 2008. The costs of medication were derived from Pharmaca Fennica.

The statistical information of the Finnish Cancer Registry, gender-specific expected lifetimes and future population projections were used to estimate the future RCC incidence and life years lost due to the disease. Productivity loss was estimated using the time from the diagnosis to retirement and the assumption that the patient would not return to work after the diagnosis. The model for future costs realized drug prices, treatment protocols for INF-α and sunitinib, and an understanding of the natural history of mRCC and therefore conveyed the prevalence of patients with different disease stages.

4.2.4 Study IV: Sunitinib in mRCC

From five different hospitals, 81 mRCC patients receiving first-line sunitinib were recruited. The study itself did not interfere with the patients' treatment. An informed consent was obtained from all patients. The quality of life was measured with two different questionnaires: 15-D and EQ-5D-3L. The questionnaires were completed at baseline and at specific time points during the sunitinib treatment. During the treatment, patient data were collected on a structured form and included background information in addition to treatment details. Follow-up ended either on 30.11.2014, or when the sunitinib treatment was ended. The costs of the treatment were calculated using average Finnish health care unit costs or costs regarding the unit of concern. The cancer medication costs were calculated with retail prices and/or based on prices from Pharmaca Fennica.

4.3 Statistical aspects

Study I: Because of the skewed distributions and outliers concerning the results, the costs were presented in terms of the medians (Md) and interquartile ranges (IQR). Differences between traditional and robotic-assisted laparoscopic surgical costs were analyzed by the nonparametric independent-samples Mann-Whitney U test. Categorical variables were tested by Pearson's chi-square test or by Fisher's exact test if the expected values were too small. Statistical analyses were performed with IBM SPSS Statistics version 23 (IBM Corp., Armonk, NY). P-values less than 0.05 were considered statistically significant.

Study II: The distributions of cost factors are shown by the medians with interquartile ranges (IQR) due to the skewed distributions and outliers. Differences between categorical patient characteristics were tested by Pearson's chi-square test or Fisher's exact test. Due to the skewed distributions, continuous patient factors were analyzed by the Mann-Whitney test. Analyses were performed using IBM SPSS Statistics for Windows (version 23.0, IBM Corp., Armonk, NY, USA).

Study III: A statistical package (SPSS 14.0) and a spreadsheet (MS Excel) were used for data management and analyses. Kaplan-Meier analysis was used in the survival estimates, and linear regression in defining the determinants of treatment costs.

Study IV: The minimum clinically important change or difference in the 15D score has been estimated to be ±0.015 on the basis that people on average can feel such a difference. The HRQoL measured with the 15D questionnaire was compared to a sample of the age- and gender-standardized general population based on an earlier National Health Survey.

4.4 Ethical aspects

The cost studies and calculations did not interfere with the patients' treatment in any way. The Declaration of Helsinki was the basis of ethical considerations. Ethical approval was received from the Research Ethics committee of Tampere University Hospital for the different studies (Identification codes Study I: ETL R10081, Study II: R17126, and Study IV: R09045). The clinical studies were registered in the Clinical Trials database (no. I: NCT01466777, no. IV: NCT00980213). Informed consent was obtained for the original study designs in Studies I, III and IV. According to

good clinical practice guidelines during the time, Study III was approved by the chief physicians of the Turku and Tampere University hospital districts.

5 RESULTS

5.1 Study I: Robotic-assisted vs. traditional laparoscopy

The median cost of robotic-assisted laparoscopy was 7,415 €, which means that it was 1,928 € (35%) more expensive than traditional laparoscopy in the case of the standard operation for EC or hysterectomy, bilateral salpingo-oophorectomy and pelvic lymphadenectomy. When late complications concerning the six-month follow-up period were included, the median cost of the robotic-assisted laparoscopy was 7,983 €, and that of the traditional laparoscopy was 5,823 €. The main difference in the costs derives from the robotic instrumentation and the amortization of the robot console, which are presented in Figure 1 (page 1791) of the original article as variables "Instrumentation" and "Equipment and OR". The shorter operation time utilized by the robotic arm was not enough to compensate for the difference in the costs, although there are many time-related costs in these operations. The more specific results are presented in Table 2 (page 1791) of the original article.

5.2 Study II: Bevacizumab in ovarian cancer

Of the 75 OC patients identified, 66 received chemotherapy and were included in the analysis. The median age at diagnosis was 66.6 years. In 24 of these patients, bevacizumab was included in the treatment, either as a first- or a later-line treatment. The patients treated with bevacizumab more often had Stage III or IV disease (23 of the 24 patients in the bevacizumab group vs. 24 out of 42 in the non-bevacizumab group), more recurrences (88% vs. 17%, respectively), and longer treatments as expected, considering the nature of the disease (follow-up days, Md 662 vs. 139). Even though less than half of the patients (32%) received bevacizumab, this treatment represented the single largest relative expense of 47.1% when all costs of the 66 patients were taken into account. In the group of bevacizumab patients, the share of bevacizumab from the total treatment costs was 62.7%, with a total 1,132,870 € for the 24 patients during the follow-up period. The median total costs of the entire treatment of a patient not treated with bevacizumab was 7,700 €, and

the median total costs of the entire treatment of a patient treated with bevacizumab was 82,542 €. These costs are presented in more detail in the table of the original article. While four patients had on-going treatment at the end of the follow-up, in total 41 (62%) patients had died, 19 (79%) in the bevacizumab group and 22 (52%) in the non-bevacizumab group.

5.3 Study III: Interferon-α in mRCC

Medication accounted for most of the treatment costs during active IFN-α treatment, comprising 60% of the total treatment costs. IFN-α accounted for 89% of the medication costs during the entire follow-up. After active treatment, the composition of costs changed radically, with medication comprising only 6% of the total costs. After IFN-α treatment, the main driver of cost was inpatient stay, comprising 79% of the non-medication costs. These costs are presented in more detail in Table IV of the original article (page 840). The burden of new RCC cases was estimated to increase by nearly 2% a year by 2020. The burden of mRCC IFN-α treatment with 227 annual patients in the future would incur a cost of 15.6 M € during five years. If half of these patients were estimated to receive sunitinib treatment, it would increase the cost burden by an additional 2.7 M € per year. This additional cost can be considered to be a significant burden to society considering the limited number of mRCC patients.

5.4 Study IV: Sunitinib in mRCC

The major driver of cost in the treatment of these mRCC patients was the sunitinib medication itself, which accounted for 73% of the costs. The mean sunitinib treatment cost per patient was 22,268 €, ranging from 274 € to 105,121 €. Inpatient stay was the second largest expense, comprising 15.2% of the treatment costs. More results are presented in Table I of the original article (page 5561). The health-related quality of life (HRQoL) score was initially lower than in the age- and gender-standardized general Finnish population, as presented in Figure 3 of the original article (page 5562), but it remained rather stable and was lower than that in the control group during the treatment.

6 DISCUSSION

The costs of cancer treatment affect the health care service and the whole community in a substantial way. Cancer research is developing rapidly and leads to the introduction of new interventions, from molecular genetics to targeted therapies to advanced surgical techniques. As these new approaches emerge, it is crucial to study their financial impact along with the efficacy. Organizations such as the National Institute for Health and Care Excellence (NICE, www.nice.org.uk) have been created solely for the purpose of improving health care through evidence-based guidance. The Finnish Medicines Agency (FIMEA) is a rather similar national level organization in Finland. However, while cost-effectiveness is evaluated in trial setting, it is also important to produce real-time and real-life data regarding these costs as guidance for clinical practices. It is, however, notable that in Finland, cancer treatment costs have actually decreased per patient when comparing the expense levels of 2009 and 2014 (Torkki et al. 2018). Considering all these aspects, this thesis was planned to evaluate the total costs of EC surgery and both OC and mRCC medication, and the results showed a high cost burden of these newer treatment modalities (Studies I-IV). However, all these approaches present an advantage to individual patients.

For this thesis these treatment modalities were chosen because all of them have been considered expensive during the time they were novel approaches. Sunitinib and bevacizumab are still expensive, and also robotic assisted surgery is still considered to be rather costly. All the studied drug treatments are anti-angiogenetic which gives the therapies a common nominator, even though they are not comparable. Robotic assisted surgery was included, because surgery is the cornerstone of endometrial cancer treatment. Robotic-assisted surgery was greeted with considerable enthusiasm by gynecologic surgeons, who switched from traditional approaches to the robot-assisted rather fast since its introduction.

The main focus has been the direct costs related to the treatment. We have mostly ruled out the non-healthcare related societal costs, since the evaluation and calculation of these costs in these study designs would not have been reliable. Furthermore the costs related to treatments at the referral hospital can be more reliably evaluated. The treatment of these patients also primarily takes place in the

referral hospitals and therefore the cost calculations concerning these hospitals give valuable and rather accurate information on total treatment costs.

6.1 Endometrial cancer

The unique layout of our randomized study comparing traditional laparoscopy and robotic-assisted laparoscopy presents a true evidence-based comparison between these two treatment modalities. Because this type of comparison has not been previously performed, it makes the comparison of results rather difficult. For instance, this type of study does not exist for the surgical approach in prostate cancer, even though it is the most common cancer treated with robotic-assisted surgery (Schroeck et al. 2017). The main advantage, in terms of cost, of the robotic-assisted laparoscopy in EC compared to traditional laparoscopy is the advantage related to the conversion risk of traditional laparoscopy. Previously, the open and robotic-assisted approaches have been shown to be the more expensive methods compared to traditional laparoscopy, as presented in the literature review in chapter 2.1.4. Our calculations of the five converted surgeries in the traditional group also apply to the expensiveness of an open approach. The converted surgeries presented a median cost of 7,149 € vs. the cost of the robotic-assisted operation of 7,415 €, while the cost for traditional laparoscopy was only 5,487 €. The cost difference was in line with other findings in the literature, indicating that traditional laparoscopy is less expensive.

For the robotic-assisted approach to be less expensive, according to our study, the main variables worth influencing are the costs of the robot console and the robotic instrumentation. For these costs to diminish, the robot console should be used efficiently throughout the day, and the delays between the operations should be minimized. The instruments related to the robotic-assisted operation can only be used up to 10 times, while the practice instruments can be used up to 20 times. It would be worthwhile for the manufacturer to investigate if the actual instruments could be used more times. These actions could significantly influence the total costs and increase the usefulness of the approach, since the benefit for the patient and the surgeon have been proven in the literature (Schreuder and Verheijen, 2009; Ramirez et al. 2012).

6.2 Ovarian cancer

Our mean cost for first-line bevacizumab was 52,766 €/patient (Md 57,800 €), which is comparable to the GOG-0218 trial results of a mean cost of 44,286 €. The mean cost of second-line treatment in our study was 36,060 € (Md 40,163 €), which is between the results of AURELIA (28,529 €) and OCEANS (53,591 €) trials, respectively. (Neyt et al. 2018). Even though the cost of bevacizumab is significant it is still lower than the costs of recent new innovations, such as PARP inhibitors as presented in the literature review in chapter 2.2.4, where the costs are between 350,000 € (396,800 USD) and 540,000 € (595,500 USD). In addition, adverse events related to bevacizumab can increase the treatment costs. These costs also elevate the ICER and are incorporated in the NICE report (NICE guidelines). In our study, these costs were not separately analyzed or distinguished from the adverse events of the basic chemotherapy. The complications related to the basic chemotherapy might be more substantial than the costs of adverse events related solely to bevacizumab. However, most of the inpatient stay was due to adverse-events related to the treatment, chemotherapy and/or bevacizumab; therefore, our results present a rather accurate description of the treatment costs and of the adverse events.

As Torkki et al. have shown, inpatient stay is the main cost driver (45-50%) in many cancers, such as lung, colorectal and non-Hodgkin lymphoma (Torkki et al. 2018). We found similar results in our non-bevacizumab OC patients, in which inpatient stay comprised 44% of the treatment costs. The cost distribution was completely different in our bevacizumab OC patients, as the main driver of cost was the medication itself, representing 63% of the total treatment costs. Even in the second-line bevacizumab treatment, the proportion of the medication itself was 49%.

6.3 Metastatic renal cell cancer

The cost of medication, especially the interferon-α, was determined to comprise most of the total costs during the active treatment period. The same was found in the sunitinib trial. However, it is notable in our studies that during the IFN-α treatment period, the median OS was only 11.9 months, and it already increased along with sunitinib treatment to 17.9 months, which was observed in our unpublished results. In the randomized study comparing sunitinib to the ipilimumab-nivolumab combination in intermediate- and poor-risk mRCC patients, the median OS of sunitinib-treated patients was 37.9 months while the median OS

of the combination treatment had not yet been reached during the extended follow-up; the study is still ongoing (CheckMate 214 trial). Therefore, the patients do benefit from these treatments, even though their cost-effectiveness is not optimal.

Since the IFN era, the drug costs have been the main driver of cost, even more so today. However, the treatment costs and the burden to society were previously much lower than the current levels when using a combined treatment of check-point inhibitors, ipilimumab and nivolumab. The combined treatment cost is over 100,000 USD/patient. In addition, the treatment has many serious side effects, and the recommendation is to refrain from its use in favorable-risk patients. In ESMO guidelines, there is still the combination of bevacizumab and IFN-α for this patient group (Escudier et al. 2019). However, in Finland, this approach is no longer used in daily practice, while TKI inhibitors, such as sunitinib, as per oral drugs and with a better tolerability, are used as first-line treatment in good-risk mRCC. Due to the high drug costs of ipilimumab combined with nivolumab, the Finnish health care advisor board, or Terveydenhuollon palveluvalikoimaneuvosto (PALKO), very carefully reviewed the possibility of adding this combination to the treatment options and just recently gave permission for its use. This combination has been previously accepted for clinical use in many European countries and is already among the common treatment options. PALKO has calculated the additional cost of this treatment combination compared to sunitinib to be 125,000 € per patient. (PALKO recommendations)

In addition, in a recent report on patient-reported outcomes in the CheckMate 214 trial, the combination of ipilimumab and nivolumab led to fewer symptoms and better HRQoL than sunitinib in these intermediate- or poor-risk advanced RCC patients. Compared to sunitinib, the combination treatment reduced deterioration risk in the EQ-5D-3L visual analog scale (VAS) score (HR 0.71, 95%, CI 0.63-0.89). In the same trial the EQ-5D-3L utility index, which is the same index we measured, behaved similar to that in our study. (Cella et al. 2019)

6.4 Strengths

Study I: The study design is the major strength in the calculations comparing traditional laparoscopy and robotic-assisted laparoscopy. This design enabled the comparison of identical operations with well-balanced groups, avoiding inherent bias of calculations based on retrospective data. The costs of different variables were searched and calculated in a very detailed fashion for each operation, and no

modeling was used. Each operation was calculated independently for the combined results and the comparison between the groups. The results were in line with previous studies comparing these costs.

Study II: This study introduces a real-life setting and real-life costs, which are not modeled or based on clinical studies. Moreover, in this study, the costs were individually calculated in a very detailed manner for each patient. Even though our study was based on real-life clinical routine practice and revealed the heterogeneity in patient treatments, the results were in line with and comparable to other studies and can therefore be used in further cost analyses.

Study III: During the time of our study, there were only a few studies concerning the cost and burden of mRCC treatment. The study results offered detailed information about the costs of the mRCC treatment and valuable data of the future burden of mRCC. This study gave valuable information also on the changing treatment scenery considering the transition from cytokine era to TKI era.

Study IV: The study presented detailed information concerning the costs of sunitinib treatment of mRCC patients. The QoL was measured with two different questionnaires to reach a thorough understanding of the patient's wellbeing. The results were in line with previous studies; the cancer-specific targeted therapy is the main driver of the costs in cancer treatment, and concerning the findings with respect to patient treatment choices. The treatments were performed according to international guidelines, providing reliability of the study results.

6.5 Limitations

Study I: The cohort of patients was rather limited, but the results were in line with those of other studies concerning the topic. Some local factors had an impact on the results that restrained the generalizability of the results. QoL or the OS benefit was not measured in the original study, and therefore, cost-effectiveness or QALY was not calculated. As the standard operation has been altered to include para-aortic lymp node dissection after this study was executed, these results are not entirely comparable to other studies that may be based on different types of operations. However, the newest approach is to evaluate the sentinel lymph nodes and conduct the operation according to the pathological findings. This approach might reduce the extent of future operations so that our results can be more comparable again.

Study II: The limited number of patients in the cohort restrains the possibility of reliably comparing the patient groups. The Finnish Current Guidelines for OC were

not established until 2012, which explains some of the heterogeneity in the treatments of our patients. This heterogeneity makes the comparison to other studies more difficult, even though the treatment choices were based on the labeled use of bevacizumab. If a later cohort had been chosen, the treatments would have been more homogenous, but the follow-up would have been shorter. In addition, we were not able to reliably identify the exact costs of the complications.

Study III: The limited size of the study population did not allow sufficient subgroup analyses. We were also not able to collect all of the resource use information we would have hoped for from all of the study patients. There is a slight possibility of overestimation in the future broadcast of the burden of mRCC, since the estimations were based on the 2004 level. The patient's performance status was not recorded at baseline, which can also be considered a limitation.

Study IV: Even though there were several study hospitals, the number of the patients included was limited. The lack of treatment protocol related to the study design can be considered a limitation, but the treatment choices were still consistent with national and international guidelines.

6.6 Future trends

Study I: The comparison of costs between the traditional laparoscopic and robotic-assisted laparoscopic EC surgeries should be conducted, including the para-aortic lymphadenectomy, at a national level. This comparison might offer more information about the differences or similarities between these two methods. Our original study design reported the robotic-assisted surgeries to be slightly faster, yet the difference was not enough to eliminate the difference in cost. If there were hypothetically larger time differences between the two methods when para-aortic lymphadenectomy was involved, given the robot's advantage, the robotic-assisted approach might present more tolerable additional costs or no additional costs at all.

Study II-IV: When new cancer treatments emerge, cost-effectiveness studies should follow close behind. The economic burden of these treatments can be significant even though they might benefit only a small group of patients. International guidelines should also provide suggestions for the proper use of these treatments early so that there are evidence-based protocols to support medical staff worldwide. The societal aspect of these treatments should also be assessed and considered more carefully, since the increasing cancer burden may present a significant impact on the national economy. The burden and costs of adverse effects,

complications, hospitalization and other variables should also be calculated when considering new and existing treatments so that a thorough understanding of the costs of cancer treatment can be reached. Prospective study designs might benefit from these types of calculations by creating an ongoing expense calculation during the patient's treatment. In this way, the small details in the treatment path can be more accurately recorded.

7 WIDER ASPECTS

Cost calculations, in their simplicity, offer very little ethical questions. The patient's treatment is not interfered with in these studies. The results do not deny any patient of their treatment. The question raised is, how much can cancer treatment cost? New treatments are merging at a rapid pace and often with a rather high cost, which has created global problems of the accessibility of these treatments when considering countries' national willingness-to-pay thresholds. For a further ethical consideration, is the cost of a treatment reason important enough to define someone outside the treatment even though, treatment might provide a few more months to live? Where do we draw the line in the medication budget when considering if one patient benefits from an expensive and efficient treatment but due to this treatment choice, many others are denied of their less effective treatment because of the lack of funding?

How much can money influence the way we treat patients? Is there a price for human life? Clinicians everywhere are the holders of this secret. Globally, people are in very different situations considering their country's willingness-to-pay threshold. If the threshold is set as the WHO suggests, according to per-capita gross domestic product, thresholds vary from nation to nation, and some countries still cannot afford expensive new treatments. Moreover, this issue arises even though some treatments might have been calculated to be cost-effective in studies. Nevertheless, as said about thresholds in the WHO article by Bertram et al.: "They are simply an indication that, in a given setting, an intervention may represent poor, good or very good value for money."

Can the costs of cancer treatment be reduced? Would the following considerations be beneficial: switch from routine to symptom-based follow-up; using calls instead of follow-up visits; using digital systems and applications for patient driven follow-up; considering if monotherapy offers sufficient treatment compared to combined therapy; accurately choosing the patients who benefit from chemotherapy or other specific drug treatments; accurately choosing the patients who benefit from vast surgical operations; and actively assessing the patient's performance status to consider treatment options that do not cause more damage than what it is worthwhile. Even discussing end-of-life decisions and the option to

stop active treatment and switch to palliative treatment guides the patient to the right stages of health care and reduces treatment costs (Smith et al 2011). When patients in poor condition are treated with chemotherapy for too long, it increases the cost of cancer treatment in terms of the chemotherapy and the treatment of the complications. These mentioned suggestions have already been sporadically implemented in cancer treatment.

The cost comparisons performed internationally are sometimes difficult due to different types of funding and insurance systems, not to mention the differences in drug administration and daily practices. Nevertheless, chemotherapy or other therapy drug costs are usually fixed.

Cost-effectiveness studies try to identify suitable thresholds and reasonable prices for a quality-adjusted life year. International societies create guidelines by also searching for effective, novel solutions and cost-effective results. The results are not always convergent, yet even differing results can provide guidance towards solutions.

8 SUMMARY AND CONCLUSIONS

- The difference between traditional laparoscopy and robotic-assisted laparoscopy is approximately 2,000 € when performing an identical operation in the treatment of endometrial cancer. The instrumentation and the amortization of the robot console principally explain the cost difference.
- Bevacizumab is the single largest expense in the medical treatment of ovarian cancer patients. Bevacizumab constitutes almost half (47.1%) of all the costs when patients treated with or without bevacizumab are considered, and more than half (62%) of all the costs in the bevacizumab group.
- During interferon-α treatment, medications formed the largest part of the costs at 60%. During the entire follow-up, interferon-α comprised 89% of all medication used. The role of interferon-α was significant, as other medication comprised a notably smaller part of the medication costs, with other cancer medication at 6%, bisphosphonates at 3% and analgesics at 2%.
- Sunitinib comprised 73% of the total costs in the treatment of patients with metastatic renal cell carcinoma. Sunitinib treatment decreased the quality of life in these patients during treatment, but the effect was withdrawn as the treatment was suspended or stopped.

9 REFERENCES

Aghajanian, C., Blank, S. V., Goff, B. A., Judson, P. L., Teneriello, M. G., Husain, A., … Nycum, L. R. (2012). OCEANS: A randomized, double-blind, placebo-controlled phase III trial of chemotherapy with or without bevacizumab in patients with platinum-sensitive recurrent epithelial ovarian, primary peritoneal, or fallopian tube cancer. *Journal of Clinical Oncology*, *30*(17), 2039–2045. https://doi.org/10.1200/JCO.2012.42.0505

Amant, F., Mirza, M. R., Koskas, M., & Creutzberg, C. L. (2018). Cancer of the corpus uteri. *International Journal of Gynecology and Obstetrics*, *143*(2), 37–50. https://doi.org/10.1002/ijgo.12612

Amant, F., Moerman, P., Neven, P., Timmerman, D., Van Limbergen, E., & Vergote, I. (2005). Endometrial cancer. *The Lancet*, *366*(9484), 491–505. https://doi.org/https://doi.org/10.1016/S0140-6736(05)67063-8

Arora, V., & Quinn, M. A. (2012). Endometrial cancer. *Best Practice & Research Clinical Obstetrics & Gynaecology*, *26*(3), 311–324. https://doi.org/https://doi.org/10.1016/j.bpobgyn.2011.12.007

Atkins, M. B., & Tannir, N. M. (2018). Current and emerging therapies for first-line treatment of metastatic clear cell renal cell carcinoma. *Cancer Treatment Reviews*, *70*, 127–137. https://doi.org/10.1016/j.ctrv.2018.07.009

Auvray, M., Auclin, E., Barthelemy, P., Bono, P., Kellokumpu-Lehtinen, P., Gross-Goupil, M., … Albiges, L. (2019). Second-line targeted therapies after nivolumab-ipilimumab failure in metastatic renal cell carcinoma. *European Journal of Cancer*, *108*, 33–40. https://doi.org/10.1016/j.ejca.2018.11.031

Barnett, J. C., Judd, J. P., Wu, J. M., Scales, C. D., Myers, E. R., & Havrilesky, L. J. (2010). Cost Comparison Among Robotic, Laparoscopic, and Open Hysterectomy for Endometrial Cancer. In *Obstet Gynecol, 116*(3), 685-93. Retrieved from http://links.lww.com/AOG/A192]

Bercow, A. S., Chen, L., Chatterjee, S., Tergas, A. I., Hou, J. Y., Burke, W. M., … Wright, J. D. (2017). Cost of care for the initial management of ovarian cancer. *Obstetrics and Gynecology*, *130*(6), 1269–1275. https://doi.org/10.1097/AOG.0000000000002317

Berek, J. S., Kehoe, S. T., Kumar, L., & Friedlander, M. (2018). Cancer of the ovary, fallopian tube, and peritoneum. *International Journal of Gynecology and Obstetrics*, *143*(2), 59–78. https://doi.org/10.1002/ijgo.12614

Bernard, D. S. M., Farr, S. L., & Fang, Z. (2011). National estimates of out-of-pocket health care expenditure burdens among nonelderly adults with cancer: 2001 to 2008. *Journal of Clinical Oncology*, *29*(20), 2821–2826. https://doi.org/10.1200/JCO.2010.33.0522

Bertram M.Y., Lauer, J. A., De, J. K., Edejer, T., & Hutubessy, Raymond, Marie-Paule Kieny, S. R. H. (2016). Cost–effectiveness thresholds: pros and cons. WHO publications. https://doi.org/http://dx.doi.org/10.2471/BLT.15.164418

Burger, R. A., Brady, M. F., Bookman, M. A., Fleming, G. F., Monk, B. J., Huang, H., … Liang, S. X. (2011). Incorporation of Bevacizumab in the Primary Treatment of Ovarian Cancer Abstract. *The New England Journal of Medicine*, *365*(22), 2473–2483.

Capitanio, U., & Montorsi, F. (2016). Renal cancer. *The Lancet*, *387*(10021), 894–906. https://doi.org/10.1016/S0140-6736(15)00046-X

Capriglione, S., Luvero, D., Plotti, F., Terranova, C., Montera, R., Scaletta, G., … Angioli, R. (2017). Ovarian cancer recurrence and early detection: may HE4 play a key role in this open challenge? A systematic review of literature. *Medical Oncology*, *34*(9), 164. https://doi.org/10.1007/s12032-017-1026-y

Cella, D., Grunwald, V., Escudier, B., Hammers, H. J., George, S., Nathan, P., … Motzer, R. J. (2019). Patient-reported outcomes of patients with advanced renal cell carcinoma treated with nivolumab plus ipilimumab versus sunitinib (CheckMate 214): a randomised, phase 3 trial. *The Lancet. Oncology*, *20*(2), 297–310. https://doi.org/10.1016/S1470-2045(18)30778-2

Chappell, N. P., Miller, C. R., Fielden, A. D., & Barnett, J. C. (2016). Is FDA-Approved Bevacizumab Cost-Effective When Included in the Treatment of Platinum-Resistant Recurrent Ovarian Cancer? *Journal of Oncology Practice*, *12*(7), e775–e783. https://doi.org/10.1200/jop.2015.010470

Charo, L. M., & Plaxe, S. C. (2019). Recent advances in endometrial cancer: a review of key clinical trials from 2015 to 2019. *F1000Research*, *8*, 1–13. https://doi.org/10.12688/f1000research.17408.1

Chien, C. R., Geynisman, D. M., Kim, B., Xu, Y., & Shih, Y. C. T. (2019). Economic Burden of Renal Cell Carcinoma—Part I: An Updated Review. *PharmacoEconomics 37*(3), 301-331. https://doi.org/10.1007/s40273-018-0746-y

Chiou, H. Y., Chiu, L. H., Chen, C. H., Yen, Y. K., Chang, C. W., & Liu, W. M. (2015). Comparing robotic surgery with laparoscopy and laparotomy for endometrial cancer management: A cohort study. *International Journal of Surgery*, *13*, 17–22. https://doi.org/10.1016/j.ijsu.2014.11.015

Chow, W.-H., Dong, L. M., & Devesa, S. S. (2010). Epidemiology and risk factors for kidney cancer. *Nature Reviews. Urology*, *7*(5), 245–257. https://doi.org/10.1038/nrurol.2010.46

Cohn, D. E., Kim, K. H., Resnick, K. E., O'Malley, D. M., & Straughn, J. M. (2011). At what cost does a potential survival advantage of bevacizumab make sense for the primary treatment of ovarian cancer? A cost-effectiveness analysis. *Journal of Clinical Oncology*, *29*(10), 1247–1251. https://doi.org/10.1200/JCO.2010.32.1075

Cole, A. L., Barber, E. L., Gogate, A., Tran, A. Q., & Wheeler, S. B. (2018). Economic Analysis of Neoadjuvant Chemotherapy Versus Primary Debulking Surgery for Advanced Epithelial Ovarian Cancer Using an Aggressive Surgical Paradigm. *International Journal of Gynecological Cancer*, *28*(6), 1077–1084. https://doi.org/10.1097/IGC.0000000000001271

Coleman, R. L., Brady, M. F., Herzog, T. J., Sabbatini, P., Armstrong, D. K., Walker, J. L., … Mannel, R. S. (2017). Bevacizumab and paclitaxel–carboplatin chemotherapy and secondary cytoreduction in recurrent, platinum-sensitive ovarian cancer (NRG Oncology/Gynecologic Oncology Group study GOG-0213): a multicentre, open-label, randomised, phase 3 trial. *The Lancet Oncology*, *18*(6), 779–791. https://doi.org/10.1016/S1470-2045(17)30279-6

Colombo, N., Creutzberg, C., Amant, F., Bosse, T., González-Martín, A., Ledermann, J., … Sessa, C. (2016). ESMO-ESGO-ESTRO Consensus Conference on Endometrial Cancer. *International Journal of Gynecological Cancer*, *26*(1), 2–30. https://doi.org/10.1097/igc.0000000000000609

Corrado, G., Cutillo, G., Pomati, G., Mancini, E., Sperduti, I., Patrizi, L., … Vizza, E. (2015). Surgical and oncological outcome of robotic surgery compared to laparoscopic and abdominal surgery in the management of endometrial cancer. *European Journal of Surgical Oncology*, *41*(8), 1074–1081. https://doi.org/10.1016/j.ejso.2015.04.020

de Boer, S. M., Powell, M. E., Mileshkin, L., Katsaros, D., Bessette, P., Haie-Meder, C., … Tubiana-Mathieu, N. (2018). Adjuvant chemoradiotherapy versus radiotherapy alone for women with high-risk endometrial cancer (PORTEC-3): final results of an international, open-label, multicentre, randomised, phase 3 trial. *The Lancet Oncology*, *19*(3), 295–309. https://doi.org/10.1016/S1470-2045(18)30079-2

Deng, H., Liu, W., He, T., Hong, Z., Yi, F., Wei, Y., & Zhang, W. (2019). Comparative Efficacy, Safety, and Costs of Sorafenib vs. Sunitinib as First-Line Therapy for Metastatic Renal Cell Carcinoma: A Systematic Review and Meta-Analysis. *Frontiers in Oncology*, *9*, 479. https://doi.org/10.3389/fonc.2019.00479

Di Tucci, C., Capone, C., Galati, G., Iacobelli, V., Schiavi, M. C., Di Donato, V., … Panici, P. B. (2019). Immunotherapy in endometrial cancer: New scenarios on the horizon. *Journal of Gynecologic Oncology*, *30*(3), 1-20. https://doi.org/10.3802/jgo.2019.30.e46

Diaz-Arrastia, C., Jurnalov, C., Gomez, G., & Townsend, C. (2002). Laparoscopic hysterectomy using a computer-enhanced surgical robot. *Surgical Endoscopy and Other Interventional Techniques*, *16*(9), 1271–1273. https://doi.org/10.1007/s00464-002-8523-5

Dilley, S. E., Havrilesky, L. J., Bakkum-Gamez, J., Cohn, D. E., Michael Straughn, J., Caughey, A. B., & Rodriguez, M. I. (2017). Cost-effectiveness of opportunistic salpingectomy for ovarian cancer prevention. *Gynecologic Oncology*, *146*(2), 373–379. https://doi.org/10.1016/j.ygyno.2017.05.034

Dinkelspiel, H. E., Champer, M., Hou, J., Tergas, A., Burke, W. M., Huang, Y., … Wright, J. D. (2015). Long-term mortality among women with epithelial ovarian cancer. *Gynecologic Oncology*, *138*(2), 421–428. https://doi.org/10.1016/j.ygyno.2015.06.005

Dolgin, E. (2018). Cancer ' s cost conundrum. *Nature*, *555*, S26–S29.

Eccleston, A., Bentley, A., Dyer, M., Strydom, A., Vereecken, W., George, A., & Rahman, N. (2017). A Cost-Effectiveness Evaluation of Germline BRCA1 and BRCA2 Testing in UK Women with Ovarian Cancer. *Value in Health*, *20*(4), 567–576. https://doi.org/10.1016/j.jval.2017.01.004

Escudier, B., Porta, C., Schmidinger, M., Rioux-Leclercq, N., Bex, A., Khoo, V., … Horwich, A. (2019). Renal cell carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†. *Annals of Oncology : Official Journal of the European Society for Medical Oncology*, *30*(5), 706–720. https://doi.org/10.1093/annonc/mdz056

Falconer, H., Yin, L., Grönberg, H., & Altman, D. (2015). Ovarian cancer risk after salpingectomy: A nationwide population-based study. *Journal of the National Cancer Institute*, *107*(2), 1–6. https://doi.org/10.1093/jnci/dju410

Ferrara, N. (2002). VEGF and the quest for tumour angiogenesis factors. *Nature Reviews Cancer*, *2*(10), 795–803. https://doi.org/10.1038/nrc909

Finnish cancer registry. https://syoparekisteri.fi/ (Last accessed 26.8.2019)

Flanigan, R. C., Campbell, S. C., Clark, J. I., & Picken, M. M. (2003). Metastatic renal cell carcinoma. *Current Treatment Options in Oncology*, *4*(5), 385–390. https://doi.org/10.1007/s11864-003-0039-2

Fleming, G. F., Brunetto, V. L., Cella, D., Look, K. Y., Reid, G. C., Munkarah, A. R., … Mackey, D. (2004). Phase III trial of doxorubicin plus cisplatin with or without paclitaxel plus filgrastim in advanced endometrial carcinoma: A gynecologic oncology group study. *Journal of Clinical Oncology*, *22*(11), 2159–2166. https://doi.org/10.1200/JCO.2004.07.184

Forde, G. K., Chang, J., & Ziogas, A. (2016). Cost-effectiveness of primary debulking surgery when compared to neoadjuvant chemotherapy in the management of stage IIIC and IV epithelial ovarian cancer. *ClinicoEconomics and Outcomes Research*, *8*, 397–406. https://doi.org/10.2147/CEOR.S91844

Funakoshi, T., Lee, C. H., & Hsieh, J. J. (2014). A systematic review of predictive and prognostic biomarkers for VEGF-targeted therapy in renal cell carcinoma. *Cancer Treatment Reviews*, *40*(4), 533–547. https://doi.org/10.1016/j.ctrv.2013.11.008

Gabionline: http://www.gabionline.net/Biosimilars/General/Biosimilars-of-bevacizumab, update 2019 (Last accessed 18.12.2019)

Galaal, K., Donkers, H., Bryant, A., & Lopes, A. D. (20181). Laparoscopy versus laparotomy for the management of early stage endometrial cancer. *Cochrane Database of Systematic Reviews*, 2018 (10). https://doi.org/10.1002/14651858.CD006655.pub3

Giornelli, G. H. (2016). Management of relapsed ovarian cancer: a review. *SpringerPlus*, *5*(1). https://doi.org/10.1186/s40064-016-2660-0

González-Martín, A., Pothuri, B., Vergote, I., DePont Christensen, R., Graybill, W., Mirza, M. R., … Monk, B. J. (2019). Niraparib in Patients with Newly Diagnosed Advanced Ovarian Cancer. *New England Journal of Medicine*, *381*(25), 2391-2402. https://doi.org/10.1056/nejmoa1910962

Gupta, D. (2017). Clinical behavior and treatment of endometrial cancer. A*dvances in Experimental Medicine and Biology 943*, 47–74. https://doi.org/10.1007/978-3-319-43139-0_2

Guy, H., Walder, L., & Fisher, M. (2019). Cost-Effectiveness of Niraparib Versus Routine Surveillance, Olaparib and Rucaparib for the Maintenance Treatment of Patients with Ovarian Cancer in the United States. *PharmacoEconomics*, *37*(3), 391–405. https://doi.org/10.1007/s40273-018-0745-z

Hacker, N. F., & Rao, A. (2017). Surgery for advanced epithelial ovarian cancer. *Best Practice and Research: Clinical Obstetrics and Gynaecology*, *41*, 71–87. https://doi.org/10.1016/j.bpobgyn.2016.10.007

Hennessy, B. T., Coleman, R. L., & Markman, M. (2009). Ovarian cancer Epidemiology and risk factors. *The Lancet*, *374*(9698), 1371–1382. https://doi.org/10.1016/S0140

Herling, S. F., Palle, C., Møller, A. M., Thomsen, T., & Sørensen, J. (2016). Cost-analysis of robotic-assisted laparoscopic hysterectomy versus total abdominal hysterectomy for women with endometrial cancer and atypical complex hyperplasia. *Acta Obstetricia et Gynecologica Scandinavica*, *95*(3), 299–308. https://doi.org/10.1111/aogs.12820

Hillner, B. E., & Smith, T. J. (2009). Efficacy does not necessarily translate to cost effectiveness: A case study in the challenges associated with 21st-century cancer drug pricing. *Journal of Clinical Oncology*, *27*(13), 2111–2113. https://doi.org/10.1200/JCO.2008.21.0534

Hinde, S., Epstein, D., Cook, A., Embleton, A., Perren, T., & Sculpher, M. (2016). The Cost-Effectiveness of Bevacizumab in Advanced Ovarian Cancer Using Evidence from the ICON7 Trial. *Value in Health*, *19*(4), 431–439. https://doi.org/10.1016/j.jval.2016.01.013

Hua, H., Kong, Q., Zhang, H., Wang, J., Luo, T., & Jiang, Y. (2019). Targeting mTOR for cancer therapy. *Journal of Hematology and Oncology*, *12*(1), 1–19. https://doi.org/10.1186/s13045-019-0754-1

Huhtinen, K., Suvitie, P., Hiissa, J., Junnila, J., Huvila, J., Kujari, H., … Perheentupa, A. (2009). Serum HE4 concentration differentiates malignant ovarian tumours from ovarian endometriotic cysts. *British Journal of Cancer*, *100*(8), 1315–1319. https://doi.org/10.1038/sj.bjc.6605011

Huijgens, A. N. J., & Mertens, H. J. M. M. (2013). Factors predicting recurrent endometrial cancer. *Facts, Views & Vision in ObGyn*, *5*(3), 179–186.

Johansson, M. E., & Axelson, H. (2013). Kidney cancer. *Seminars in Cancer Biology*, *23*(1), 1–2. https://doi.org/10.1016/j.semcancer.2012.05.006

Jönsson, B., Hofmarcher, T., Lindgren, P., & Wilking, N. (2016). The cost and burden of cancer in the European Union 1995–2014. *European Journal of Cancer*, *66*, 162–170. https://doi.org/10.1016/j.ejca.2016.06.022

Jönsson, B., & Wilking, N. (2007). The burden and cost of cancer. *Annals of Oncology*, *18*(SUPPL. 3), iii8–iii22. https://doi.org/10.1093/annonc/mdm097

Kang, R., Goodney, P. P., & Wong, S. L. (2016). Importance of cost-effectiveness and value in cancer care and healthcare policy. *Journal of Surgical Oncology*, *114*(3), 275–280. https://doi.org/10.1002/jso.24331

Kapiainen S, Väisänen A, H. T. (2011). *Terveyden- ja sosiaalihuollon yksikkökustannukset Suomessa vuonna 2011*. https://doi.org/http://urn.fi/URN:ISBN:978-952-302-079-5

Kuoppala, T., Tomás, E., & Heinonen, P. K. (2004). Clinical outcome and complications of laparoscopic surgery compared with traditional surgery in women with endometrial cancer. *Archives of Gynecology and Obstetrics*, *270*(1), 25–30. https://doi.org/10.1007/s00404-003-0488-7

Kwon, J. S. (2017). Cost-effectiveness of Ovarian Cancer Prevention Strategies Cost-effectiveness of Ovarian Cancer Prevention Strategies Ovarian Cancer Prevention in the General Population Ovarian cancer screening using a multimo-dality screening (MMS) algorithm comprised. *Clinical Obstetrics and gynecology, 60*(4), 780-788.

Lee, Y. C., Lheureux, S., & Oza, A. M. (2017). Treatment strategies for endometrial cancer: current practice and perspective. *Current Opinion in Obstetrics and Gynecology*, *29*(1). Retrieved from https://journals.lww.com/co-obgyn/Fulltext/2017/02000/Treatment_strategies_for_endometrial_cancer__.9.aspx

Leitao, M. M., Bartashnik, A., Wagner, I., Lee, S. J., Caroline, A., Hoskins, W. J., … Gardner, G. J. (2014). Cost-effectiveness analysis of robotically assisted laparoscopy for newly diagnosed uterine cancers. *Obstetrics and Gynecology*, *123*(5), 1031–1037. https://doi.org/10.1097/AOG.0000000000000223

Leslie, K. K., Thiel, K. W., Goodheart, M. J., De Geest, K., Jia, Y., & Yang, S. (2012). Endometrial Cancer. *Obstetrics and Gynecology Clinics of North America*, *39*(2), 255–268. https://doi.org/10.1016/J.OGC.2012.04.001

Luengo-Fernandez, R., Leal, J., Gray, A., & Sullivan, R. (2013). Economic burden of cancer across the European Union: A population-based cost analysis. *The Lancet Oncology*, *14*(12), 1165–1174. https://doi.org/10.1016/S1470-2045(13)70442-X

Lyon, T. D., Thompson, R. H., Shah, P. H., Lohse, C. M., Boorjian, S. A., Costello, B. A., … Leibovich, B. C. (2019). Complete Surgical Metastasectomy of Renal Cell Carcinoma in the Post-Cytokine Era. *The Journal of Urology*, 101097JU0000000000000488. https://doi.org/10.1097/JU.0000000000000488

MacLean, E., Mardekian, J., Cisar, L. A., Hoang, C. J., & Harnett, J. (2016). Real-World Treatment Patterns and Costs for Patients with Renal Cell Carcinoma Initiating Treatment with Sunitinib and Pazopanib. *Journal of Managed Care & Specialty Pharmacy*, *22*(8), 979–990. https://doi.org/10.18553/jmcp.2016.22.8.979

Makker, V., Taylor, M. H., Aghajanian, ; Carol, Oaknin, A., Mier, J., Cohn, A. L., … Casado Herraez, A. (2020). Lenvatinib Plus Pembrolizumab in Patients With Advanced Endometrial Cancer. *J Clin Oncol*, *38*. https://doi.org/10.1200/JCO.1902627

Marino, P., Houvenaeghel, G., Narducci, F., Boyer-Chammard, A., Ferron, G., Uzan, C., … Lambaudie, E. (2015). Cost-Effectiveness of Conventional vs Robotic-Assisted Laparoscopy in Gynecologic Oncologic Indications. *International. journal of gynecological cancer*, *25*(6), 1102-8. doi: 10.1097/IGC.0000000000000458

May, J., & Mehasseb, M. K. (2013). Endometrial cancer. *Obstetrics, Gynaecology and Reproductive Medicine*, *23*(9), 263–269. https://doi.org/10.1016/j.ogrm.2013.06.006

Maynard, M. A., & Ohh, M. (2004). Von Hippel-Lindau Tumor Suppressor Protein and Hypoxia-Inducible Factor in Kidney Cancer. *American Journal of Nephrology*, *24*(1), 1–13. https://doi.org/10.1159/000075346

Mazzucato, M. (2016). High cost of new drugs. *BMJ (Online)*, 354:i4136. https://doi.org/10.1136/bmj.i4136

Méjean, A., Ravaud, A., Thezenas, S., Colas, S., Beauval, J. B., Bensalah, K., … Escudier, B. (2018). Sunitinib alone or after nephrectomy in metastatic renal-cell carcinoma. *New England Journal of Medicine*, *379*(5), 417–427. https://doi.org/10.1056/NEJMoa1803675

Mirza, M. R., Monk, B. J., Herrstedt, J., Oza, A. M., Mahner, S., Redondo, A., … Matulonis, U. A. (2016). Niraparib maintenance therapy in platinum-sensitive, recurrent ovarian cancer. *New England Journal of Medicine*, *375*(22), 2154–2164. https://doi.org/10.1056/NEJMoa1611310

Mittica, G., Ghisoni, E., Giannone, G., Aglietta, M., Genta, S., & Valabrega, G. (2017). Checkpoint inhibitors in endometrial cancer: Preclinical rationale and clinical activity. *Oncotarget*, *8*(52), 90532–90544. https://doi.org/10.18632/oncotarget.20042

Moch, H. (2013). An overview of renal cell cancer: Pathology and genetics. *Seminars in Cancer Biology*, *23*(1), 3–9. https://doi.org/10.1016/j.semcancer.2012.06.006

Molina, A. M., & Motzer, R. J. (2011). Clinical Practice Guidelines for the Treatment of Metastatic Renal Cell Carcinoma: Today and Tomorrow. *The Oncologist*, *16*(Suppl 2), 45–50. https://doi.org/10.1634/theoncologist.2011-s2-45

Moore, K., Colombo, N., Scambia, G., Kim, B. G., Oaknin, A., Friedlander, M., … Disilvestro, P. (2018). Maintenance Olaparib in Patients With Newly Diagnosed Advanced Ovarian Cancer. *New England Journal of Medicine*, *379*(26), 2495-2505. https://doi.org/10.1097/01.ogx.0000552695.03241.d6

Moran, M., Nickens, D., Adcock, K., Bennetts, M., Desscan, A., Charnley, N., & Fife, K. (2019). Sunitinib for Metastatic Renal Cell Carcinoma: A Systematic Review and Meta-Analysis of Real-World and Clinical Trials Data. *Targeted Oncology, 14*(4), 405-416. https://doi.org/10.1007/s11523-019-00653-5

Morice, P., Leary, A., Creutzberg, C., Abu-Rustum, N., & Darai, E. (2016). Endometrial cancer. *The Lancet*, *387*(10023), 1094–1108. https://doi.org/https://doi.org/10.1016/S0140-6736(15)00130-0

Motzer, R. J., Bander, N. H., & Nanus, D. M. (1996). Renal-Cell Carcinoma. *New England Journal of Medicine*, *335*(12), 865–875. https://doi.org/10.1056/NEJM199609193351207

Motzer, R. J., Escudier, B., McDermott, D. F., George, S., Hammers, H. J., Srinivas, S., … CheckMate 025 Investigators. (2015). Nivolumab versus Everolimus in Advanced Renal-Cell Carcinoma. *The New England Journal of Medicine*, *373*(19), 1803–1813. https://doi.org/10.1056/NEJMoa1510665

Motzer, R. J., Hutson, T. E., Cella, D., Reeves, J., Hawkins, R., Guo, J., … Choueiri, T. K. (2013). Pazopanib versus Sunitinib in Metastatic Renal-Cell Carcinoma. *New England Journal of Medicine*, *369*(8), 722–731. https://doi.org/10.1056/NEJMoa1303989

Motzer, R. J., Hutson, T. E., Tomczak, P., Michaelson, M. D., Bukowski, R. M., Rixe, O., … Figlin, R. A. (2007). Sunitinib versus Interferon Alfa in Metastatic Renal-Cell Carcinoma. *New England Journal of Medicine*, *356*(2), 115–124. https://doi.org/10.1056/nejmoa065044

Motzer, R. J., & Molina, A. M. (2009). Targeting Renal Cell Carcinoma. *Journal of Clinical Oncology*, *27*(20), 3274–3276. https://doi.org/10.1200/JCO.2009.21.8461

Mäenpää, M. M., Nieminen, K., Tomás, E. I., Laurila, M., Luukkaala, T. H., & Mäenpää, J. U. (2016). Robotic-assisted vs traditional laparoscopic surgery for endometrial cancer: a randomized controlled trial. *American Journal of Obstetrics and Gynecology*, *215*(5), 588.e1-588.e7. https://doi.org/10.1016/j.ajog.2016.06.005

Mäenpää, M., Nieminen, K., Tomás, E., Luukkaala, T., & Mäenpää, J. U. (2015). Implementing robotic surgery to gynecologic oncology: The first 300 operations performed at a tertiary hospital. *Acta Obstetricia et Gynecologica Scandinavica*, *94*(5), 482–488. https://doi.org/10.1111/aogs.12620

Naumann, R. W., Coleman, R. L., Brown, J., & Moore, K. N. (2019, May 1). Phase III trials in ovarian cancer: The evolving landscape of front line therapy. *Gynecologic Oncology*, *153*(2), 436–444. https://doi.org/10.1016/j.ygyno.2019.02.008

NCCN Clinical Practice guidelines in Oncology: Kidney Cancer. (2019). https://doi.org/https://www.nccn.org/patients/guidelines/kidney/index.html

Neyt, M., Vlayen, J., Devriese, S., & Camberlin, C. (2018). First- and second-line bevacizumab in ovarian cancer: A Belgian cost-utility analysis. *PLoS ONE*, *13*(4): e0195134. https://doi.org/10.1371/journal.pone.0195134

NICE guidelines: Bevacizumab in combination with paclitaxel and carboplatin for first-line treatment of advanced ovarian cancer. https://www.nice.org.uk/guidance/ta284/chapter/4-Consideration-of-the-evidence#cost-effectiveness (Last accessed 19.11.2019)

Nickerson, M. L., Jaeger, E., Shi, Y., Durocher, J. A., Mahurkar, S., Zaridze, D., … Moore, L. E. (2008). Improved identification of von Hippel-Lindau gene alterations in clear cell renal tumors. *Clinical Cancer Research*, *14*(15), 4726–4734. https://doi.org/10.1158/1078-0432.CCR-07-4921

Niemi, R. J., Saarelainen, S. K., Luukkaala, T. H., & Mäenpää, J. U. (2017). Reliability of preoperative evaluation of postmenopausal ovarian tumors. *Journal of Ovarian Research*, *10*(1), 1–7. https://doi.org/10.1186/s13048-017-0309-4

Ovarian cancer overview NICE Pathways bring together everything NICE says on a topic in an interactive Ovarian cancer. (2019). Retrieved from http://pathways.nice.org.uk/pathways/ovarian-cancer

Oza, A. M., Cook, A. D., Pfisterer, J., Embleton, A., Ledermann, J. A., Pujade-Lauraine, E., … Perren, T. J. (2015). Standard chemotherapy with or without bevacizumab for women with newly diagnosed ovarian cancer (ICON7): Overall survival results of a phase 3 randomised trial. *The Lancet Oncology*, *16*(8), 928–936. https://doi.org/10.1016/S1470-2045(15)00086-8

PALKO, recommendations: https://palveluvalikoima.fi/documents/1237350/16817905/Suositus_Nivolumabi%2Bipilimumabi_Final_fi.pdf/c5653b39-70d7-4f51-0f57-c7f8599ad264/Suositus_Nivolumabi%2Bipilimumabi_Final_fi.pdf (Last accessed 26.11.2019)

Permuth-Way J. Sellers T.A. (2009). Epidemiology of Ovarian Cancer. *Cancer epidemiology, vol 2 by Mukesh Verma*, 413-437

Perren, T. J., Swart, A. M., Pfisterer, J., Ledermann, J. A., Pujade-Lauraine, E., Kristensen, G., … Oza, A. M. (2011). A Phase 3 Trial of Bevacizumab in Ovarian Cancer. *New England Journal of Medicine*, *365*(26), 2484–2496. https://doi.org/10.1056/NEJMoa1103799

Piulats, J. M., Guerra, E., Gil-Martín, M., Roman-Canal, B., Gatius, S., Sanz-Pamplona, R., … Matias-Guiu, X. (2017). Molecular approaches for classifying endometrial carcinoma. *Gynecologic Oncology*, *145*(1), 200–207. https://doi.org/10.1016/j.ygyno.2016.12.015

Poonawalla, I. B., Parikh, R. C., Du, X. L., VonVille, H. M., & Lairson, D. R. (2015, November 1). Cost Effectiveness of Chemotherapeutic Agents and Targeted Biologics in Ovarian Cancer: A Systematic Review. *PharmacoEconomics*, *33*(11), 1155–1185. https://doi.org/10.1007/s40273-015-0304-9

Pujade-Lauraine, E., Hilpert, F., Weber, B., Reuss, A., Poveda, A., Kristensen, G., … Ray-Coquard, I. (2014). Bevacizumab combined with chemotherapy for platinum-resistant recurrent ovarian cancer: The AURELIA open-label randomized phase III trial. *Journal of Clinical Oncology*, *32*(13), 1302–1308. https://doi.org/10.1200/JCO.2013.51.4489

Pyrhönen, S., Salminen, E., Ruutu, M., Lehtonen, T., Nurmi, M., Tammela, T., … Kellokumpu-Lehtinen, P. L. (1999). Prospective randomized trial of interferon alfa-2a plus vinblastine versus vinblastine alone in patients with advanced renal cell cancer. *Journal Of Clinical Oncology: Official Journal Of The American Society Of Clinical Oncology*, *17*(9), 2859–2867.

Rabinovich, A. (2015). Minimally invasive surgery for endometrial cancer: a comprehensive review. *Archives of Gynecology and Obstetrics*, *291*(4), 721–727. https://doi.org/10.1007/s00404-014-3517-9

Ramirez, P. T., Adams, S., Boggess, J. F., Burke, W. M., Frumovitz, M. M., Gardner, G. J., … Yap, S. (2012). Robotic-assisted surgery in gynecologic oncology: A Society of Gynecologic Oncology consensus statement: Developed by the Society of Gynecologic Oncology's Clinical Practice Robotics Task Force. *Gynecologic Oncology*, *124*(2), 180–184. https://doi.org/10.1016/j.ygyno.2011.11.006

Randall, M. E., Filiaci, V., McMeekin, D. S., Von Gruenigen, V., Huang, H., Yashar, C. M., … Miller, D. S. (2019). Phase III trial: Adjuvant pelvic radiation therapy versus vaginal brachytherapy plus paclitaxel/ carboplatin in high-intermediate and high-risk early stage endometrial cancer. *Journal of Clinical Oncology*, *37*(21), 1810–1818. https://doi.org/10.1200/JCO.18.01575

Ray-Coquard, I., Pautier, P., Pignata, S., Pérol, D., González-Martín, A., Berger, R., … Harter, P. (2019). Olaparib plus Bevacizumab as First-Line Maintenance in Ovarian Cancer. *New England Journal of Medicine*, *381*(25), 2416–2428. https://doi.org/10.1056/NEJMoa1911361

Redig, J., Dalén, J., Harmenberg, U., Lindskog, M., Ljungberg, B., Lundstam, S., … Jakobsson, M. (2019). Real-world cost-effectiveness of targeted therapy in metastatic renal cell carcinoma in Sweden: A population-based retrospective analysis. *Cancer Management and Research*, *11,* 1289-1297. https://doi.org/10.2147/CMAR.S188849

Reinhorn, D., Sarfaty, M., Leshno, M., Moore, A., Neiman, V., Rosenbaum, E., & Goldstein, D. A. (2019). A Cost-Effectiveness Analysis of Nivolumab and Ipilimumab Versus Sunitinib in First-Line Intermediate- to Poor-Risk Advanced Renal Cell Carcinoma. *The Oncologist*, *24*(3), 366–371. https://doi.org/10.1634/theoncologist.2018-0656

Renkonen-Sinisalo, L., Bützow, R., Leminen, A., Lehtovirta, P., Mecklin, J. P., & Järvinen, H. J. (2007). Surveillance for endometrial cancer in hereditary nonpolyposis colorectal cancer syndrome. *International Journal of Cancer*, *120*(4), 821–824. https://doi.org/10.1002/ijc.22446

Reynisson, P., & Persson, J. (2013). Hospital costs for robot-assisted laparoscopic radical hysterectomy and pelvic lymphadenectomy. *Gynecologic Oncology*, *130*(1), 95–99. https://doi.org/10.1016/j.ygyno.2013.04.014

Rini, B. I., Campbell, S. C., & Escudier, B. (2009). Renal cell carcinoma. *The Lancet*, *373*(9669), 1119–1132. https://doi.org/10.1016/S0140

Rose, P. G., Ali, S., Moslemi-Kebria, M., & Simpkins, F. (2017). Paclitaxel, Carboplatin, and Bevacizumab in Advanced and Recurrent Endometrial Carcinoma. *International Journal of Gynecological Cancer : Official Journal of the International Gynecological Cancer Society*, *27*(3), 452–458. https://doi.org/10.1097/IGC.0000000000000891

Ruiz-Morales, J. M., Swierkowski, M., Wells, J. C., Fraccon, A. P., Pasini, F., Donskov, F., … Heng, D. Y. C. (2016). First-line sunitinib versus pazopanib in metastatic renal cell carcinoma: Results from the International Metastatic Renal Cell Carcinoma Database Consortium. *European Journal of Cancer*, *65*, 102–108. https://doi.org/10.1016/j.ejca.2016.06.016

Rustin, G. J. S., Van Der Burg, M. E. L., Griffin, C. L., Guthrie, D., Lamont, A., Jayson, G. C., … Swart, A. M. (2010). Early versus delayed treatment of relapsed ovarian cancer (MRC OV05/EORTC 55955): A randomised trial. *The Lancet*, *376*(9747), 1155–1163. https://doi.org/10.1016/S0140-6736(10)61268-8

Saarelainen, S. K., Vuento, M. H., Kirkinen, P., & Mäenpää, J. U. (2012). Preoperative assessment of endometrial carcinoma by three-dimensional power Doppler angiography. *Ultrasound in Obstetrics and Gynecology*, *39*(4), 466–472. https://doi.org/10.1002/uog.10103

Sarantaus, L., Auranen, A., & Nevanlinna, H. (2001). BRCA1 and BRCA2 mutations among Finnish ovarian carcinoma families. *International Journal of Oncology*, *18*(4), 831–835. https://doi.org/10.3892/ijo.18.4.831

Sarfaty, M., Leshno, M., Gordon, N., Moore, A., Neiman, V., Rosenbaum, E., & Goldstein, D. A. (2018). Cost Effectiveness of Nivolumab in Advanced Renal Cell Carcinoma. *European Urology*, *73*(4), 628–634. https://doi.org/10.1016/j.eururo.2017.07.041

Schreuder, H. W. R., & Verheijen, R. H. M. (2009). Robotic surgery. *BJOG : An International Journal of Obstetrics and Gynaecology*, *116*(2), 198–213. https://doi.org/10.1111/j.1471-0528.2008.02038.x

Schroeck, F. R., Jacobs, B. L., Bhayani, S. B., Nguyen, P. L., Penson, D., & Hu, J. (2017). Cost of New Technologies in Prostate Cancer Treatment: Systematic Review of Costs and Cost Effectiveness of Robotic-assisted Laparoscopic Prostatectomy, Intensity-modulated Radiotherapy, and Proton Beam Therapy. *European Urology*, *72*(5), 712–735. https://doi.org/10.1016/j.eururo.2017.03.028

Serna-Gallegos, T. R., La-Fargue, C. J., & Tewari, K. S. (2018). The Ecstacy of Gold: Patent Expirations for Trastuzumab, Bevacizumab, Rituximab, and Cetuximab. *Recent Patents on Biotechnology*, *12*(2), 101–112. https://doi.org/10.2174/1872208311666171122152131

Shih, Y.-C. T., Xu, Y., Chien, C.-R., Kim, B., Shen, Y., Li, L., & Geynisman, D. M. (2019). Rising Economic Burden of Renal Cell Carcinoma among Elderly Patients in the USA: Part II—An Updated Analysis of SEER-Medicare Data. *PharmacoEconomics, 37*(12), 1495-1507. https://doi.org/10.1007/s40273-019-00824-2

Shingarev, R., & Jaimes, E. A. (2017). Renal cell carcinoma: new insights and challenges for a clinician scientist. *American Journal of Physiology-Renal Physiology*, *313*(2), F145–F154. https://doi.org/10.1152/ajprenal.00480.2016

Smith, T. J., & Hillner, B. E. (2011). Bending the Cost Curve in Cancer Care. *New England Journal of Medicine*, *364*(21), 2060–2065. https://doi.org/10.1056/nejmsb1013826

Sorosky, J. I. (2012). Endometrial Cancer. *Obstetrics & Gynecology*, *120*(2 Part 1), 383-397. https://journals.lww.com/greenjournal/Fulltext/2012/08000/Endometrial_Cancer.30.aspx

Suidan, R. S., He, W., Sun, C. C., Zhao, H., Rauh-Hain, J. A., Fleming, N. D., … Meyer, L. A. (2019). Total and out-of-pocket costs of different primary management strategies in ovarian cancer. *American Journal of Obstetrics and Gynecology, 221*(2), 136.e1-136.e9. https://doi.org/10.1016/j.ajog.2019.04.005

Sunela, K. L., Lehtinen, E. T., Kataja, M. J., Kujala, P. M., Soimakallio, S., & Kellokumpu-Lehtinen, P. L. I. (2014). Development of renal cell carcinoma (RCC) diagnostics and impact on prognosis. *BJU International*, *113*(2), 228–235. https://doi.org/10.1111/bju.12242

Taylor, K. N., & Eskander, R. N. (2017). PARP inhibitors in epithelial ovarian cancer. *Recent Patents on Anti-Cancer Drug Discovery*, *13*(2), 145-158. https://doi.org/10.2174/1574892813666171204094822

Tew, W. P. (2016). Ovarian cancer in the older woman. *Journal of Geriatric Oncology*,. *7*(5), 354–361. https://doi.org/10.1016/j.jgo.2016.07.008

Tewari, K. S., Burger, R. A., Enserro, D., Norquist, B. M., Swisher, E. M., Brady, M. F., … Monk, B. J. (2019). Final Overall Survival of a Randomized Trial of Bevacizumab for Primary Treatment of Ovarian Cancer. *Journal of Clinical Oncology, 37(6), 2317-2328*, JCO.19.01009. https://doi.org/10.1200/JCO.19.01009

Thigpen, T. J., Brady, M. F., Homesley, H. D., Malfetano, J., Dubeshter, B., Burger, R. A., … Mackey, D. (2004). Phase III trial of doxorubicin with or without cisplatin in advanced endometrial carcinoma: A gynecologic oncology group study. *Journal of Clinical Oncology*, *22*(19), 3902–3908. https://doi.org/10.1200/JCO.2004.02.088

Torkki, P., Leskelä, R. L., Linna, M., Mäklin, S., Mecklin, J. P., Bono, P., … Karjalainen, S. (2018). Cancer costs and outcomes in the Finnish population 2004–2014. *Acta Oncologica*, *57*(2), 297–303. https://doi.org/10.1080/0284186X.2017.1343495

Torre, L. A., Bray, F., Siegel, R. L., Ferlay, J., Lortet-Tieulent, J., & Jemal, A. (2015). Global cancer statistics, 2012. *CA: A Cancer Journal for Clinicians*, *65*(2), 87–108. https://doi.org/10.3322/caac.21262

Torre, L. A., Islami, F., Siegel, R. L., Ward, E. M., & Jemal, A. (2017). Global Cancer in Women: Burden and Trends. *Cancer Epidemiology Biomarkers &Amp; Prevention*, *26*(4), 444. https://doi.org/10.1158/1055-9965.EPI-16-0858

Torre, L. A., Siegel, R. L., Ward, E. M., & Jemal, A. (2016). Global Cancer Incidence and Mortality Rates and Trends—An Update. *Cancer Epidemiology Biomarkers &Amp; Prevention*, *25*(1), 16. https://doi.org/10.1158/1055-9965.EPI-15-0578

Trimbos, J. B. (2017). Surgical treatment of early-stage ovarian cancer. *Best Practice and Research: Clinical Obstetrics and Gynaecology*, *41*, 60–70. https://doi.org/10.1016/j.bpobgyn.2016.10.001

van de Vrie, R., van Meurs, H. S., Rutten, M. J., Naaktgeboren, C. A., Opmeer, B. C., Gaarenstroom, K. N., … Buist, M. R. (2017). Cost-effectiveness of laparoscopy as diagnostic tool before primary cytoreductive surgery in ovarian cancer. *Gynecologic Oncology*, *146*(3), 449–456. https://doi.org/10.1016/j.ygyno.2017.06.019

Vargas, C., Balmaceda, C., Rodríguez, F., Rojas, R., Giglio, A., & Espinoza, M. A. (2019). Economic evaluation of sunitinib versus pazopanib and best supportive care for the treatment of metastatic renal cell carcinoma in Chile: cost-effectiveness analysis and a mixed treatment comparison. *Expert Review of Pharmacoeconomics & Outcomes Research*, *19*(5), 609-617. https://doi.org/10.1080/14737167.2019.1580572

Venkat, P., Chen, L. M., Young-Lin, N., Kiet, T. K., Young, G., Amatori, D., … Chan, J. K. (2012). An economic analysis of robotic versus laparoscopic surgery for endometrial cancer: Costs, charges and reimbursements to hospitals and professionals. *Gynecologic Oncology*, *125*(1), 237–240. https://doi.org/10.1016/j.ygyno.2011.11.036

Ventriglia, J., Paciolla, I., Pisano, C., Cecere, S. C., Di Napoli, M., Tambaro, R., … Della Pepa, C. (2017). Immunotherapy in ovarian, endometrial and cervical cancer: State of the art and future perspectives. *Cancer Treatment Reviews*, *59*, 109–116. https://doi.org/10.1016/j.ctrv.2017.07.008

Voda, A. I., & Bostan, I. (2018). Public health care financing and the costs of cancer care: A cross-national analysis. *Cancers*, *10*(4). https://doi.org/10.3390/cancers10040117

Vuorinen, R.-L., Purmonen, T., Kellokumpu-Lehtinen, P.-L., Lapela, M., & Pyrhönen, S. (2010). Mitä levinneen munuaissyövän hoito maksaa? *Suomen Lääkärilehti*, *10*, 919–925.

Wan, X., Zhang, Y., Tan, C., Zeng, X., & Peng, L. (2019). First-line Nivolumab Plus Ipilimumab vs Sunitinib for Metastatic Renal Cell Carcinoma: A Cost-effectiveness Analysis. *JAMA Oncology*, *5*(4), 491–496. https://doi.org/10.1001/jamaoncol.2018.7086

Webb, P. M., & Jordan, S. J. (2017). Epidemiology of epithelial ovarian cancer. *Best Practice and Research: Clinical Obstetrics and Gynaecology*, *41*, 3–14. https://doi.org/10.1016/j.bpobgyn.2016.08.006

WHO statistics, International Agency for Research on Cancer, Cancer Today. Available at gco.iarc.fr/today/online-analysis-table?v=2018&mode=cancer&mode_population=continents&population=900&populations=900&key=asr&sex=0&cancer=39&type=0&statistic=5&prevalence=0&population_group=0&ages_group%5B%5D=0&ages_group%5B%5D=17&nb_items=5&group_cancer=1&include_nmsc=1&include_nmsc_other=1 (Last accessed 26.8.2016)

Wright, J. D., Ananth, C. V., Tergas, A. I., Herzog, T. J., Burke, W. M., Lewin, S. N., … Hershman, D. L. (2014). An economic analysis of robotically assisted hysterectomy. *Obstetrics and Gynecology*, *123*(5), 1038–1048. https://doi.org/10.1097/AOG.0000000000000244

Yang, J. C., Haworth, L., Sherry, R. M., Hwu, P., Schwartzentruber, D. J., Topalian, S. L., … Rosenberg, S. A. (2003). A randomized trial of bevacizumab, an anti-vascular endothelial growth factor antibody, for metastatic renal cancer. *The New England Journal of Medicine*, *349*(5), 427–434. https://doi.org/10.1056/NEJMoa021491

Zhong, L., Tran, A. T., Tomasino, T., Nugent, E., & Smith, J. A. (2018). Cost-effectiveness of niraparib and olaparib as maintenance therapy for patients with platinum-sensitive recurrent ovarian cancer. *Journal of Managed Care and Specialty Pharmacy*, *24*(12), 1219–1228. https://doi.org/10.18553/jmcp.2018.24.12.1219

10 ORIGINAL PUBLICATIONS

PUBLICATION I

Costs of robotic surgery vs traditional laparoscopy in endometrial cancer

Vuorinen R-L, Mäenpää M, Nieminen K, Tomas E, Luukkaala T, Mäenpää J.

International Journal of Gynecological Cancer 2017;27(8):1788-1793.

Costs of Robotic-Assisted Versus Traditional Laparoscopy in Endometrial Cancer

Riikka-Liisa K. Vuorinen, MD, Minna M. Mäenpää, MD,* Kari Nieminen, PhD,* Eija I. Tomás, PhD,* Tiina H. Luukkaala, MSc,†‡ Anssi Auvinen, PhD,§ and Johanna U. Mäenpää, PhD*‡*

Objectives: The purpose of this study was to compare the costs of traditional laparoscopy and robotic-assisted laparoscopy in the treatment of endometrial cancer.

Methods and Materials: A total of 101 patients with endometrial cancer were randomized to the study and operated on starting from 2010 until 2013, at the Department of Obstetrics and Gynecology of Tampere University Hospital, Tampere, Finland. Costs were calculated based on internal accounting, hospital database, and purchase prices and were compared using intention-to-treat analysis. Main outcome measures were item costs and total costs related to the operation, including a 6-month postoperative follow-up.

Results: The total costs including late complications were 2160 € higher in the robotic group (median for traditional 5823 €, vs robot median 7983 €, $P < 0.001$). The difference was due to higher costs for instruments and equipment as well as to more expensive operating room and postanesthesia care unit time. Traditional laparoscopy involved higher costs for operation personnel, general costs, medication used in the operation, and surgeon, although these costs were not substantial. There was no significant difference in in-patient stay, laboratory, radiology, blood products, or costs related to complications.

Conclusions: According to this study, robotic-assisted laparoscopy is 37% more expensive than traditional laparoscopy in the treatment of endometrial cancer. The cost difference is mainly explained by amortization of the robot and its instrumentation.

Key Words: Robotic-assisted surgery, Endometrial cancer, Cost analysis, Gynecologic oncology

Received March 27, 2017, and in revised form May 9, 2017.
Accepted for publication May 18, 2017.

(*Int J Gynecol Cancer* 2017;27: 1788–1793)

Endometrial cancer is the most common gynecologic malignancy in the developed countries with 167,900 estimated new cases and 34,700 estimated deaths in 2012.[1] Primary treatment of endometrial cancer is hysterectomy and bilateral salpingo-oophorectomy, commonly accompanied by pelvic or pelvic and para-aortic lymphadenectomy (PALND).[2] Surgical methods for treating endometrial cancer include laparotomy, traditional laparoscopy, and robotic-assisted laparoscopy. According to cost-effectiveness analysis by Leitao et al,[3] laparotomy was the most expensive approach compared with

*Department of Obstetrics and Gynecology, Tampere University Hospital; †Science Centre, Pirkanmaa Hospital District; ‡Faculty of Medicine and Life Sciences, University of Tampere; §Faculty of Social Sciences, University of Tampere, Tampere, Finland.

Address correspondence and reprint requests to Riikka-Liisa Vuorinen, MD, Department of Obstetrics and Gynecology, Tampere University Hospital, PO Box 2000, FI-33521, Tampere, Finland. E-mail: riikka.vuorinen@pshp.fi.

No funding was obtained for this study.

The authors declare no conflicts of interest.

Riikka-Liisa K. Vuorinen, MD, and Minna M. Mäenpää, MD, equally contributed to the study.

Clinical trial registration: ClinicalTrials.gov, www.clinicaltrials.gov, NCT01466777.

Supplemental digital content is available for this article. Direct URL citation appears in the printed text and is provided in the HTML and PDF versions of this article on the journal's Web site (www.ijgc.net).

ISSN: 1048-891X
DOI: 10.1097/IGC.0000000000001073

traditional laparoscopy and robotic-assisted laparoscopy (total costs without equipment: USD 24,433, USD 20,289, and USD 20,467, respectively). The robot platform has been in use at Tampere University Hospital since 2009, and the robot is used by urologists, gynecologists, and thoracic surgeons, with an annual rate of 345 to 400 operations.

The aim of this analysis was to compare the costs of conventional laparoscopy and robotic-assisted laparoscopy in the treatment of endometrial cancer, to evaluate possible differences and identify factors influencing the costs within a randomized trial.

MATERIALS AND METHODS

In a clinical trial, 101 patients presenting with endometrial cancer were randomized into 2 arms, traditional laparoscopy (traditional, n = 51) and robotic-assisted laparoscopy (robot, n = 50). Inclusion criteria were a low-grade (Grade 1–2) endometrial cancer, a scheduled staging operation, and a signed informed consent. Exclusion criteria included a narrow vagina or a uterus too large to be removed through the vagina and ineligibility for a deep Trendelenburg position. The details of the study population, randomization procedure, and operations have been described in detail previously.[4]

The operations were performed at a tertiary referral center, the Department of Obstetrics and Gynecology of Tampere University Hospital, Tampere, Finland from 2010 to 2013 by gynecologic oncologists with several years of experience with laparoscopic surgery. The study protocol was approved by the Research Ethics Committee of Tampere University Hospital (identification code ETL R10081) and is registered at www.clinicaltrials.gov (NCT 01466777).

TABLE 1. Variable definitions

Variables	Both Groups	Traditional	Robot	Comment
Instruments	Disposable instruments and materials, maintenance costs for reusable instruments, and OR supplies hemostatic matrix if used	Energy instrument costs	Instrument cost per operation (4 basic instruments)	
In-patient stay	Room and board, ward personnel, and ward basic medication			
Laboratory	Based on the needed studies during operation and in-patient stay			
Radiology	Based on the needed imaging studies during operation and in-patient stay			
Blood products	Blood transfusions and laboratory samples related to preparation or transfusions			
Operation personnel	0.5 anesthesiologist and 3.25 OR nurses for each operation			Related to OR time
Equipment and OR	Costs of running the OR and the fixed equipment	Amortization of a basic laparoscopy tower	Amortization of the robot console	Related to OR time
General costs	Administrative costs, costs that cannot be calculated elsewhere			Related to OR time
Operation medication	Anesthesia costs and local anesthetics			Related to OR time
Surgeon costs	2 operating specialists			Related to operation time
PACU costs	0.3 nurses per patient and facilities			Related to PACU time
Complications	Additional clinical visits, readmissions, and radiology			

OR=operating room
PACU=post-anesthesia care unit

The costs were calculated retrospectively in euros. The cost variables are presented in Table 1.

The patient data were collected from the operation and onwards over the subsequent follow-up period of 6 months. All contacts and procedures at follow-up hospitals (imaging studies, readmissions, operative treatment) were recorded. These contacts and the costs related to them were calculated in complications and are referred in this article also as late complications. In complication costs, all expenses related to the contact have been taken into account. This includes also all out-patient visits, which led or did not lead to any procedures. Patients contacted clinics for various reasons such as swelling, bruises, and vaginal bleeding among other complaints. Most of these were normal postoperative symptoms. Because of swelling in lower extremities, many patients underwent a Doppler ultrasound imaging to exclude deep venous thrombosis with no findings.[4]

Public health care in Finland uses an internal accounting and billing system within the hospitals. Different hospital units offer services based on their expertise such as anesthetic services, operating room (OR) services, laboratory services, and consultations provided by other specialties like urologic surgery. We searched the hospital databases to retrieve the actual costs of each operation.

The original expense data from 2012 was used as the basis for calculating costs for operation personnel, amortization of the laparoscopy towers and the robot console, OR costs, medication during the operation, and general costs related to the hospital infrastructure. The 2012 expense data was chosen because it represents the midpoint of the study period.

The amortization and use of an energy instrument in traditional laparoscopy group was also included in the instrument costs; an energy instrument was used in 15 operations, based on the operating surgeon's judgment.

Costs related to the instrumentation, in-patient stay, radiology, and laboratory services as well as blood products were calculated or retrieved from the database according to the actual time (exact date or at least year) of the operation. In-patient stay, radiology, laboratory, and blood product expenses were retrieved from the internal accounting system. For disposable instruments and products, we used the real hospital purchase costs, according to the reported data on each operation, and we included in every operation a basic array of instruments and equipment involved in the operative set-up. Traditional and robotic operations had a different basic package based on the needs of the operative method. For reusable instruments, the maintenance costs were calculated. For robot instruments, the cost of amortizing (maximum 10 operations per instrument), and the maintenance costs were taken into account.

The robot at Tampere University Hospital is the Da Vinci S surgical system (Intuitive Surgical, Inc, Sunnyvale, Calif). It is a leased product with a 10-year contract. The annual leasing and maintenance costs are 196,000 € and 140,000 €, respectively. We divided these costs with the total number of operations during the year 2012 to calculate the robot platform amortization cost per robot operation.

One patient was originally randomized into the traditional laparoscopy group, but the surgeon decided to change the operative procedure to robotic-assisted laparoscopy because of the obesity of the patient. Because of this randomization violation, secondary analyses were performed besides the primary intention-to-treat analysis, which is a per protocol analysis with groups based on the actual operative manner (this patient was included in the robot arm), and also excluding this patient.

Two patients from the traditional laparoscopy group who were not suitable for laparoscopic operation were operated through laparotomy, and their data was not analyzed in the study.[4] Consequently, the final number of patients in the analysis was 49 in the traditional group and 50 in the robotic-assisted group.

Distributions of cost factors were shown by medians with interquartile ranges due to the skewed distributions and outliers. Differences between traditional and robotic-assisted laparoscopic surgical costs were analyzed by nonparametric independent-samples Mann-Whitney U test. Categorical variables were tested by Pearson χ^2 test or by Fisher exact test if the expected values were too small. Statistical analyses were performed by IBM SPSS Statistics version 23 (IBM Corp, Armonk, NY). P values less than 0.05 were considered statistically significant.

RESULTS

Because there were no substantial differences in the results of the intention-to-treat and treatment received analyses, only the results of the intention-to-treat analysis are presented here. Results using the secondary analyses are given in the Supplemental Tables (S1 to S4 http://links.lww.com/IGC/A545).

The item costs were higher in the robotic-assisted laparoscopy arm for instruments, equipment, and OR, as well as postanesthesia care unit (PACU) (Table 2). Traditional laparoscopy had higher costs for operation personnel and medication, general costs and surgeon costs, but these differences were relatively small (Table 1 for variable definitions, Table 2). There were no significant differences in costs related to in-patient stay, laboratory and radiology services, or blood products. The median total costs for the robotic-assisted laparoscopy, including late complications were 2160 € higher than for traditional laparoscopy (1.4-fold, cost per operation: 7982 € vs 5823 €, respectively; Fig. 1).

There were 5 conversions to laparotomy in the traditional laparoscopy group and none in the robot group.[4] The total costs without late complications for these patients were substantially higher than for the rest of the traditional laparoscopy patients (nonconversions Md 5352 € vs conversions 7149 €, $P < 0.001$) There was also a significant difference in the length of in-patient stay (Md 1 vs 4 days, $P < 0.001$), which increased the costs of the in-patient stay (1114 € vs 2148 €, $P = 0.002$). Moreover, there was a significant difference in PACU time (Md 2 hours and 22 minutes vs 3 hours 33 minutes, $P < 0.001$), which also affected the PACU costs (704 € vs 938 €, $P < 0.001$). The median total costs related to the laparoscopy-laparotomy converted operations are close to the median total cost of the robot arm without complications (7415 €).

Ten patients in the traditional group and 20 patients in the robot group contacted the follow-up hospitals or had

TABLE 2. Itemized median costs for traditional vs robot-assisted laparoscopy for endometrial carcinoma, intention-to-treat analysis within the Tampere randomized trial, and cost factors

	Traditional (n = 49)			Robot (n = 50)			Difference	
Variables	**Md €**	**(IQR €)**	**%**	**Md €**	**(IQR €)**	**%**	**€**	***P***
Instruments	214	(171–421)	5.9	1813	(1798–1817)	23.9	−1599	<0.001
In-patient stay	1387	(1002–1635)	25.2	1092	(932–1422)	15.8	295	0.130
Laboratory	824	(457–918)	13.3	791	(526–909)	9.3	33	0.845
Radiology	0	(0–37)	0.6	0	(0–0)	1.1	0	0.321
Blood products	18	(17–35)	0.6	18	(0–40)	0.6	0	0.674
Operation personnel*	844	(797–995)	16.2	729	(661–833)	9.7	115	<0.001
Equipment and OR	232	(217–295)	4.7	1172	(1064–1340)	15.7	−940	<0.001
General costs	78	(73–91)	1.5	67	(61–77)	0.9	11	<0.001
Operation medication	91	(86–108)	1.8	79	(72–90)	1.1	12	<0.001
Surgeon costs	896	(806–1,049)	17.0	735	(643–866)	9.8	161	<0.001
PACU costs	704	(704–938)	13.3	938	(704–938)	12.1	−234	<0.001
Total costs without late complications	5487	(4766–6184)		7415	(6937–8057)		−1928	<0.001
Complications	766	(349–1532)		844	(421–2883)		−78	0.530
Total costs with complications	5823	(4912–6243)		7983	(7236–8400)		−2160	<0.001

Md = median value.
IQR = interquartile range.
*Nurses and an anesthesiologist.

complications reported. The related median costs were 766 € and 844 € per patient, respectively ($P = 0.530$).

The operative time as well as the OR time were significantly shorter in the robot group, whereas PACU time was shorter in the traditional group (Table 3).[4]

Although there was no significant difference in the median length of postoperative in-patient stay (Table 3), 1 patient in the traditional group was not discharged until postoperative day 7. Physically, the patient's recovery from the surgery did not differ from that of other patients, but the patient's mental status did not allow discharge, and she was waiting for a transfer to a municipal hospital. This created an outlier in the in-patient stay costs (3343 €). We were unable to calculate the costs of the following municipal hospital stay.

One patient in the robot group underwent embolization while she was in the PACU because of a bleeding complication. This patient stayed in the PACU for 16 hours and 2 minutes causing an outlier in the PACU time and PACU costs (4492 €), as well as the embolization cost in the Radiology Department (2884 €). We included the costs (embolization, laboratory, radiology, PACU) in this patient's primary operation period, not itemizing them stratified according to the complications,

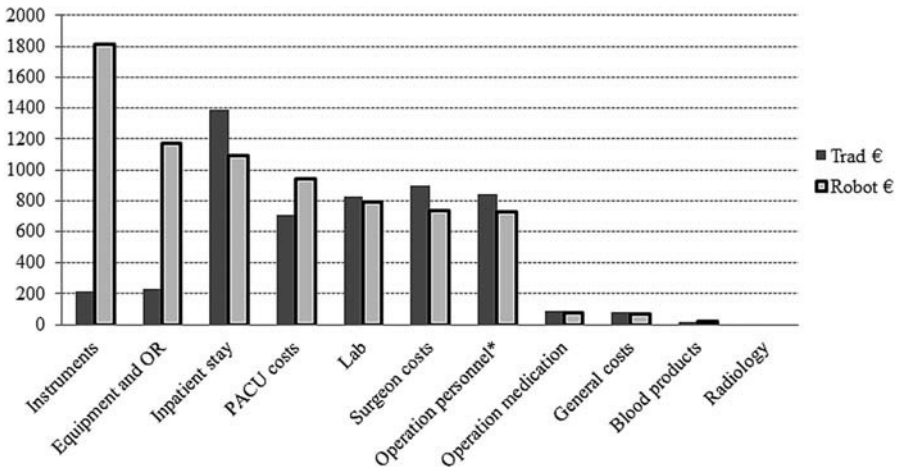


FIGURE 1. Cost variables, comparison (accompanying.tif-file). Median values (€). *Nurses and anesthesiologist.

TABLE 3. Time-related items in traditional vs robot-assisted laparoscopy for endometrial carcinoma in the Tampere randomized trial, intention-to-treat analysis

	Traditional (n = 49)		Robot (n = 50)		
Variables	**Md**	**(IQR)**	**Md**	**(IQR)**	***P***
Sick leave, d	27.5 (n = 12)	(24–33)	28 (n = 13)	(25–29.5)	0.728
OR time	3:48	(3:35–4:29)	3:17	(2:59–3:45)	<0.001
Operation time	2:50	(2:33–3:19)	2:19	(2:02–2:44)	<0.001
PACU time	2:36	(2:03–3:08)	3:05	(2:38–3:31)	0.001
Discharge, d	2	(1–2)	1	(1–2)	0.215

Md = median value.
IQR = interquartile range.

because it was difficult to reliably differentiate the costs of this complication from the costs of the surgery itself, for example, in the PACU costs.

One patient in the robot group needed 2 reoperations because of a rectovaginal-fistula. This patient also had repeated imaging studies and readmissions because of the complication. These costs created an outlier in complication costs (14,818 €).

No postoperative deaths occurred during the study period nor were there any thromboembolic events during the follow-up.[4]

There was no significant difference between the 2 arms in duration of sick leave (Table 3). Most of the patients did not receive sick leave because they were already retired. Consequently, sick leave costs were not calculated in this analysis.

Robot instrument cost per operation was 1030 € (including 4 basic instruments used in the operations), and the amortization cost of the robot console per operation was 939 € according to the 2012 expense data (taken into account in equipment and OR costs). On this basis, we calculated costs per duration of OR time–related amortization cost (5.95 € per minute) and applied it individually for each operation in accordance with the operating time. Therefore, the equipment and OR costs for some patients can be less than 939 € (range, 844 €–1503 €).

CONCLUSIONS

The median actual costs of the robotic-assisted laparoscopy were 1928 € (35%) higher per patient than the costs related to traditional laparoscopy. Although direct international comparisons are difficult to make because of differences in national health care funding systems, our results seem to be comparable with findings in previous studies, showing robotic-assisted laparoscopy to be 17% to 33% more expensive.[5,6] Amortization of the robot console and costs involved with robot instrumentation are the major determinants of the incremental costs related to robotic-assisted surgery.[5–9] Amortization can be minimized by increasing the number of operations. However, because a set of robot instruments can only be used in 10 operations, the instrument costs are practically fixed. Although we have previously shown that the operation time is shorter in robotic-assisted than traditional laparoscopic operations,[4] the shorter operation time was not enough to balance out the costs of amortization of the robot console and the use of robot instruments.

In Finland, doctors and surgeons in the public health care receive a monthly salary instead of fee for service. This explains the lower labor cost of surgeon per operation compared with a previous US study.[3] In our study, the surgeon cost is related only to the duration of the operation.

The major strength of this study is the randomized design, ensuring an unbiased comparison between the treatment arms. The learning curve effect was also minimized as robotic surgery for gynecologic indications was started at our hospital already in March 2009. We have previously shown that the learning curve for robotic surgery is relatively short or 10 operations.[10] Moreover, our experience with laparoscopic surgery for endometrial cancer dates from 1990s.[11] Both operative techniques were therefore already well-established at the time the randomized trial was initiated.

The 2 groups were well balanced in relation to all major patient characters.[4]

The costs were calculated in a detailed fashion for each operation based on actual cost items, including even from the surgeons' gloves and threads used.

During the time of the study design, the standard surgical treatment of endometrial cancer at our institution was hysterectomy, bilateral salpingo-oophorectomy, and in most cases, pelvic lymphadenectomy (PLND). These 3 procedures were scheduled to be performed to all of the randomized patients. However, PLND was not performed on 2 patients in both arms (total n = 4) because of a disseminated disease.[4]

The costs of PALND were not evaluated. Current guidelines encourage PALND, besides PLND, to be performed in patients with high-risk endometrial cancer, whereas in the case of low-risk cancer, only hysterectomy and bilateral salpingo-oophorectomy without LND should be performed.[12] Because extending the lymphadenectomy to the para-aortic area makes traditional laparoscopy challenging to perform the cost difference might have been smaller if PALND were included in the randomized study design.[13]

Although the number of patients was rather limited, the outliers encountered in some variables did not substantially affect the final results.

There are some local factors that inevitably constrain the generalizability of the results. Our robot console and its PACU are located in a separate building apart from the Department of Obstetrics and Gynecology and its ORs. This increases the expenses because of additional PACU time.

Quality of life was not investigated in this study, which can be considered a limitation.

Laparoscopic approach has replaced laparotomy in the operative treatment for endometrial cancer.[12] At present, laparotomy should not be considered as the primary operation method anymore now that minimally invasive methods have been evolved.[13,14] Moreover, according to a recent study comparing the costs of robotic-assisted laparoscopic hysterectomy to open hysterectomy, laparotomy was more expensive, mainly because of longer in-patient stay.[15] In the field of laparoscopy, the robotic-assisted technique has introduced many advantages such as diminished blood loss, wristed instruments, 3-dimensional stereoscopic vision, better ergonomics for surgeon, and a shorter learning curve.[9–11,16,17] This was reflected also in the present study, where no conversions to laparotomy had to be undertaken in the robot group as opposed to 5 conversions in the traditional group. The total costs of the converted operations were almost as high as the costs of the robotic-assisted operations (Md 7149 € vs 7415 €, respectively).

In contrast to clinical operations performed for real patients, in which setting each robotic instrument can be used only 10 times, in the preclinical training phase, the same instruments can be used 30 times (data obtained during from robotic training at Tampere University Hospital, Da Vinci S surgical system; Intuitive Surgical, Inc, Sunnyvale, Calif). If robotic instruments could also clinically be used 30 times, it would decrease the instrument costs by 688 €. On the other hand, if the annual number of gynecological operations at our institution would be increased from 84 to 120, with 3 instead of 2 daily operation, the amortization costs would decrease by 282 € per operation. By such means, the median total costs for robotic surgery would be 6445 €, and the difference between the 2 operation types would decrease to 17%.

We were unable to assess patient outcomes in terms of quality-adjusted life year (QALY) (because no obvious difference in complications or other patient outcomes were found), so real cost-effectiveness analysis was not possible. However, applying a cost-effectiveness threshold of 50,000 €; per QALY to the observed cost difference of 2160 € per operation, it would mean that 1 QALY would need to be gained per 26 patients operated to reach the threshold.

The robotic-assisted technique in the staging of endometrial carcinoma (hysterectomy, bilateral salpingo-oophorectomy, and PLND) increases the total treatment costs by one third compared with the traditional technique. In our setting, this translates into roughly 2000 € per patient. For further research, it would be beneficial to calculate the costs in similar form including the PALND.

REFERENCES

1. Torre LA, Bray F, Siegel RL, et al. Global cancer statistics, 2012. *CA Cancer J Clin*. 2015;65:87–108.
2. Leslie KK, Thiel KW, Goodheart MJ, et al. Endometrial cancer. *Obstet Gynecol Clin North Am*. 2012;39:255–268.
3. Leitao MM Jr, Bartashnik A, Wagner I, et al. Cost-effectiveness analysis of robotically assisted laparoscopy for newly diagnosed uterine cancers. *Obstet Gynecol*. 2014;123:1031–1037.
4. Mäenpää MM, Nieminen K, Tomás EI, et al. Robotic-assisted vs traditional laparoscopic surgery for endometrial cancer: a randomized controlled trial. *Am J Obstet Gynecol*. 2016;215:588.e1–588.e7.
5. Barnett JC, Judd JP, Wu JM, et al. Cost comparison among robotic, laparoscopic, and open hysterectomy for endometrial cancer. *Obstet Gynecol*. 2010;116:685–693.
6. Wright JD, Ananth CV, Tergas AI, et al. An economic analysis of robotically assisted hysterectomy. *Obstet Gynecol*. 2014;123:1038–1048.
7. Reynisson P, Persson J. Hospital costs for robot-assisted laparoscopic radical hysterectomy and pelvic lymphadenectomy. *Gynecol Oncol*. 2013;130:95–99.
8. Lönnerfors C, Reynisson P, Persson J. A randomized trial comparing vaginal and laparoscopic hysterectomy vs robot-assisted hysterectomy. *J Minim Invasive Gynecol*. 2015;22:78–86.
9. Schreuder HW, Verheijen RH. Robotic surgery. *BJOG*. 2009;116:198–213.
10. Kuoppala T, Tomás EI, Heinonen PK. Clinical outcome and complications of laparoscopic surgery compared with traditional surgery in women with endometrial cancer. *Arch Cynecol Obstet*. 2004;270:25–30.
11. Mäenpää M, Nieminen K, Tomás E, et al. Implementing robotic surgery to gynecologic oncology: the first 300 operations performed at a tertiary hospital. *Acta Obstet Gynecol Scand*. 2015;94:482–488.
12. Colombo N, Creutzberg C, Amant F, et al. ESMO-ESGO-ESTRO Consensus Conference on Endometrial Cancer: diagnosis, treatment and follow-up. *Ann Oncol*. 2016;27:16–41.
13. Soliman PT, Frumovitz M, Spannuth W, et al. Lymphadenectomy during endometrial cancer staging: practice patterns among gynecologic oncologists. *Gynecol Oncol*. 2010;119:291–294.
14. Galaal K, Bryant A, Fisher AD, et al. Laparoscopy versus laparotomy for the management of early stage endometrial cancer. *Cochrane Database Syst Rev*. 2012;9:CD006655.
15. Herling S, Palle C, Møller A, et al. Cost-analysis of robotic-assisted laparoscopic hysterectomy versus total abdominal hysterectomy for women with endometrial cancer and atypical complex hyperplasia. *Acta Obstet Gynecol Scand*. 2016;95:299–308.
16. Ramirez PT, Adams S, Boggess JF, et al. Robotic-assisted surgery in gynecologic oncology: a society of gynecologic oncology consensus statement. developed by the society of gynecologic oncology's clinical practice robotics task force. *Gynecol Oncol*. 2012;124:180–184.
17. Diaz-Arrastia C, Jurnalov C, Gomez G, et al. Laparoscopic hysterectomy using a computer-enhanced surgical robot. *Surg Endosc*. 2002;16:1271–1273.

PUBLICATION
II

The Influence of bevacizumab on the costs of ovarian cancer treatment in routine clinical practice

Vuorinen R-L, Luukkaala T, Mäenpää J.

Acta Oncologica 2020;59(4):453-457.

The Influence of Bevacizumab on the Costs of Ovarian Cancer Treatment in Routine Clinical Practice

Riikka-Liisa K. VUORINEN, MD [a,b*], Tiina H. LUUKKAALA, MSc[c, d], Johanna U. MÄENPÄÄ, PhD[a,b]

[a] *Department of Obstetrics and Gynecology, and Tays Cancer Center, Tampere University Hospital, Tampere, Finland;* [b] *Faculty of Medicine and Health Technology, Tampere University, Tampere, Finland;* [c] *Research, Development and Innovation center, Tampere University Hospital, Tampere, Finland;* [d] *Faculty of Social Sciences, Tampere University, Tampere, Finland*

Correspondence:

Riikka-Liisa Vuorinen, Tampere University Hospital, Department of Obstetrics and Gynecology, P.O. Box 2000, FI-33521, Tampere, Finland.

Tel. +358 3 31166567, Fax +358 3 31164391, E-mail: riikka-liisa.vuorinen@tuni.fi

Manuscript Word count 1966 (in the main text)

Introduction

In 2018, the estimated number of new ovarian cancer cases worldwide was over 295,000, with almost 185,000 deaths, making it the eighth most common cancer in women in terms of incidence and mortality. Among gynecological cancers, it is the second leading cause of death worldwide [1].

The cornerstones of epithelial ovarian cancer (EOC) treatment are surgery and chemotherapy. Operative treatment includes surgical staging and tumor debulking, while paclitaxel-carboplatin is the standard chemotherapy [2]. The role of vascular endothelial growth factor (VEGF) and angiogenesis is important in EOC treatment. However, bevacizumab is the only anti-angiogenetic agent with a label for use in EOC [3, 4]. Studies have found an approximately four-month benefit in progression free-survival (PFS) when bevacizumab is incorporated in the first-line treatment of advanced EOC or in a recurrent setting [4- 8]. A subgroup analysis of the first-line trial ICON7 showed that in high-risk patients, there was a significant improvement (nine months) in overall survival (OS) [9]. In recurrent platinum sensitive setting, an OS benefit of 5 months was achieved in the GOG-0213 trial [10]. In the Nordic countries, the use of bevacizumab in the first line treatment is generally restricted to patients with either stage IV, or suboptimally debulked stage III disease at a dose of 7.5 mg/kg Q3wk. In many hospitals, including ours, the high cost of bevacizumab generally allows it to be used only once in a patient's treatment program, i.e. either in the primary or recurrent setting.

The aim of this study was to evaluate the true costs related to the non-surgical treatments of ovarian cancer from the first-line treatment to several later lines of therapy for up to five years of follow-up, with a special emphasis on the role of bevacizumab.

Material and Methods

The cohort for this analysis consisted of patients who had received the diagnosis of EOC from 01-JAN-2011 through 31-DEC-2012 at Tampere University Hospital, Finland. The rationale of using this cohort was to create a follow-up of at least five years.

Patient information was collected retrospectively from the patient registry in 2017 – 2018. A structured form was used to collect the following data: date of diagnosis, operations concerning EOC, bevacizumab treatment (dates of drug administration and doses), chemotherapy (drugs, doses, dates of drug administration and number of treatment lines), other relevant medication which was used during and related to the EOC treatment, clinic visits (scheduled and emergency) and inpatient stays, relevant laboratory and imaging tests, and additional operations.

The cost calculations were performed based on the records from the internal management accounting systems (Ecomed ICS and Tableau), and using yearly information related to clinical expense data. Costs were calculated for each patient individually. Only costs concerning the Department of Obstetrics and Gynecology were taken into account. The costs of the primary operative treatment were not

included since the objective was to analyze medical costs. Therefore, only costs during chemotherapy and/or bevacizumab treatment were calculated.

The chemotherapy medication costs include the work related to handling the medication and preparing the medication at the hospital pharmacy. Laboratory costs include the use of blood products.

We calculated the cost of G-CSF by using the Finnish market price during spring 2019 from Pharmaca Fennica as these were mainly used as prescription drugs.

If a patient participated in a clinical trial concerning EOC medication, those costs and medications were left out of the calculations and this ended her follow-up on our behalf. However, the possible occurrence of death was recorded.

The distributions of cost factors are shown by medians with interquartile ranges (IQR) due to the skewed distributions and outliers (Table). Differences between categorical patient characteristics were tested by Pearson's chi-square test or Fisher's exact test. Due to the skew distributions, continuous patient factors were analyzed by the Mann-Whitney test. Analyses were performed using IBM SPSS Statistics for Windows (version 23.0, Armonk, IBM Corp., NY).

The study was approved by the Ethics Committee of Tampere University Hospital (Identification code R17126). No informed consent was needed as there was no interference with the patient medication nor did it effect the patient's treatment in any way. Individual patients cannot be identified from this report.

Results

A total of 75 patients were diagnosed with EOC from 2011 through 2012 at Tampere University Hospital. Of them, 66 patients received chemotherapy, and their treatment costs form the focus of this analysis. Twenty-four patients (36%) received bevacizumab: 16 (67%) as a first-line therapy and 8 (33%) as a later line of therapy (Figure). The mean age at diagnosis was 66.6 years, and most patients had a FIGO Stage III or IV disease at the time of the diagnosis, 30 and 17 patients, respectively. Almost 76% of patients needed hospitalization at some point during chemotherapy or bevacizumab treatment.

Most patients received 1-3 lines of chemotherapy, but up to six treatment lines were recorded from one patient. Only four patients had ongoing treatment at the end of the follow-up or at 31-DEC-2017 (Figure).

The combined total costs of the medical EOC treatment including all variables for the entire cohort of 66 patients were 2,404,251 € of which the proportion of chemotherapy was 306,086 € or 13%. Of the total non-surgical costs for all patients, bevacizumab costs comprised 47.1%, which was the largest single expense even though it was administered to only 24 patients. In the bevacizumab group the cost of the drug itself was 1,132,740 € or almost two-thirds or of all treatment costs. The median cost for ovarian cancer treatment/patient in the non-bevacizumab group was 7,700 €, while in the bevacizumab group it was more than 10 times higher or 82,542 €. All variables presented higher costs in the bevacizumab group. (Table)

Of the 24 bevacizumab patients, 16 received bevacizumab as a first-line treatment and 8 as a second-line treatment. The median costs of the treatment/patient were

85,795 € and 76,311 €, respectively. In both groups, bevacizumab was the single largest expense (69% vs 49%). Only one patient in the bevacizumab group was enrolled into a clinical trial during the follow-up. The costs prior to enrolment are included in the calculations.

Discussion

For the costs of all included patients, the cost of bevacizumab comprised almost half, or 47.1%. The relatively high contribution of the second largest cost or inpatient stay can be explained by the long follow-up during the course of the disease over consecutive recurrences and re-treatments, ending to progressive disease and death.

The bevacizumab group had higher median costs for all variables, which can partly be explained by the difference in the initial disease staging and the characteristics of a low-grade disease vs. a high-grade disease, as bevacizumab is used in patients with high-risk disease. Thus, the bevacizumab group more often had recurrence, resulting in more numerous lines of therapy. When the treatments stretched over a longer time period, the risk of complications and side-effects increased, and therefore the risk of emergency visits and hospitalization increased in parallel. The increased costs of imaging, laboratory and clinic visits are simply explained by the time consumed i.e. the longer follow-up. When more treatment lines are used, the risk of neutropenia also increases, which explains the higher costs for G-CSF.

Neyt et al. made a cost-effectiveness analysis based on the material of four large trials on bevacizumab and ovarian cancer, GOG-0218, ICON7, OCEANS and AURELIA [4, 5, 7, 6, 11]. Compared to the present results, their calculations are in the same range. In the first line setting, Neyt et al. calculated based on GOG-0218 data that the mean costs related to bevacizumab are 44,286 €, while the actual costs were 52,766 € (Md 57,800 €) in our study. The mean costs of bevacizumab treatment for recurrent disease in the present study are 36,060 € (Md 40,163 €), which is between the mean cost of bevacizumab in AURELIA and OCEANS trials, or 28,529 € and 53,591 €, respectively. If the chemotherapy visits are included in the calculations, the mean costs in our study and the OCEANS trial are quite similar or 45,991 € (Md 48,811 €) and 53,591 €, respectively.

The cost-effectiveness of bevacizumab has been questioned, as the main advantage of bevacizumab is a PFS benefit of approximately four months, but there is in general no overall survival benefit [8]. As the cost-effectiveness is better in stage III and stage IV disease [12], bevacizumab treatment should be prioritized in these patients [13]. In ICON7, the median over-all survival (OS) of high-risk patients treated with bevacizumab was 39.7 months, while it was 30.2 months in the control patients [9]. Our median costs per patient for bevacizumab medication itself in first-line treatment was 57,800 €. If these costs are applied to the above OS figures, the incremental cost-effectiveness ratio (ICER) would be 73,010 €/quality adjusted life-year (QALY). This figure is low compared to the analysis by Neyt et al., who calculated an ICER of 157,816 € for GOG-0218 and 82,277 € for ICON7 in high-risk patients [11]. The lower ICER in our calculations

can partly be explained by the fact that some patients received only 2-4 doses of bevacizumab, which reduces costs significantly. In our first-line patients, there was also some diversity in doses (7.5 mg/kg n=4, 15 mg/kg n=12), which also contributes to our smaller bevacizumab costs compared to GOG-0218. This emphasizes the uniqueness of real-life calculations. If the threshold of reasonable QALY is considered to be 100,000 USD or 89,026 €, the role of bevacizumab at least in first-line treatment is supported. If our first-line costs were calculated with the dose of 7.5 mg/kg (which was proven to be a sufficient dose for first-line treatment in ICON7) by dividing the bevacizumab drug costs in half in patients who had received the dose of 15 mg/kg, we would reach an ICER of 44,763 €/QALY. This outcome makes the use of bevacizumab as the first-line treatment more acceptable from the health economic point of view.

Societal costs were not included in this study. As most of the patients were already retired, these costs were unlikely to have significant influence. We were neither able to reliably calculate the costs of treatment complications, as patients were not always treated at our Department. However, it is well known that bevacizumab treatment increases the risk of gastrointestinal events, hypertension, proteinuria and thromboembolism [8]. If all these costs were included in the analysis, the costs of bevacizumab treatment would be even higher. Anyway, the higher inpatient stay costs in the bevacizumab group can at least partially be explained by the complications related to its use.

The cohort of patients turned out to be very heterogeneous as the current guidelines for the use of bevacizumab in Finland were not established until 2012

[14]. There was diversity in the treatment doses (first-line bevacizumab 7.5 mg/kg vs 15 mg/kg), initiation and duration of treatment. If a later cohort had been chosen, the treatments would have been more homogenous, but the follow-up would have been shorter, and we wanted to calculate the costs over the entire course of the disease.

The major strength of this study is that the calculations are based on real-life situations rather than modeling costs to a specific drug administration protocol or guideline. As it was possible to obtain very accurate data from the internal management accounting system and the yearly expense data, the costs were processed in a very precise manner. Therefore, these calculations can be assumed to present a very accurate description of the chemotherapy and bevacizumab costs of EOC in a real-life setting, even though the cohort was rather small.

In conclusion, bevacizumab treatment was the single largest medical expense in EOC patients. For estimating future treatment costs, models can be helpful and accurate to a certain extent. However, real-life calculations provide a more accurate picture of all variables related to the treatment and show individual differences in the treatment.

Conflicts of interest/disclosure statement: Dr Vuorinen and MSc Luukkaala report no conflicts of interest. Dr Mäenpää has received honoraria from Roche, AstraZeneca, Tesaro, Clovis, Lilly, MSD and OrionPharma.

Acknowledgements: We thank Dr Anssi Auvinen for giving valuable advice regarding this project.

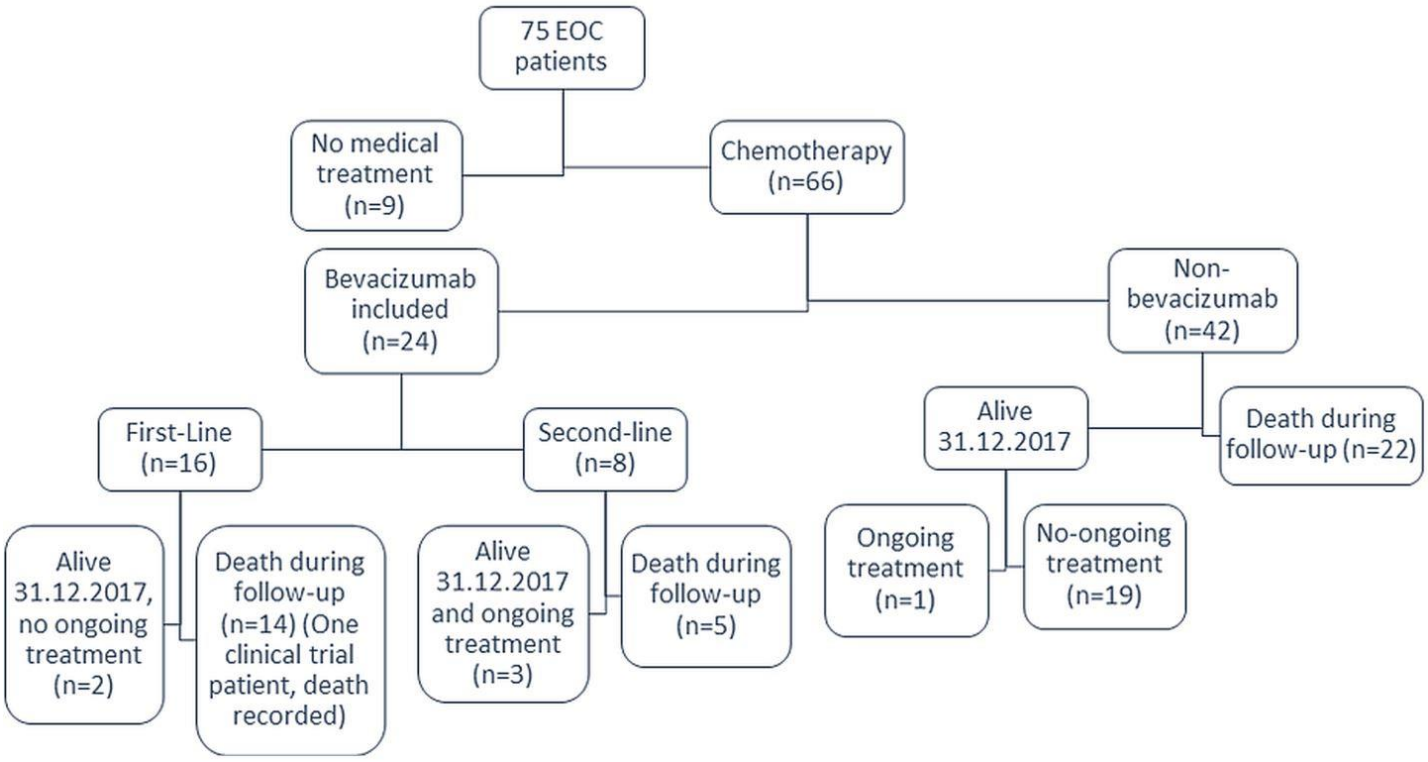
Table. Costs of the EOC treatment

Total costs of the treatment variables, percentages from the total costs of the treatment, and median costs per patient.

	All patients (n=66)			Non-bevacizumab (n=42)			Bevacizumab (n=24)			Bevacizumab, First-Line (n=16)		Bevacizumab, Second-Line (n=8)	
	Total €	(%)	Median € (IQR)	Total €	(%)	Median € (IQR)	Total €	(%)	Median € (IQR)	(%)	Median € (IQR)	(%)	Median € (IQR)
Chemotherapy, medication	306,086	(13)	1,415 (646-7,589)	117,360	(20)	750 (524-2,889)	188,726	(11)	6,468 (2,944-11,666)	(7.3)	4,603 (2,506-7,361)	(17)	12,083 (4,803-20,784)
Chemotherapy, visits	286,277	(12)	2,804 (1,100-7,113)	97,989	(16)	1,130 (846-2,984)	188,288	(10)	7,162 (5,037-9,940)	(8.9)	6,704 (4,711-8,596)	(14)	8,648 (5,625-12,619)
Chemotherapy, lab	83,759	(3.5)	1,019 (412-1,782)	34,951	(5.8)	495 (309-1,485)	48,809	(2.7)	1,808 (1,186-2,802)	(2.6)	1,808 (1,165-2,727)	(3.0)	1,901 (1,246-3,072)
Imaging	20,319	(0.85)	0 (0-358)	4,581	(0.77)	0 (0-137)	15,739	(0.87)	371 (0-1,156)	(1.0)	371 (12-1,164)	(0.7)	366 (0-1,077))
On-call visits	50,657	(2.1)	378 (0-1,090)	27,442	(4.6)	237 (0-877)	23,215	(1.3)	655 (233-1,425)	(1.1)	454 (233-1,236)	(1.7)	948 (289-1,688)
Inpatient stay	416,873	(17)	3,257 (310-7,437)	264,301	(44)	2,551 (0-5,209)	152,572	(8.5)	5,899 (2,424-9,679)	(6.8)	5,053 (568-7,343)	(12)	7,988 (3,597-12,483)
G-CSF*	107,539	(4.5)	392 (0-1,801)	51,531	(8.6)	285 (0-1,424)	56,008	(3.1)	847 (0-2,250)	(2.9)	70 (0-1,482)	(3.4)	1,510 (586-3,866)
Bevacizumab	1.132,740	(47)	44,238 (26,206-72,133)	-	-	- -	1.132,740	(63)	44,238 (26,206-72,134)	(69)	57,800 (26,336-80,256)	(49)	40,163 (22,586-46,426)
Total cost per patient			22,115 (5,279-104,741)			7,700 (2,863-20,752)			82,542 (50,517-100,123)		85,795 (44,596-105,815)		76,311 (63,214-91,895)

* Granulocyte-colony stimulating factors
IQR = Interquartile range

Figure legend: Flow chart of the patients



References

1. WHO statistics, Cancer today, International Agency for research on Cancer. http://gco.iarc.fr/today/ (Accessed 16.4.2019)
2. Hennessy BT, Coleman RL, Markman M. Ovarian cancer. Lancet 2009;374:1371–82
3. Gaitskell K, Martinek I, Bryant A et al. Angiogenesis inhibitors for the treatment of ovarian cancer. Cochrane Database of Syst Rev 2014;9:CD007930
4. Burger RA, Brady MF, Bookman MA et al. Incorporation of Bevacizumab in the Primary Treatment of Ovarian Cancer. N Engl J Med 2011;365:2473-83
5. Perren TJ, Swart AM, Pfistere J et al. A Phase 3 Trial of Bevacizumab in Ovarian Cancer. N Engl J Med 2011;365:2484-96.
6. Pujade-Lauraine E, Hilpert E, Weber B et al. Bevacizumab Combined With Chemotherapy for Platinum Resistant Recurrent Ovarian Cancer: The AURELIA Open Label Randomized Phase III Trial. J Clin Oncol 2014;32:1302-1308
7. Aghajanian C, Blank SV, Goff BA et al. OCEANS: A Randomized, Double-Blind, Placebo-Controlled Phase III Trial of Chemotherapy With or Without Bevacizumab in Patients With Platinum-Sensitive Recurrent Epithelial Ovarian, Primary Peritoneal, or Fallopian Tube Cancer. J Clin Oncol 2012;30:2039-2045
8. Ye Q, Chen H-L. Bevacizumab in the treatment of ovarian cancer: a meta-analysis from four phase III randomized controlled trials. Arch Gynecol Obstet 2013;288:655–666
9. Oza AM, Cook AD, Pfisterer J et al. Standard chemotherapy with or without bevacizumab for women with newly diagnosed ovarian cancer (ICON7): overall survival results of a phase 3 randomised trial. Lancet Oncol 2015;16:928–36
10. Coleman RL, Brady MF, Herzog TJ et al. Bevacizumab and paclitaxel–carboplatin chemotherapy and secondary cytoreduction in recurrent, platinum-sensitive ovarian cancer (NRG Oncology/Gynecologic Oncology Group study GOG-0213): a multicentre, open-label, randomised, phase 3 trial. Lancet Oncol 2017;18:779–91
11. Neyt M, Vlayen J, Devriese S et al. First- and second-line bevacizumab in ovarian cancer: A Belgian cost-utility analysis. PLoS ONE 2018;13(4):e0195134

12. Barnett JC, Secord AA, Cohn DE et al. Cost Effectiveness of Alternative Strategies for Incorporating Bevacizumab Into the Primary Treatment of Ovarian Cancer. Cancer 2013;119:3653-61
13. Randall L, Nguyen H et al. Outcome differences in patients with advanced epithelial ovarian, primary peritoneal and fallopian tube cancers treated with and without bevacizumab. Gynecologic Oncology 2013;130:e33-e34
14. Leminen A, Auranen A, Bützow R et al. Ovarian cancer. Current Care Guidelines, The Finnish Medical Society Duodecim, 2012. Duodecim 2012;128(12):1300-1

PUBLICATION III

Current and predicted cost of metastatic renal cell carcinoma in Finland

Purmonen T, Nuttunen P, Vuorinen R, Pyrhönen S, Kataja V, Kellokumpu-Lehtinen P-L.

Acta Oncologica 2010;49(6):837-843.

PUBLICATION IV

Sunitinib first-line treatment in metastatic renal cell carcinoma: costs and effects

Vuorinen R-L, Paunu N, Turpeenniemi-Hujanen T, Reunamo T, Jekunen A, Kataja V, Sintonen H, Purmonen T, Kellokumpu-Lehtinen P-L.

Anticancer Research 2019;39(10):5559-5564.

ANTICANCER RESEARCH *39*: 5559-5564 (2019)
doi:10.21873/anticanres.13749

Sunitinib First-line Treatment in Metastatic Renal Cell Carcinoma: Costs and Effects

RIIKKA-LIISA VUORINEN[1,2], NIINA PAUNU[3], TAINA TURPEENNIEMI-HUJANEN[4], TAINA REUNAMO[5], ANTTI JEKUNEN[6], VESA KATAJA[7], HARRI SINTONEN[8], TIMO PURMONEN[9] and PIRKKO-LIISA KELLOKUMPU-LEHTINEN[1,3]

[1]*Faculty of Medicine and Health Technology, Tampere University and Tays Cancer Center, Tampere University Hospital, Tampere, Finland;*
[2]*Department of Gynecology and Obstetrics, Tampere University Hospital, Tampere, Finland;*
[3]*Department of Oncology, Tampere University Hospital, Tampere, Finland;*
[4]*Department of Oncology, Medical Research Center, Oulu University Hospital, Cancer and Translational Research Unit, Oulu University, Oulu, Finland;*
[5]*Department of Oncology, Turku University Hospital, Turku, Finland;*
[6]*Department of Oncology, Vaasa Central Hospital, Turku University, Vaasa, Finland;*
[7]*Department of Oncology, Kuopio University Hospital and Central Finland Central Hospital, Kuopio, Finland;*
[8]*Department of Public Health, University of Helsinki, Helsinki, Finland;*
[9]*Oy Medfiles Ltd, Kuopio, Finland*

Abstract. *Background/Aim: Tyrosine kinase inhibitors are important in the treatment of metastatic renal cell cancer (mRCC). The aim of the study was to evaluate the costs and effects of sunitinib in mRCC. Patients and Methods: A total of 81 mRCC patients who received first-line sunitinib therapy between 2010 and 2014 were recruited. Drug doses, laboratory and imaging studies, outpatient visits and inpatient stays were recorded. Health-related quality of life (HRQoL) was measured (15D- and EQ-5D – 3L questionnaires). Results: The cost of sunitinib (mean 22,268 €/patient range 274 € to 105,121 €) covered 73% of the total costs during the treatment period. The total treatment cost was 30,530 €/patient (range=1,661-111,516 €). The median overall survival was 17.9 months. HRQoL decreased during treatment. Conclusion: The main cost during sunitinib treatment of mRCC was the drug itself (73% of the total costs). Drug costs and HRQoL should be considered when choosing treatment for mRCC.*

Renal cell carcinoma (RCC) is the most common kidney carcinoma (other malignancies in kidney occur in the cortex, pelvis and ureters). In 2018, kidney cancers accounted for over 400,000 new cases and approximately 175,000 deaths worldwide (1). Lifestyle and health-related issues, such as smoking and obesity, have been identified as risk factors for RCC in many reports during recent decades (2, 3). Renal cell carcinoma presents little or no symptoms in its early stages (4). Due to a lack of symptoms, the disease is diagnosed in an advanced or metastatic phase (mRCC) in approximately one third of the cases. Currently, most RCC cases are discovered as an incidental finding (5).

Medical treatments for mRCC are constantly evolving, and many drugs targeting different pathways are used today (6). Originally, immunotherapy with high-dose interleukin-2 (IL-2) or interferon-alfa (IFN-α) was considered the primary choice (7-9). The recognition of the von Hippel-Lindau (VHL) tumor suppressor gene led to the presentation of vascular endothelial growth factor (VEGF) and VEGF receptor-targeted therapies, such as bevacizumab and tyrosine kinase inhibitors (TKIs) (10-12). Today, immune-check-point inhibitors, such as nivolumab and ipilimumab have changed the landscape for mRCC treatment (13-15). These agents have increased the overall survival and objective response rates of mRCC compared to sunitinib. Sunitinib is a TKI, that has shown an increase in progression-free survival (PFS) compared to IFN-α (16). Sunitinib is still the current standard of care especially in low-risk mRCC (15). It has been compared to several new TKIs, to their combination with check-point inhibitors and to everolimus (17-19). Recently, the combination of nivolumab and ipilimumab was shown to be superior to

Correspondence to: Riikka-Liisa Vuorinen, MD, Faculty of Medicine and Health Technology, Arvo Ylpön katu 34, 33520 Tampere, Finland. Tel: +35 8331166567, e-mail: Riikka-Liisa.Vuorinen@tuni.fi

Key Words: RCC, mRCC, metastatic, sunitinib, costs.

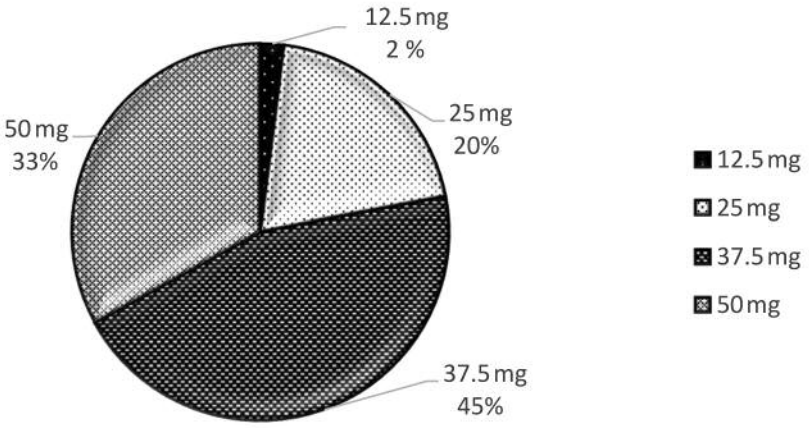


Figure 1. *First-line sunitinib treatment doses divided (%) according to duration of treatment (days).*

sunitinib as a first-line treatment of mRCC (14), but according to our new results, sunitinib may still have a beneficial effect after the combined treatment of nivolumab and ipilimumab (20). There is still a need to investigate sunitinib as a first-line treatment in mRCC patients, the costs of this treatment and the patients' use of other healthcare services during this treatment.

Patients and Methods

Based on real-world clinical practice, we conducted a prospective observational clinical study. We collected data from different clinical practices in four university hospitals and one central hospital in Finland during first-line sunitinib treatment from January 12, 2010, to November 30, 2014. The patients (n=81) were recruited among regular mRCC patients in the different clinics, and the study itself did not have an effect on physicians' decisions concerning the patients' treatment.

The inclusion criteria were as follows: patient was clinically fit for first-line sunitinib treatment in mRCC and signed an informed consent. The exclusion criteria were as follows: patient was not treated with sunitinib and/or did not give consent for collecting data from the patient register. The local ethics committee (R09045) approved the study. The trial identifier is NTC00980213.

Health related quality of life (HRQoL) was measured with the 15D- and EQ-5D-3L- questionnaires at baseline, at day 28 during sunitinib treatment and at the beginning of each new cycle (21, 22). The 15D- measures mobility, vision, hearing, breathing, sleeping, eating, speech (communication), excretion, usual activities, mental function, discomfort and symptoms, depression, distress, vitality, and sexual activity. The patient chooses a grade from one to five, that best describes his/her state of health at the moment. The 15D score, representing the overall HRQoL on a 0-1 scale (1=full health, 0=being dead) and the score on the different dimensions mentioned above (scale 0-1: 1=no problems, 0=being dead), are calculated from the questionnaire by using a set of population-based preference or utility weights. The minimum clinically important change or difference in the 15D-score has been estimated to be ±0.015 on the basis that people on average can feel such a difference (21). HRQoL measured with the 15D-questionnaire was compared to a sample of age- and gender- standardized general population based on an earlier National Health Survey (23).

Researchers in the participating clinics collected the data, and the data collection ended on November 30, 2014, or on the day that the patient died, if prior to the end of follow-up. The basic patient information, the data of their carcinoma and the data concerning the use of other health care services were collected on a structured form.

The recorded information was background information (date of birth, gender, nephrectomy information, date of diagnosis, and information on the risk-groups) and the use of health care resources (active medical cancer treatment, other medical treatment related to cancer, clinical visits, inpatient stay, radiation therapy, radiological imaging, laboratory tests and blood transfusions). The reason for ending the sunitinib treatment was to be recorded at the time when the final decision was made. The collected data were entered into a digital database.

The use of health care resources was valued mainly by using the average Finnish health care unit costs (24). If these costs were not available, unit costs (Helsinki University Central Hospital price tables) were used. The unit costs were converted to the 2014 value using the price index for public healthcare expenditures (24). The medical treatment costs based on the patients' individual dose were calculated with retail prices without taxes. The costs of medical treatment given in the hospital were calculated with wholesale prices without value-added tax. A national price catalogue was used as a source of single drug costs.

Results

In total, 81 patients were included in the analysis. The mean age of patients was 66.1 years (range=41.1-85.7 years), 55 were male and 26 were female (68% *vs.* 32%, respectively). Nephrectomy had been performed on 58 patients (72%). At the end of the follow-up, over half of the patients had died (n=47, 58%).

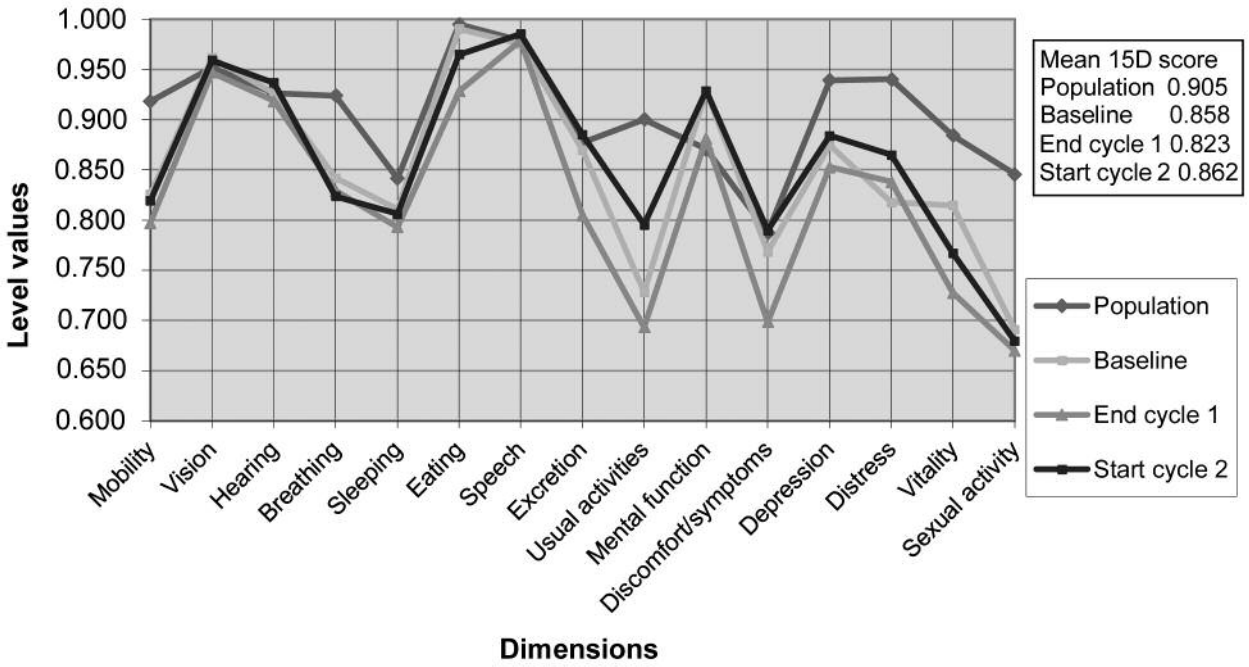


Figure 2. *The mean 15D profiles and scores of the patients and those of an age- and gender-standardized sample of the general population.*

Table I. *All the costs during first-line sunitinib treatment (N=81).*

Variable	Cost, €	Percentage from the total costs	Cost per patient, mean (range), €
Sunitinib	1,803,714	72.9%	22,268 (274-105,121)
Clinic visits, special health care	164,932	6.7%	2,036 (0-9,795)
Clinic visits, public health care	8,509	0.3%	105 (0-1,429)
Radiotherapy	56,996	2.3%	704 (0-9,421)
Inpatient stay	376,385	15.2%	4,647 (0-46,478)
Imaging	62,358	2.5%	770 (0-5,147)
Total cost	2,472,894	100.0%	30,530 (1,661-11,516)

The six-week treatment cycles included a four-week sunitinib period and a two-week-cycle pause. Treatment discontinuation for a longer period was considered a prolonged pause. For the entire study population (n=81), we received 20,513 follow-up days for sunitinib treatment, including pauses during treatment, with a mean of 253 days/patient (range=3-1,389 days). Sunitinib was given for a total of 12,741 days, with a mean of 157 days/patient (range=3-728 days). Figure 1 describes the doses used combined with the time of use during the treatment period.

The total cost of sunitinib treatment was 1,803,714 € and 88€/treatment day when pauses were also taken into account. The average cost for a sunitinib treatment day was 142 €, and the mean cost per patient was 22,268 € (range=274-105,121 €) for the entire treatment and follow-up period. The most often used dose of sunitinib was 37.5 mg, which represents 42% of all treatment days. The second most common dose used was 50 mg, equivalent to 33% of all treatment days.

At the end of the study, 77 out of 81 patients had discontinued sunitinib treatment. The most common reasons for ending the treatment were disease progression (55%) or side effects (25%). Four patients proceeded with first-line sunitinib treatment at the study endpoint. The drug costs related to adverse effects were not reported.

Concerning the total costs of sunitinib first-line treatment, the expense of the medication itself was significant (73% during the sunitinib treatment period). Costs and their breakdown are presented in Table I. Inpatient stays and

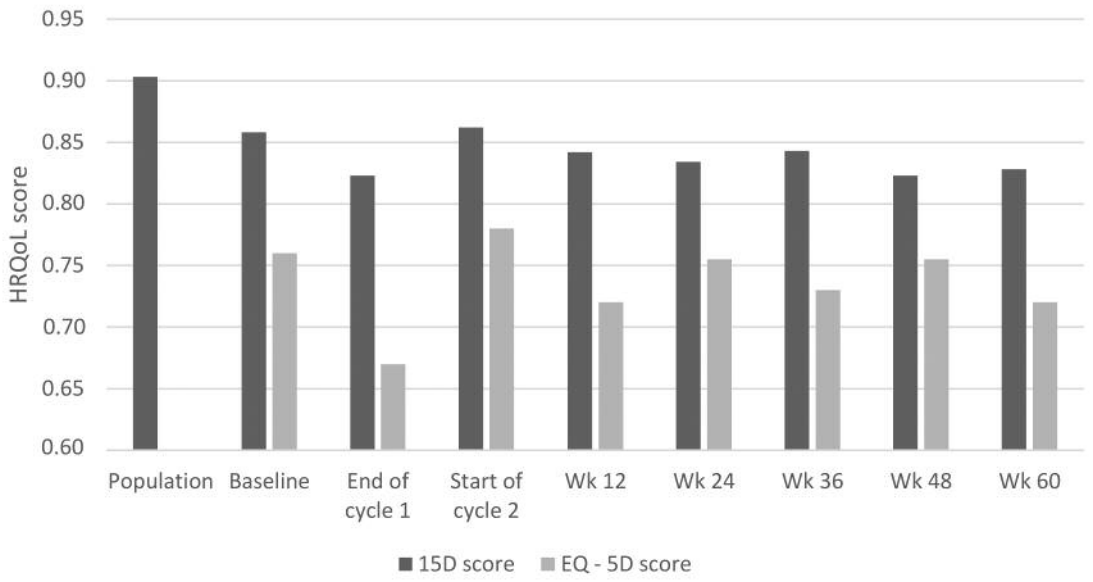


Figure 3. *The mean 15D- and EQ-5D-3L scores at different time points.*

outpatient visits created most of the costs related to the use of other healthcare resources (other than relevant medical treatment) during first-line sunitinib treatment. The cost for individual patients based on these findings was 30,530 € (range=1,661-111,516 €). The average cost per month was 3,617 €.

Approximately 51% of patients who had received first-line sunitinib treatment proceeded with a second-line active treatment. The most common second-line treatment medications were everolimus (27.3%), pazopanib (10.4%) and sorafenib (9%). In general, active treatment was discontinued after the third- or fourth-line medication, yet some patients received up to seven lines of treatment. The mean drug costs for treatment lines 2, 3, 4, 5, 6 and 7 were 19,794 €, 20,429 €, 59,106 €, 11,706 €, 2,923 € and 18,696 €, respectively.

At the beginning of treatment, the average 15D-score of patients was lower than that of the age- and gender-standardized general population (0.858 *vs*. 0.903). The difference was statistically significant and clinically important. The patients were significantly worse off, especially on the dimensions of mobility, breathing, daily activities, mental functions, depression, anxiety, vitality and sexual activity (Figure 2). The mean 15D-score declined 0.035 from the beginning to 28 days of sunitinib treatment, and the score returned to its original level during the two weeks of medication pause. In some cases, the 15D-score during the pause was even higher than at the beginning of the treatment.

At the beginning of treatment, the average EQ-5D-3L-score was 0.755. It declined by 0.080 following 28 days sunitinib treatment. It also returned to its original level during the two-week break and, in some cases, to an even higher level (0.781). All of these changes in the quality of life parameters were statistically and clinically significant. During the second treatment period, the EQ-5D-3L-score declined in a statistically significant way, yet the difference was no longer clinically significant. In all the later measurements from both instruments, there were no statistically or clinically significant differences in the HRQoL of those patients continuing on sunitinib treatment (Figure 3).

Discussion

The majority of the costs (73%) for treating mRCC patients during first-line sunitinib, came from the medication itself. This finding is similar to our earlier study concerning mRCC treatment with IFN (25). It is also in line with other results in the literature: cancer-specific targeted therapy itself is the largest expense in contemporary cancer treatment, especially in the first-line treatment of many metastatic diseases.

According to our research, most patients received second-line treatment, but treatment proceedings after that were less common. In total, six complete responses were recorded, and the average overall survival from the start of the first-line sunitinib treatment was two year. These results are also similar to findings in the literature (17-19, 26). In most patients, treatment was discontinued because of disease progression, which is very typical of metastatic cancer. The general treatment doses and protocols were performed

according to international guidelines (15, 16). The overall HRQoL in our patients was already lower than that in the age- and gender-standardized general population, yet it remained stable during treatment cycles. Similar results have been observed in other RCC trials (27).

According to the latest cost-effective analysis in mRCC, life expectancy of patients receiving nivolumab plus ipilumab was 3.99 life years, which was 1.27 life-years more than that of intermediate- or poor-risk patients receiving sunitinib as first-line treatment. The cost per additional QALY gained was USD108,363 (28). As discussed earlier, the drug itself remains the largest cost driver in the treatment of mRCC. Sunitinib seems to be a much less expensive treatment option than nivolumab plus ipilumab. However, sunitinib does not offer a survival gain in intermediate- or poor-risk patients, so to reach cost-effectiveness, sunitinib should be directed to good-risk patients. According to recent guidelines, this seems to be the case (28-30). When comparing previously mentioned treatments, the adverse effects and drug administration should also be taken into account.

Conflicts of Interest

Vuorinen, Reunamo, Jekunen and Kataja have no conflicts of interest. Sintonen is the developer of the 15D and one of the developers of the EQ-5D-3L. Paunu has received conference support from Amgen, Bayer, Merck, Roche, Servier, BMS, Lilly, Pfizer and Novartis. Turpeenniemi-Hujanen has attended domestic congress (MSD). Purmonen is currently employed by Novartis Finland Oy. Kellokumpu-Lehtinen has received expert report fee from Bristol-Myers Squibb and conference support from Sanofi.

Authors' Contributions

Vuorinen has taken part in designing the study, gathering data, analyzing the data, and is the main author of the article. Paunu, Turpeenniemi-Hujanen, Reunamo Jekunen, Kataja, Sintonen, Purmonen, have taken part in designing the study, collecting the data, interpretation of the data and critically reviewing the manuscript. Kellokumpu-Lehtinen is the principle investigator.

Acknowledgements

The study was supported by Pfizer Finland and by Grants from the Research, Development and Innovation Center of Tampere University hospital (9UO020 and 9V017).

References

1 WHO, International Agency for Research on Cancer, Cancer Today. Available at: gco.iarc.fr/today/online-analysis-table?v=2018&mode=cancer&mode_population=continents&population=900&populations=900&key=asr&sex=0&cancer=39&type=0&statistic=5&prevalence=0&population_group=0&ages_group%5B%5D=0&ages_group%5B%5D=17&nb_items=5&group_cancer=1&include_nmsc=1&include_nmsc_other=1 (Last accessed June 18th 2019)

2 Rini BI, Campbell SC and Escudier B: Renal cell carcinoma. Lancet *373*: 1119-1132, 2009. PMID: 19269025. DOI: 10.1016/S0140-6736(09)60229-4

3 Sunela KL, Kataja MJ, Lehtinen ET, Salminen TK, Kujala PM, Virman JP and Kellokumpu-Lehtinen PL: Prognostic factors and long-term survival in renal cell cancer patients. Scand J Urol Nephrol *43*: 454-460, 2009. PMID: 19968581. DOI: 10.3109/00365590903286697

4 Sunela KL, Lehtinen ET, Kataja MJ, Kujala PM, Soimakallio S and Kellokumpu-Lehtinen PL: Development of renal cell carcinoma (RCC) diagnostics and impact on prognosis. BJU Int *113*: 228-235, 2014. PMID: 23890347. DOI: 10.1111/bju.12242

5 Motzer RJ, Bander NH and Nanus DM: Renal-cell carcinoma. N Engl J Med *335(12)*: 865-875, 1996. PMID: 8778606. DOI: 10.1056/NEJM199609193351207

6 Abe H and Kamai T: Recent advances in the treatment of metastatic renal cell carcinoma. Int J Urol *20*: 944-955, 2013. PMID: 23692504. DOI: 10.1111/iju.12187

7 Fisher RI, Rosenberg SA and Fyfe G: Long-term survival update for high-dose recombinant interleukin-2 in patients with renal cell carcinoma. Cancer J Sci Am *6*: S55-57, 2000. PMID: 10685660.

8 Kellokumpu-Lehtinen PL and Nordman E: Recombinant interferon-alpha 2a and vinblastine in advanced renal cell cancer: a clinical phase I-II study. J Biol Response Mod *9(4)*: 439-444, 1990. PMID: 2395008.

9 Pyrhönen S, Salminen E, Ruutu M, Lehtonen T, Nurmi M, Tammela T, Juusela H, Rintala E, Hietanen P and Kellokumpu-Lehtinen PL: Prospective randomized trial of interferon alfa-2a plus vinblastine *versus* vinblastine alone in patients with advanced renal cell cancer. J Clin Oncol *17(9)*: 2859-2867, 1999. PMID: 10561363. DOI: 10.1200/JCO.1999.17.9.2859

10 Funakoshi T, Lee CH and Hsieh J: A systematic review of predictive and prognostic biomarkers for VEGF-targeted therapy in renal cell carcinoma. Cancer Treat Rev *40*: 533-547, 2014. PMID: 24398141. DOI: 10.1016/j.ctrv.2013.11.008

11 Nickerson ML, Jaeger E, Shi Y, Durocher JA, Mahurkar S, Zaridze D, Matveev V, Janout V, Kollarova H, Bencko V, Navratilova M, Szeszenia-Dabrowska N, Mates D, Mukeria A, Holcatova I, Schmidt LS, Toro JR, Karami S, Hung R, Gerard GF, Linehan WM, Merino M, Zbar B, Boffetta P, Brennan P, Rothman N, Chow WH, Waldman FM and Moore LE: Improved identification of von Hippel-Lindau gene alterations in clear cell renal tumors. Clin Cancer Res *14(15)*: 4726-4734, 2008. PMID: 18676741. DOI: 10.1158/1078-0432.CCR-07-4921

12 DePrimo S, Bello CL, Smeraglia J, Baum CM, Spinella D, Rini BI, Michaelson MD and Motzer RJ: Circulating protein biomarkers of pharmacodynamic activity of sunitinib in patients with metastatic renal cell carcinoma: modulation of VEGF and VEGF-related proteins. J Translat Med *5*: 32, 2007. PMID: 17605814. DOI: 10.1186/1479-5876-5-32

13 Motzer RJ, Escudier B, McDermott DF, George S, Hammers HJ, Srinivas S, Tykodi SS, Sosman JA, Procopio G, Plimack ER, Castellano D, Choueiri TK, Gurney H, Donskov F, Bono P, Wagstaff J, Gauler TC, Ueda T, Tomita Y, Schutz FA, Kollmannsberger C, Larkin J, Ravaud A, Simon JS, Xu LA, Waxman IM, Sharma P and CheckMate 025 Investigators: Nivolumab *versus* everolimus in advanced renal-cell carcinoma. N Engl J Med *373(19)*: 1803-1813, 2015. PMID: 26406148. DOI: 10.1056/NEJMoa1510665

14 Motzer RJ, Tannir NM, McDermott DF, Frontera OA, Melichar B, Choueiri TK, Plimack ER, Barthélémy P, Porta C, George S, Powles T, Donskov F, Neiman V, Kollmannsberger CK, Salman P, Gurney H, Hawkins R, Ravaud A, Grimm M-O, Bracarda S, Barrios CH, Tomita Y, Castellano D, Rini BI, Chen AC, Mekan S, McHenry MB, Wind-Rotolo M, Doan J, Sharma P, Hammers HJ, Escudier B and CheckMate 214 Investigators: Nivolumab plus ipilimumab *versus* sunitinib in advanced renal-cell carcinoma. NEJM *378(14)*: 1277-1290, 2018. PMID: 29562145. DOI: 10.1056/NEJMoa1712126

15 Escudier B, Porta C, Schmidinger M Rioux-Leclercq N, Khoo V, Grünwald V, Gillessen S and Horwich A: Renal cell carcinoma: ESMO clinical practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol *30*: 706-720, 2019. PMID: 30788497. DOI: 10.1093/annonc/mdz056

16 Choueiri TK and Motzer RJ: Systemic therapy for metastatic renal-cell carcinoma. N Engl J Med *376(4)*: 354-366, 2017. PMID: 28121507. DOI: 10.1056/NEJMra1601333

17 Motzer RJ, Penkov K, Haanen J, Rini B, Albiges L, Campbell MT, Venugopal B, Kollmannsberger C, Negrier S, Uemura M, Lee JL, Vasiliev A, Miller WH Jr, Gurney H, Schmidinger M, Larkin J, Atkins MB, Bedke J, Alekseev B, Wang J, Mariani M, Robbins PB, Chudnovsky A, Fowst C, Hariharan S, Huang B, di Pietro A and Choueiri TK: Avelumab plus axitinib *versus* sunitinib for advanced renal-cell carcinoma. N Engl J Med *380(12)*: 1103-1115, 2019. PMID: 30779531. DOI: 10.1056/NEJMoa1816047

18 Motzer RJ, Hutson TE, Cella D, Reeves J, Hawkins R, Guo J, Nathan P, Staehler M, de Souza P, Merchan JR, Boleti E, Fife K, Jin J, Jones R, Uemura H, De Giorgi U, Harmenberg U, Wang J, Sternberg CN, Deen K, McCann L, Hackshaw MD, Crescenzo R, Pandite LN and Choueiri TK: Pazopanib *versus* sunitinib in metastatic renal-cell carcinoma. N Engl J Med *369(8)*: 722-731, 2013. PMID: 23964934. DOI: 10.1056/NEJMoa1303989

19 Motzer RJ, Barrios CH, Kim TM, Falcon S, Cosgriff T, Harker WG, Srimuninnimit V, Pittman K, Sabbatini R, Rha SY, Flaig TW, Page R, Bavbek S, Beck JT, Patel P, Cheung FY, Yadav S, Schiff EM, Wang X, Niolat J, Sellami D, Anak O and Knox JJ: Phase II randomized trial comparing sequential first-line everolimus and second-line sunitinib *versus* first-line sunitinib and second-line everolimus in patients with metastatic renal cell carcinoma. J Clin Oncol *32*: 2765-2772, 2015. PMID: 25049330. DOI: 10.1200/JCO.2013.54.6911

20 Auvray M, Auclin E, Barthelemy P, Bono P, Kellokumpu-Lehtinen PL, Gross-Goupil M, De Velasco G, Powles T, Mouillet G, Vano YA, Gravis G, Mourey L, Priou F, Rolland F, Escudier B and Albiges L: Second-line targeted therapies after nivolumab-ipilimumab failure in metastatic renal cell carcinoma. Eur J Cancer *108*: 33-40, 2019. PMID: 30616146. DOI: 10.1016/j.ejca.2018.11.031

21 The 15D© health-related quality of life (HRQoL) instrument home page. Available at: http://www.15d-instrument.net/15D. (Last accessed June 30th 2019).

22 van Reenen M and Oppe M: EQ-5D-3L user guide. Version 5.1, 2015.

23 Koskinen S, Lundqvist A and Ristiluoma N: Terveys, toimintakyky ja hyvinvointi Suomessa 2011. Available at http://urn.fi/URN:ISBN:978-952-245-769-1.

24 Kapiainen S, Väisänen A and Haula T: Terveyden- ja sosiaalihuollon yksikkökustannukset Suomessa vuonna 2011. Available at http://urn.fi/URN:ISBN:978-952-302-079-5.

25 Purmonen T, Nuttunen P, Vuorinen R, Pyrhönen S, Kataja V and Kellokumpu-Lehtinen P: Current and predicted costs of metastatic renal cell carcinoma in Finland. Acta Oncologica *49(6)*: 837-843, 2010. PMID: 20331406. DOI: 10.3109/02841861003660049

26 Hanna N, Sun M, Meyer CP, Nguyen PL, Pal SK, Chang SL, de Velasco G, Trinh QD and Choueiri TK: Survival analyses of patients with metastatic renal cancer treated with targeted therapy with or without cytoreductive nephrectomy: a national cancer data base study. J Clin Oncol *34(27)*: 3267-3275, 2016. PMID: 27325852. DOI: 10.1200/JCO.2016.66.7931

27 Cella D, Escudier B, Tannir NM, Powles T, Donskov F, Peltola K, Schmidinger M, Heng DYC, Mainwaring PN, Hammers HJ, Lee JL, Roth BJ, Marteau F, Williams P, Baer J, Mangeshkar M, Scheffold C, Hutson TE, Pal S, Motzer RJ and Choueiri TK: Quality of life outcomes for cabozantinib *versus* everolimus in patients with metastatic renal cell carcinoma: METEOR Phase III Randomized Trial. J Clin Oncol *36(8)*: 757-764, 2018. PMID: 29377755. DOI: 10.1200/JCO.2017.75.2170

28 Wan X, Zhang Y, Tan C, Zeng X and Peng L: First-line nivolumab plus ipilimumab vs sunitinib for metastatic renal cell carcinoma. a cost-effectiveness analysis. JAMA Oncol *5(4)*: 491-496, 2019. PMID: 30789633. DOI: 10.1001/jamaoncol. 2018.7086

29 Ljungberg B, Albiges L, Abu-Ghanem Y, Bensalah K, Dabestani S, Fernández-Pello S, Giles RH, Hofmann F, Hora M, Kuczyk MA, Kuusk T, Lam TB, Marconi L, Merseburger AS, Powles T, Staehler M, Tahbaz R, Volpe A and Bex A: European association of Urology Guidelines on Renal Cell Carcinoma: The 2019 Update. Eur Urol *75(5)*: 311-315, 2018. PMID: 30803729. DOI: 10.1016/j.eururo.2019.02.011

30 NCCN Clinical Practice guidelines in Oncology: Kidney Cancer. Available at: https://www.nccn.org/patients/guidelines/kidney/index.html (Last accessed June 8th 2019)

Received August 24, 2019
Revised September 3, 2019
Accepted September 10, 2019