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Editorial Board Member of *World Journal of Clinical Oncology*, Mehmet Yildirim, MD, PhD, Professor, Department of Surgery, University of Health Sciences, Izmir Bozyaka Education and Research Hospital, Izmir 35900, Turkey. mehmetyildi@gmail.com

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REVIEW

Modulation of the immune response by heterogeneous monocytes and dendritic cells in lung cancer

Iwona Kwiecień, Elżbieta Rutkowska, Agata Raniszewska, Piotr Rzepecki, Joanna Domagała-Kulawik

ORCID number: Iwona Kwiecień 0000-0003-2266-971X; Elżbieta Rutkowska 0000-0002-9727-2576; Agata Raniszewska 0000-0003-3917-6030; Piotr Rzepecki 0000-0003-0694-390X; Joanna Domagała-Kulawik 0000-0002-2260-3676.

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Iwona Kwiecień, Elżbieta Rutkowska, Agata Raniszewska, Department of Internal Medicine and Hematology, Laboratory of Hematology and Flow Cytometry, Military Institute of Medicine, Warsaw 04-141, Poland

Piotr Rzepecki, Department of Internal Medicine and Hematology, Military Institute of Medicine, Warsaw 04-141, Poland

Joanna Domagała-Kulawik, Department of Internal Medicine, Pulmonary Diseases and Allergy, Medical University of Warsaw, Warsaw 02-091, Poland

Corresponding author: Iwona Kwiecień, MSc, PhD, Research Scientist, Department of Internal Medicine and Hematology, Laboratory of Hematology and Flow Cytometry, Military Institute of Medicine, Szaserów 128 Street, Warsaw 04-141, Poland. ikwiecien@wim.mil.pl

Abstract

Different subpopulations of monocytes and dendritic cells (DCs) may have a key impact on the modulation of the immune response in malignancy. In this review, we summarize the monocyte and DCs heterogeneity and their function in the context of modulating the immune response in cancer. Subgroups of monocytes may play opposing roles in cancer, depending on the tumour growth and progression as well as the type of cancer. Monocytes can have pro-tumour and anti-tumour functions and can also differentiate into monocyte-derived DCs (moDCs). MoDCs have a similar antigen presentation ability as classical DCs, including cross-priming, a process by which DCs activate CD8 T-cells by cross-presenting exogenous antigens. DCs play a critical role in generating anti-tumour CD8 T-cell immunity. DCs have plastic characteristics and show distinct phenotypes depending on their mature state and depending on the influence of the tumour microenvironment. MoDCs and other DC subsets have been attracting increased interest owing to their possible beneficial effects in cancer immunotherapy. This review also highlights key strategies deploying specific DC subpopulations in combination with other therapies to enhance the anti-tumour response and summarizes the latest ongoing and completed clinical trials using DCs in lung cancer.

Key Words: Lung cancer; Dendritic cell; Monocyte; Tumour microenvironment; Cancer immunotherapy; Dendritic-cell vaccination

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Core Tip: Monocytes and dendritic cells (DCs) as heterogeneous subpopulations may play a key role in the modulation of the immune response in malignant tumours. Monocytes may have a pro- and anti-tumour function and may differentiate into monocyte-derived DC. DCs have the properties of antigen presenting cells. These cells show a different phenotype depending on their maturity and on the influence of the tumour microenvironment. The DCs are of growing interest for their possible beneficial effects in lung cancer immunotherapy. This review highlights specific DC subpopulations in the anti-tumour response and summarizes the latest ongoing DC clinical trials in lung cancer.

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INTRODUCTION

Lung cancer is responsible for approximately 1.8 million deaths annually worldwide and is now one of the most common cancers and the leading cause of cancer mortality [1,2]. The prognosis for lung cancer remains poor despite advances in treatment strategies including immunotherapy with immune check inhibitors (ICIs)[3,4]. Further investigation of tumour immunology and the different cells subpopulations influencing the anti-tumour immune response could enable the development of novel immunomodulatory strategies such as targeted monoclonal antibodies against specific cell receptors.

The results of research on lung cancer show that cells of the same type can have both pro-cancer and anti-cancer properties. Tumour heterogeneity drives a diverse and plastic spectrum of various subpopulations of non-cancer cells. In this review, we focus on assessing different subpopulations of monocytes and dendritic cells (DCs) that may have a key impact on the modulation of immune response in lung cancer.

The role of macrophages, mainly of tumour associated macrophages (TAM) is well recognized. However, the place of monocytes in the anticancer immune response is not fully understoood. We previously presented the results of investigation of macrophages in the direct lung cancer milieu[5] and preliminary studies on monocytes maturation in lung cancer[6]. Monocytes have both pro-inflammatory and anti-inflammatory properties. A phenotype of monocytes can be divided into classical (pro-inflammatory) and non-classical (anti-inflammatory). Both monocyte subpopulations have been detected among the peripheral blood (PB) mononuclear cells and may differentiate into macrophages. Studies demonstrate that monocytes are capable of both inhibition and stimulation of tumour growth[7]. Previous research on monocytes shows that their function in different cancer microenvironments may vary[8,9].

DCs form another heterogeneous population with the most efficient function of antigen presenting cells (APCs)[10]. They take up antigens and pathogens, generate major histocompatibility complex (MHC) peptide complexes, migrate from antigen acquisition sites to secondary lymphoid organs and finally interact with T lymphocytes. DCs infiltrate a tumour, next they process it and then they present tumour-derived antigens to naïve T-cells. DCs play a critical role in priming anti-tumour T-cell immunity and thereby represent a possible therapeutic target for cancer immunotherapy[11].

Moreover, various cell types and factors within the tumour microenvironment (TME) can act on monocytes and DCs, control their differentiation, and affect their biology, function and longevity. The local TME can also influence the activation and the direction of maturation of monocytes and DCs. Specific local microenvironmental factors may influence the formation of monocytes and DCs with tolerogenic or immunosuppressive activity and conversely, specific subpopulations of these cells can stimulate and inhibit the anti-tumour response.

In this review, we summarize the ongoing investigations on monocyte and DCs heterogeneity and function in the context of modulation of the immune response in lung cancer and highlight key strategies using specific monocyte subpopulations and

DCs to improve cancer therapies.

We discuss the heterogeneity of monocytes, their relationship with DCs and the potential of monocyte-derived DCs (moDCs) in the design of vaccines against lung cancer.

HETEROGENEITY OF MONOCYTES

Monocytes are mononuclear immune cells that circulate in PB and direct to tissues at a steady state and at an increased rate during inflammation. Apart from their key role in supporting tissue homeostasis and promoting the immune response to pathogens monocytes take part as regulators of cancer development and progression[12]. As a heterogeneous population, monocytes play opposing roles in inhibiting and stimulating tumour growth and metastases. Monocytes are also precursors of TAM and DCs which are involved in shaping the TME[13]. Monocyte subpopulations perform functions that are involved in both pro- and anti-tumour immunity, including promoting angiogenesis, tumour mediators secretion, phagocytosis, remodelling of the extracellular matrix, influencing lymphocytes, and differentiating into TAM and DCs [14]. Human monocytes express the MHC-II receptor Human Leukocyte Antigen–DR isotype (HLA-DR), integrin αM (CD11b) and CD86. Recent studies demonstrate that monocytes can be divided into three subsets based on the specific surface markers[15, 16]. They develop from the lineage-associated bone marrow (BM) precursor, a common monocyte progenitor (cMoP)[17]. cMoPs are monocyte progenitors that express stem cell marker CD117, C-type lectin CLEC12A, CD64 and CD135, a cytokine receptor and an early hematopoietic marker. cMoP may differentiate into classical monocytes and then convert to non-classical monocytes in the blood, with intermediate monocytes at a transition state[18,19].

These cells perform specific functions: Classical (approximately 85%), intermediate (approximately 5%) and non-classical (approximately 10% of the monocyte population), which are characterized by the degree of CD14 and the expression of CD16[20,21]. There are three types of monocytes in PB: Classical monocytes with high the expression of CD14 cell surface receptor and no CD16 expression (CD14++ CD16-), non-classical monocytes with the low/negative level of CD14 expression and the co-expression of CD16 receptor (CD14- CD16++) and intermediate monocytes with the expression of CD14 and the expression of CD16 (CD14+ CD16+)[22,23]. The majority of non-classical monocytes appears to be derived from classical monocytes. However, the current studies show that there may be a limited progenitor lineage capable of differentiating into non-classical monocytes without classical monocyte origin[19,24, 25]. After differentiation, classical monocytes exit the BM using C-C chemokine receptor type 2 (CCR2) and next migrate into tissues and lymph nodes by l-selectin (CD62L)[26,27]. Monocyte maturation and a scheme of monocyte subpopulations are presented in Figure 1. Classical monocytes and nonclassical monocytes have a different half-life in the circulation: For classical monocytes it is less than 1 d and for nonclassical monocytes it is 7 d[28]. The mechanisms involved in the recruitment of tissue-specific monocytes remain unclear, possibly they depend on the environmental and tissue availability during both homeostasis and inflammation. However, it is known that classical monocytes are more quickly targeted at the site of inflammation and are able to attract other immune cells by secreting cytokines[26,29]. Non-classical monocytes remain in a state of homeostasis mainly in the vascular system and are likely to be able to exit vessels at a slower rate than classical monocytes during inflammation. They are likely to shift into alternative TAMs and exhibit anti-inflammatory properties[28,30].

Different subgroups of monocytes may play various roles in cancer, depending on the tumour growth and progression, differences in the type of cancer, and depending on the influence of TME[14]. Both classical and non-classical monocytes can have pro-tumour and anti-tumour functions. The protumoural phenotype properties consist of: Differentiation into pro-tumoural TAMs, metastatic cell seeding, the suppression of T-cell function, the recruitment of T regulatory cells (Tregs), the promotion of angiogenesis and contribution to extracellular matrix remodelling (ECM)[31,32]. Classical monocytes exit the vasculature to the primary tumour sites using CC-chemokine ligand 2 (CCL2). They produce carcinogenic mediators and are reprogrammed in the TME to limit their cytotoxicity[32]. Then, they differentiate into TAMs or moDCs in the tumour. TAMs are involved in promoting immunosuppression by inhibiting the activity of CD8 T-cells and in stimulating the formation of Tregs[33]. Moreover, they participate in remodelling of ECM and promote angiogenesis[34].

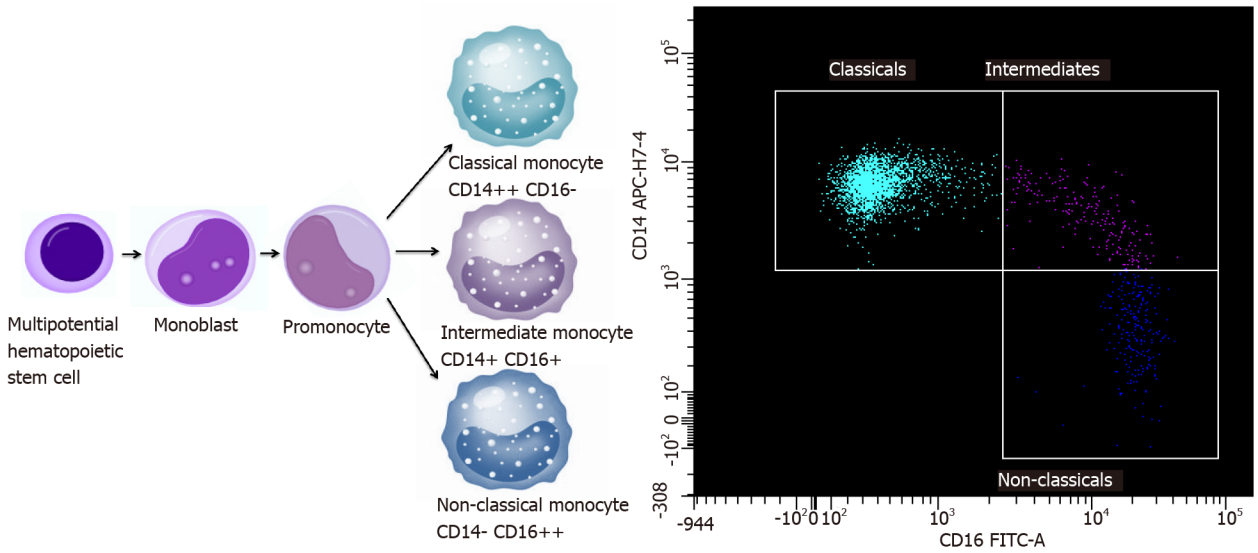

Figure 1 Monocyte maturation and subpopulations scheme. An example of identification of these cells by flow cytometry.

They have a similar protumoural effect at the metastatic sitesand are capable of promoting the spread of metastases. The number of protumoural signals at the tumour site and metastatic sites leads to the predominance of the anti-tumour response from the host's immune system. On the other hand, monocytes have a number of antitumoural functions such as: Antigen presentation, tumour cytotoxicity, the recruitment of natural killer cells, the inhibition of Tregs, the prevention of metastasis[35].

Long-lived non-classical monocytes are well adapted to the removal of cancer cells and debris. Non-classical monocytes migrate towards the sites of cancer spread where they engulf tumour material and produce cytokines that regulate the anti-tumour immunity[36,37]. This population of monocytes could control metastatic process[37]. The third population is a subset of intermediate monocytes, the function of which is under investigation. However, it is known that the relationship between non-classical and intermediate subsets is close[38,39]. The exact maturation and functional relationship between the individual blood monocyte subpopulations and their tissue distribution profiles have yet to be discovered[40,41]. The results of current research confirm that each subpopulation may play a different role depending on the homeostatic and pathological conditions[16]. Infections, inflammation as well as malignant disease can lead to sudden monopoiesis and the formation of a new subset of monocytes with altered functions[35,42].

Monocytes can differentiate into moDCs. MoDCs have a similar antigen presenting ability as classical DCs, including cross-presentation. Blood monocytes can be a reservoir of DC in response to inflammation[43].

HETEROGENEITY OF DCs

Understanding DCs heterogeneity and their role in modulating the immune response in cancer is critical to the better recognition of cancer's ability to bypass the immune system and, consequently, to the ultimate design of novel therapies aiming at boosting anti-cancer immunity.

The studies conducted in order to gain understanding of the biology of DCs have resulted in the identification of a large number of their populations. The main criterion of division is the origin, which distinguishes DCs on plasmacytoid origin cells (pDCs): CD123+ CD11c- and myeloid origin cells: CD123+ CD11c+, also called conventional (cDCs)[44,45]. Identification of antigens called blood DC antigens: BDCA-2, BDCA-3 and BDCA-4 and BDCA-1 (CD1c) allowed further discrimination of human blood DCs into two major subsets: cDC1 and cDC2: cDC1 expresses CD1c, while cDC2 (cCD141+) is characterized by the expression of BDCA-3 (CD141) and Clec9A. BDCA-2 (CD303) and BDCA-4 (CD304), together with CD123, characterize pDC. Additionally, cDCs can be divided into resident and migrating cells[46,47]. DCs derive from the CD34+ hematopoietic stem cell that produces BM myeloid precursors (MPs) and lymphoid precursors (LPs). MPs develop into monocytes, macrophages, and DC precursor

(MDP) from which they differentiate to monocytes and DC precursors (CDP). CDP are precursors of both cDCs and pDCs[48]. Also, cDCs can differentiate directly from monocytes under the influence of various cytokines[49]. Maturation and DC subpopulations scheme is presented in Figure 2.

PDCs

PDCs usually complete their differentiation in BM during the development process and as completely differentiated cells circulate into PB. They are mainly located in the vicinity of the endothelium from where they can easily circulate to the lymph nodes to reside in the T-cell zone[50]. They express the CD123 antigen and the low levels of major MHC-II, the wide range of costimulatory molecules without the expression of CD11c. Additionally, the presence of pattern recognition receptors such as Toll-like receptors (TLRs) allows them to recognize pathogen-associated molecular patterns (PAMP) derived from various microbes and secrete a large amount of type I interferon (INF), tumor necrosis factor (TNF)-α and interleukin (IL)-6[45,51]. What is more, TLR-mediated pDC activation promotes efficient antigen presentation and stimulation of T lymphocytes to the immunological response, but in a less effective manner compared to cDCs[51-53]. Nevertheless, pDCs have also been shown to stimulate Tregs for the production of IL-10, suggesting that this subgroup may also play an immunosuppressive role[54].

CDCs

On the contrary, cDC precursors emerge from the BM transiently transported through the blood and accumulate as cDC pool in tissues[55]. CDCs, also defined as myeloid DCs, expressing CD11c, refer to all DC subsets other than pDC[56]. cCD1c and cCD141 cells belong to the migrating subset of DCs, while epidermal Langerhans cells and interstitial cells are residual cDCs.

CD1c DC subpopulation is the main population of cDCs detected in blood and tissues and lymphatic organs. CD1c cells are identified by major markers CD1c, CD11c, MHC-II (HLA-DR), CD141 and also express other antigens as: CD13, CD33, CD172 and CD45RO. However, they can show a slightly different phenotype, which depends on the place they occur. CD1c+ DCs present in the skin have additional CD1a expression, whereas those present in the gut express CD103[53]. DCs heterogeneity results not only from phenotypic differences but also from the maturity stage. Immature DCs (iDC) are usually found in peripheral tissue, then migrating to the lymph nodes carrying their own antigens, maintaining immune tolerance on their own tissues. They are characterized by increased endocytosis, a decreased expression of MHC and costimulatory molecules and a low ability to produce cytokines[57]. After the antigen is absorbed, the cells begin to mature and change phenotypically and functionally. A peptide complex is formed and an MHC molecule is transported to the cell surface[58]. Maturing DCs migrate to the lymph nodes, increase the expression of MHC-peptide complex, up-regulate the costimulatory molecules and the production of cytokines essential for the T lymphocyte response[55,59]. DCs are considered to be the most important APC, activating T-cells and inducing an immune response. Many factors such as an inflammatory process, an immune response in TME, tissue damage or viruses may promote DCs maturation[60,61].

Many studies show a positive correlation of the number of DCs in the tumour area with a significant extension of patients' survival[62,63]. DCs are able to recognize cancer cells and present neoplastic antigens to effector T lymphocytes. This process depends on the state of maturity and the number of DCs and a local immune status [64].

In fact, amount of data confirm that the accumulation of DCs in the tumour area is influenced by the TME, which modulates their maturation and activation. DCs undergo incomplete differentiation and the number of mature cells decreases with the growth of immature cells[65]. Tumour cells secrete suppressor factors such as transforming growth factor β (TGF-β), IL-10 that reduce the expression of cancer antigens and costimulatory molecules on DCs and that convert them into regulatory DCs (DCreg). DCregs occur among the main cells of the immune system responsible for inhibiting of the immune response, which is conducive to the further development and tumour growth[66,67]. DCs in TME can show an increased expression of programmed death ligand (PD-L1), which interacts with PD-1 molecules on the lymphocytes T surface, inducing their apoptosis, causing the immune response to be muted. DCregs also begin to secrete IL-10, thereby stimulating the proliferation of Tregs and their own polarity to DCregs[68]. Therefore, it seems important to investigate the ways to direct DCs for activating the immune system and inducing an anti-tumour response in an attempt to reverse their suppressive effects. It was

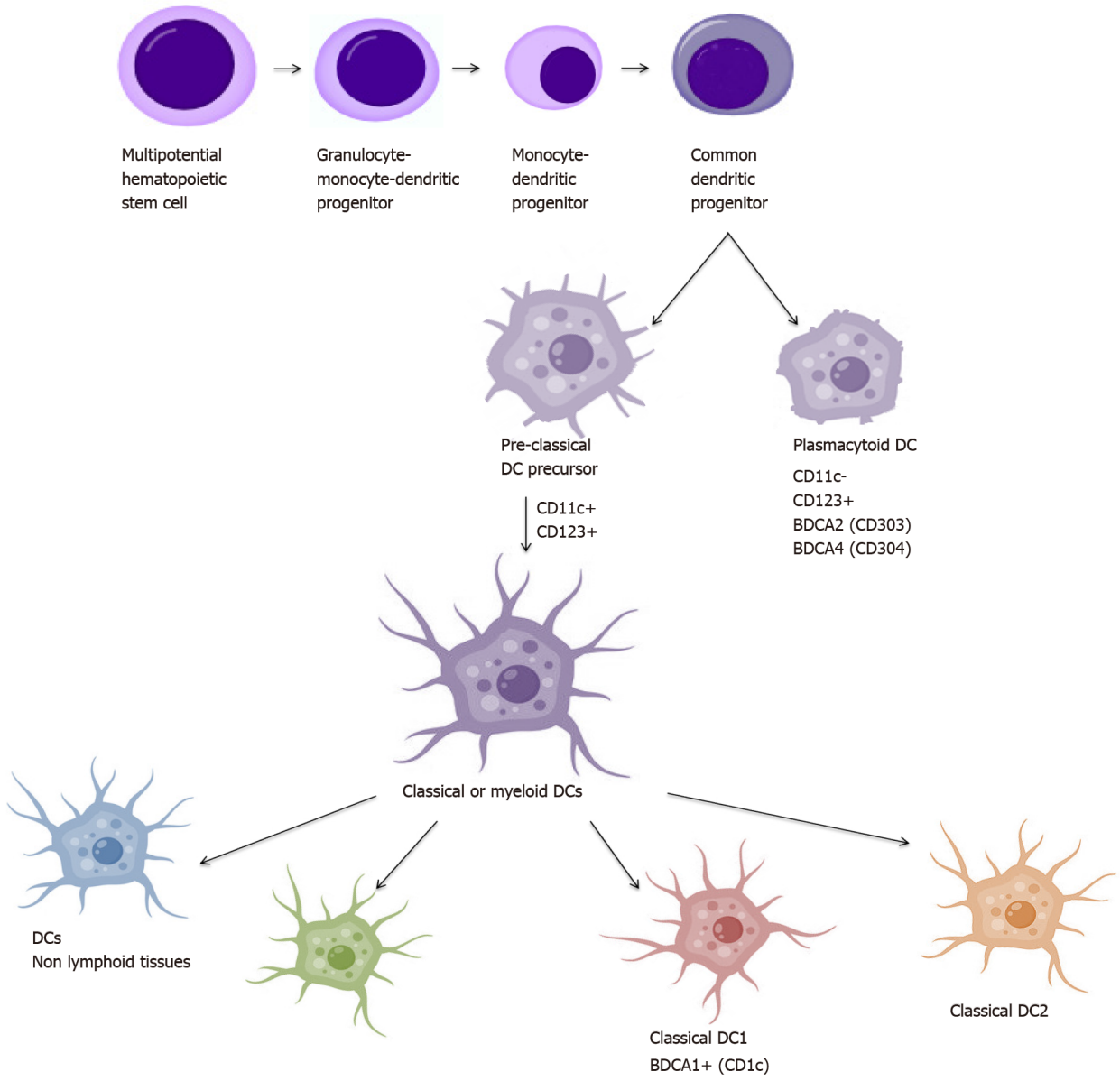

Figure 2 Dendritic cell maturation and subpopulations scheme. DCs: Dendritic cells.

supported by our studies on the identification of DCs in the aspirates from lymph nodes in lung cancer patients. We found an elevated proportion of DCs in metastatic lymph nodes with a high expression of check- point molecules and the phenotype of DCregs.

To sum up, the aforementioned findings confirm the significant participation of DCs in TME. Considering the high heterogeneity of DCs and their plasticity in anti-tumour activity, it seems reasonable to look for a specific subpopulation of these cells.

GENERATION OF moDCs AND APPLICATION IN IMMUNOTHERAPY

Due to the extensive subject matter, we find it valuable to focus on the moDCs population in this review and to discuss DC subpopulation's role in cancer therapy and a possible therapeutic value associated with these populations in lung cancer.

MoDCs arise from monocytes recruited into tissues and become the most abundant DC population during inflammation[69]. In vivo, the maturation of DCs into moDCs is induced by pathogens, tissue damage and cancer antigens. In vitro human moDCs arise from CD14+ monocytes cultured in the presence of granulocyte-macrophage colony-stimulating factor (GM-CSF) and IL-4. This process is triggered *in vitro* by incubation with pathogen recognition receptor agonists or a pro-inflammatory

cytokines cocktail such as: TNF-α, IL-1β, IL-6, IFN-α and prostaglandin E2 (PGE2) or medium conditioned with monocytes with TNF-α and PGE2[70-72]. TLRs or electroporation with coding proteins have recently been used to induce moDCs maturation [73-75].

Human moDCs always express: HLA-DR, CD11c and frequently express CD16, CD14 due to their monocytic origin upon differentiation[76,77]. Maturation scheme of moDCs is presented in Figure 3.

As an APCs, DCs are crucial in the innate and adaptive response of the immune system and play a crucial role in inducing anti-tumour immunity[78]. Mature DCs present exogenous antigens to naive CD4+ T-cells by MHC-II and endogenous peptides to CD8+ T-cells by MHC-I. What is more, they have the ability to cross-present exogenous MHC-I antigens to CD8+ T-cells, which induces a cytotoxic T-cell response against neoplastic cells[79,80]. MoDC cross-presentation plays a key role in the rapid activation of CD8+ memory T-cells residing in the tissues after infection. This process has been found to be active in immunostimulatory anticancer therapies or chemotherapy[81-84].

In order to stimulate T lymphocytes in lymphoid tissues, it requires three signals between DCs and T lymphocytes. Firstly, the antigen is presented by the MHC peptide complex, secondly stimulation by costimulatory molecules from DC to the T-cell occurs. The third one is the secretion of immunostimulating cytokines in the microenvironment[85-87].

Ex vivo produced moDCs are commonly used in clinical trials. Mature antigen loaded moDCs can be easily obtained from PB derived CD14+ monocytes or a hematopoietic stem and progenitor cell CD34+ by treatment with GM-CSF and IL-4 [88,89]. Multiple clinical trials have demonstrated the safety and immunogenicity of moDC vaccines. However, clinical responses have been largely disappointing. Admittedly, studies show that *ex vivo* produced moDCs were able to cross-prime T-cells and produce anti-cancer cytokines such as IL-12[90-92]. MoDCs seemed to be a promising population in anti-cancer therapy. Although, in clinical practice, only in a few groups of treated patients an active anti-cancer response was achieved. This may be due to functional cell deficiencies in conventional vaccines-such as insufficient antigen presentation, impaired migration, and impaired cytokine release, which is insufficient for gaining a strong immunosuppressive TME[88,93,94]. Some studies show that *ex vivo* stimulation of DCs precursors leads to the production of moDCs that are transcriptionally and phenotypically different from their naturally occurring (primary) cells[92,95]. *Ex vivo* derived moDCs have a reduced ability to stimulate T-cells compared to natural moDCs isolated from PB and may have a limited ability to migrate to lymph nodes, contributing to reduced vaccine efficacy[56,96-98]. All the aforementioned findings explain the lack of efficace vaccine in lung cancer.

APPLICATION DCs IN COMBINATION WITH OTHER THERAPIES

Although, moDCs can be produced in large quantities with minimal side effects from therapy, their effectiveness remains limited in cancer therapy[99,100].

Therefore, other ways of using personalized vaccines with DCs are also being considered. Recent studies show their use in combination with other therapies.

Emerging data suggests that combining DCs vaccination with other cancer treatments could fully unlock the potential of DCs cancer vaccines and improve patient survival. With the advent of combination immunotherapy, personalized DCs vaccination could integrate the current standard of care in the treatment of a wide variety of cancers, among them in lung cancer[88].

The first method is to combine vaccination with chemotherapy to obtain a synergistic effect. In addition to immunosuppressive activity, chemotherapy also strengthens immunity by depleting myeloid derived suppressor cells (MDSCs), Tregs and increases the permeability of cancer cells to cytolytic factors derived from CD8+ T lymphocytes[101,102]. Chemotherapy creates a specific cytokine environment by depleting immune cells, and its combination with DC vaccination and adoptive T-cell transfer has been tested in many trials[103-105]. So far, numerous studies are ongoing in which combination chemotherapy and other methods with DCs vaccines are tested. Chemotherapy with DCs vaccination has been tested with the addition of a Cytochrome c oxidase subunit II inhibitor in patients with melanoma in a phase III trial showing encouraging data. Such a therapy with the addition of autologous T-cells showed longer overall survival compared to chemotherapy alone in two randomized trials in lung cancer[106-108].

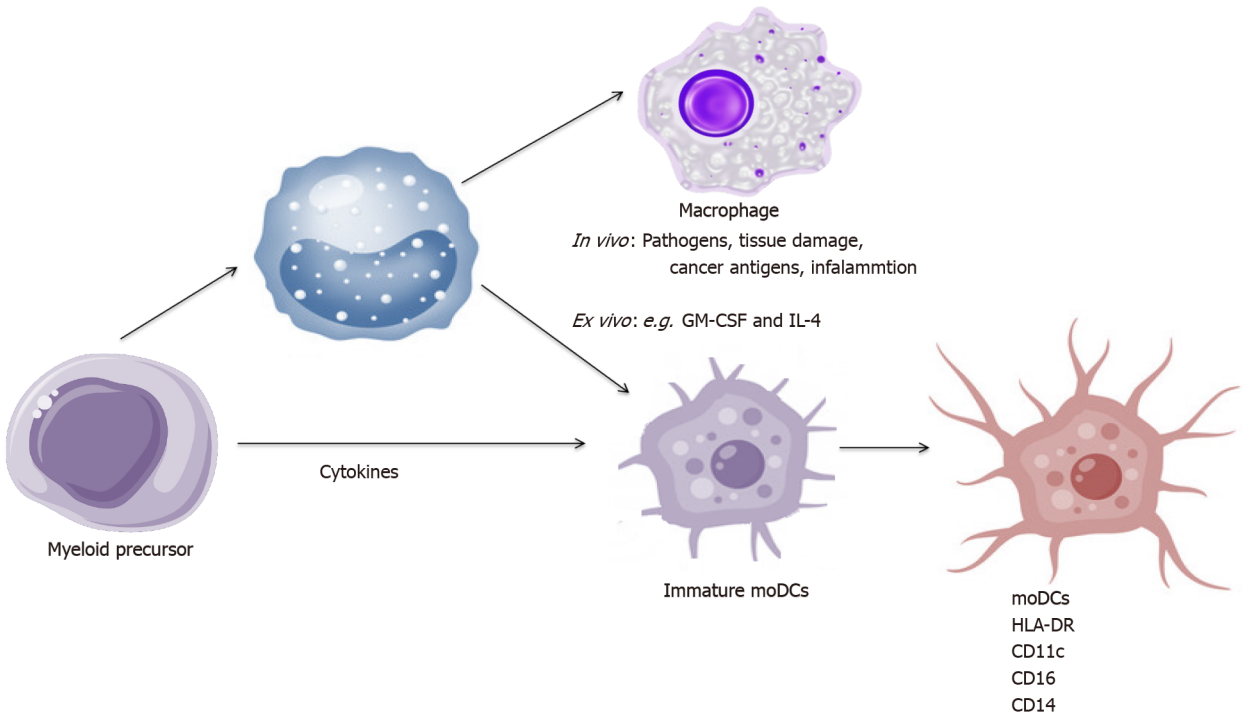

Figure 3 Maturation scheme of monocyte-derived dendritic cells. IL: Interleukin; GM-CSF: Granulocyte-macrophage colony-stimulating factor; DCs: Dendritic cells.

Other treatment method is the combination with immunotherapy. For example, preclinical studies showed that this combination decreased MDSCs in the TME, downregulated the PD-1 expression on DCs, and decreased the secretion of immunosuppressive cytokines[109,110]. One clinical trial in advanced renal cell carcinoma patients showed the expansion of CD8+ T-cells and promising survival data [111].

In general, the combination of DCs vaccines with ICIs seems to be promising. A lot of ICIs are currently being tested in clinical trials; many of them, such as: Anti–PD-L1/PD-1 and anti-*cytotoxic T-cell antigen 4* (CTLA-4) blocking antibodies have been approved by the Food and Drug Administration[112]. The combination of ICIs with the DCs vaccine seems to have the potential to drive T-cell response into a more specific action[113,114]. In addition, DCs unique ability to cross-present antigens helps to elicit the immune response to more cancer antigens when used in conjunction with ICIs[115]. The anti–CTLA-4 treatment after DCs vaccination may indeed enhance DCs vaccine–induced T-cell responses and there is some evidence that anti–CTLA-4 antibodies might be more effective after DCs vaccination[116,117]. Other studies have shown that DC-based immunotherapy in combination with anti–CTLA-4 antibodies seem to be more effective than the use of these agents alone[118,119]. Anti–PD-1 antibodies are being investigated in combination with DC vaccination, which also opens new avenues of anti-tumour therapy design[120]. The aforementioned studies are conducted in various types of cancer, mainly melanoma, pancreatic cancer, prostate cancer, renal cell carcinoma, and acute myeloid leukemia. Immunotherapy with DCs appears to be capable of eliciting strong tumour-specific responses in combination with other therapies, and is workable and safe[121]. In the recent years, the use of naturally circulating DCs (nDCs) instead of cultured moDCs may have represented the next logical step in anti-cancer therapy and had an impact on long-term clinical benefits[83,122,123].

APPLICATION OF DCs IN LUNG CANCER THERAPY

Lung cancer TME is composed of a large number of phenotypically and functionally different types of cells[124]. A major hallmark of immunosuppression in the TME is the inactivation of cytotoxic CD8+ T-cells, which is achieved through diverse pathways[61,125-130]. Immature DCs produce TGF-β, which expands the population of immunosuppressive Tregs, which in turn inhibit CD8+ T-cells. DCs are recruited

Table 1 Clinical trials with dendritic cell vaccine in lung cancer patients on the basis of clinical trials registry

Status	Major trial	Condition	Study intervention	Official trial code
Recruiting	MIDRIXNEO	NSCLC	Dendritic cell immunotherapy	NCT04078269 [132]
Recruiting	MIDRIX4-LUNG	Metastatic NSCLC	Dendritic cell immunotherapy	NCT04082182 [132]
Completed	Vaccine Therapy in Treating Patients With Stage I, Stage II, or Stage III Non-small Cell Lung Cancer	Lung cancer	Autologous dendritic cell cancer vaccine	NCT00103116 [133,134]
Recruiting	Combination Immunotherapy-Ipilimumab-Nivolumab-Dendritic Cell p53 Vac-Patients With SCLC	SCLC; Lung cancer; Relapsed	Combination immunotherapy with Ipilimumab and Nivolumab plus a Dendritic Cell based p53 Vaccine	NCT03406715
Completed	Dendritic Cells in Lung Cancer	NSCLC	Allogeneic Tumour Lysate	NCT00442754
Completed	Chemotherapy Followed By Vaccine Therapy in Treating Patients With Extensive-Stage Small Cell Lung Cancer	Lung cancer	Autologous dendritic cell-adenovirus p53 vaccine combined with Carboplatin and Etoposide	NCT00049218
Completed	Vaccine Therapy in Treating Patients With Stage IIIB, Stage IV, or Recurrent NSCLC	Lung cancer	Autologous dendritic cell-adenovirus CCL21 vaccine	NCT00601094
Completed	CSET 1437	NSCLC	Dendritic cell-derived exosomes	NCT01159288
Completed	Vaccine Therapy in Treating Patients With Stage IIINSCLC	Lung cancer	Mutant p53 peptide pulsed dendritic cell vaccine combined with adjuvant therapy	NCT00019929
Completed	Vaccine Therapy in Treating Patients With NSCLC	Lung cancer	Autologous tumor cell vaccine therapeutic autologous dendritic cells combined with conventional surgery	NCT00023985
Recruiting	AST-VAC2 Vaccine in Patients With NSCLC	NSCLC in the advanced and adjuvant settings	AST-VAC2 Vaccine	NCT03371485
Recruiting	Luscid	NSCLC	Pembrolizumab with or without intratumoral avelumab/ipilimumab plus CD1c (BDCA-1)+/CD141 (BDCA-3) + myeloid dendritic cells	NCT04571632
Completed	To Immunize Patients With Extensive Stage SCLC Combined With Chemo With or Without ATRA	SCLC	Paclitaxel Ad.p53-DC vaccines. ATRA	NCT00617409
Completed	Denileukin Diftitox Followed by Vaccine Therapy in Treating Patients With Metastatic Cancer	Lung cancer; Breast cancer; Colorectal cancer; Pancreatic cancer	Denileukin diftitox recombinant fowlpox-CEA(6D)/TRICOM vaccine therapeutic autologous dendritic cells	NCT00128622
Completed	Biological Therapy in Treating Patients With Metastatic Cancer	Lung cancer; Breast cancer; Colorectal cancer; Extrahepatic Bile Duct cancer; Gallbladder cancer; Gastric cancer; Head and Neck cancer; Liver cancer; Ovarian cancer; Pancreatic cancer	CEA RNA-pulsed DC cancer vaccine	NCT00004604
Completed	Vaccine Therapy and Biological Therapy in Treating Patients With Advanced Cancer	Lung cancer; Breast cancer; Cervical cancer; Colorectal cancer; Ovarian cancer; Pancreatic cancer	Combining DCs vaccine therapy with interleukin-2	NCT00019084

NSCLC: Non small lung cancer; SCLC: Small cell lung cancer; CCL21: Chemokine C-C motif ligand 21; ATRA: All trans retinoic acid.

into the TME and induced to upregulate PD-1 and PD-L1 in order to directly suppress CD8+ T-cells. Interactions of PD-1 with PD-L1 in the TME blocks responsiveness to danger signals and prevents T-cell activation. T-cells are preferentially drawn to tumour induced DCs as they enter the TME. In addition to the lack of appropriate activating signals, T-cell response is blocked by the engagement of PD-1 by PD-L1 on the DC surface[61]. Tregs are also recruited by the tumour induced DCs to establish a tolerogenic environment[124]. TME's effect on DCs infiltrating the lung cancer tissue is presented in Figure 4. A preclinical study conducted by Lee *et al*[131]. showed that the administration of DCs transduced with the chemoattractant CCL21 led to the

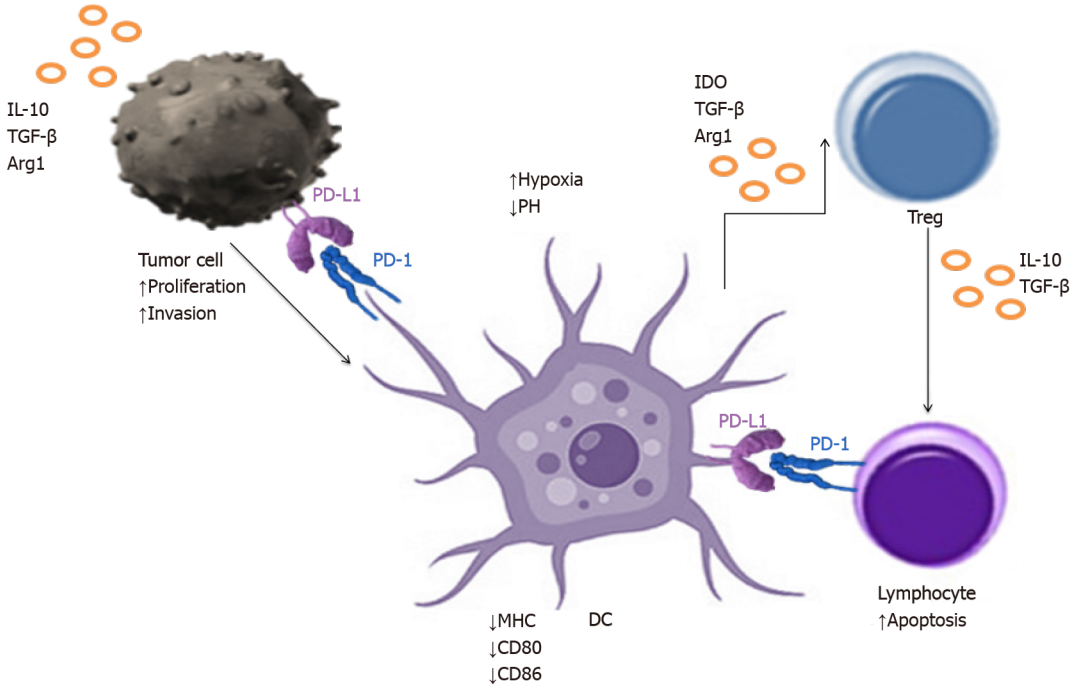

Figure 4 Tumour microenvironment effect on dendritic cells infiltrating the lung cancer tissue. IL: Interleukin; TGF-β: Transforming growth factor β; PD-L1: Programmed death ligand; DCs: Dendritic cells.

increased infiltration of DCs, CD4+ and CD8+ T-cells in the lung TME, resulting in reduced tumour burden[131]. Given that the efficacy of DC vaccines as a monotherapy is limited by immunosuppressive mechanisms in the TME, these results provide a rationale for combining DCs vaccination with immunotherapy. Combinational approach to the lung cancer treatment in order to increase the effectiveness of DCs therapy is an attractive way to promote and stimulate the anti-cancer immunity. As the molecular basis of an effective DCs therapy inducing T-cell response are still incompletely understood, it has been difficult to identify factors associated with therapeutic success. There is also no consensus how DCs vaccination efficacy should be evaluated. However, various clinical trials have been recently conducted to evaluate the immune response and clinical efficacy of DCs in lung cancer and other tumours (Table 1). Unfortunately, it is unknown whether naturally occurring DCs outperform cultured moDCs as a source for DCs therapy in lung cancer patients, because clinical trials comparing different DCs subsets as a source for DCs therapy have not been performed.

CONCLUSION

The heterogeneity of monocytes and DCs has been extensively studied and individual subpopulations of these cells have been well described. As our understanding of monocyte and DCs heterogeneity is growing, their key role as anti-tumour response modulating cells is going to become more useful and targeting the specific subgroups to modulate or stimulate their function is going to become an attractive therapeutic approach. The role of DC in TME is of particular interest in immunological research, but our knowledge is limited, especially in lung cancer. However, the present review emphasizes the role of the DC subpopulation in cancer treatment and a possible therapeutic value associated with these populations in lung cancer. Careful definition of the different subpopulations of DCs and their role in cancer will allow for more accurate targeting of immune cells and a better understanding of their role in modulating the immune response.

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REVIEW

New challenges in the combination of radiotherapy and immunotherapy in non-small cell lung cancer

Javier Luna, Juan Zafra, Mª Carmen Areses Manrique, Aurora Rodríguez, Amalia Sotoca, Jose Luis Fírvida, Rodolfo Chicas-Sett, Xabier Mielgo, Juan Carlos Trujillo Reyes, Felipe Couñago

ORCID number: Javier Luna 0000-0003-2904-8895; Juan Zafra 0000-0003-4778-4271; Mª Carmen Areses Manrique 0000-0003-1827-6323; Aurora Rodríguez 0000-0001-6591-7109; Amalia Sotoca 000-0002-9760-7698; Jose Luis Fírvida 0000-0001-8699-5800; Rodolfo Chicas-Sett 0000-0001-8127-2523; Xabier Mielgo 0000-0002-0985-6150; Juan Carlos Trujillo Reyes 0000-0002-3370-0869; Felipe Couñago 0000-0001-7233-0234.

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Javier Luna, Department of Radiation Oncology, Oncohealth Institute, Fundación Jiménez Díaz, Madrid 28040, Spain

Juan Zafra, Rodolfo Chicas-Sett, Department of Radiation Oncology, Dr. Negrín University Hospital of Gran Canaria, Las Palmas 35010, Spain

Mª Carmen Areses Manrique, Jose Luis Fírvida, Department of Medical Oncology, Ourense University Hospital, Ourense 32005, Spain

Aurora Rodríguez, Amalia Sotoca, Department of Radiation Oncology, Ruber International Hospital, Madrid 28034, Spain

Xabier Mielgo, Department of Medical Oncology, Hospital Universitario Fundación Alcorcón, Alcorcón 28922, Spain

Juan Carlos Trujillo Reyes, Department of Thoracic Surgery, Hospital de la Santa Creu i Sant Pau, Barcelona 08029, Spain

Felipe Couñago, Department of Radiation Oncology, Hospital Universitario QuirónSalud Madrid, Hospital La Luz, Universidad Europea de Madrid, Madrid 28223, Spain

Corresponding author: Javier Luna, PhD, Staff Physician, Department of Radiation Oncology, Oncohealth Institute, Fundación Jiménez Díaz, Reyes Catolicos Avenue No. 2, Madrid 28040, Spain. jluna@fjd.es

Abstract

Immunotherapy has represented one of the main medical revolutions of recent decades, and is currently a consolidated treatment for different types of tumors at different stages and scenarios, and is present in a multitude of clinical trials. One of the diseases in which it is most developed is non-small cell lung cancer. The combination of radiotherapy and immunotherapy in cancer in general and lung cancer in particular currently represents one of the main focuses of basic and clinical research in oncology, due to the synergy of this interaction, which can improve tumor response, resulting in improved survival and disease control. In this review we present the biochemical and molecular basis of the interaction between radiotherapy and immunotherapy. We also present the current clinical status of this interaction in each of the stages and cases of non-small cell lung cancer, with the main results obtained in the different studies both in terms of

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tumor response and survival as well as toxicity. Finally, we mention the main studies underway and the challenges of this interaction in the coming years, including how these treatments should be combined to achieve the greatest efficacy with the fewest possible side effects (dose, type of radiotherapy and drugs, sequence of treatments).

Key Words: Lung cancer; Radiotherapy; Immunotherapy; Main trials

Core Tip: Immunotherapy has revolutionised cancer treatment. Its association with radiotherapy has synergistic effects studied at a preclinical and clinical level, especially in metastatic patients. Currently, clinical research in this field is very prolific, and no doubt, as with the PACIFIC trial in non-small cell lung cancer (NSCLC), we will see further changes in the standard of care in the coming years. This review highlights the most important published work in NSCLC in the field of radio-immunotherapy, listing the clinical trials currently existing in each stage of NSCLC.

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INTRODUCTION

Immunotherapy, especially in the form of immune checkpoint inhibitors (ICI), is becoming a revolution in the understanding and treatment of cancer. Their interaction with radiotherapy (RT) generates synergistic effects that have been thoroughly described in preclinical studies. In the clinical setting, the benefits of combining RT and ICI have been evidenced mostly in metastatic patients. However, this concept has evolved since the publication of the PACIFIC trial, which has modified clinical practice in unresectable stage III non-small-cell lung cancer (NSCLC) by demonstrating a significant benefit derived from the addition of sequential durvalumab to standard definitive chemoradiotherapy (CRT). Research on the association of RT and ICI in NSCLC is currently an extraordinarily active field with numerous ongoing clinical trials.

IMMUNOTHERAPY IN LUNG CANCER

The development of ICI has become a turning point in the standard of care (SoC) of NSCLC through a significant increase in overall survival (OS) in these patients. ICI were initially approved as second-line therapy for patients who had received combination chemotherapy (CT) including platinum following the results of a number of trials: CheckMate 017 and 057 for nivolumab, Keynote-010 for pembrolizumab and the OAK trial for atezolizumab. These studies showed increased OS in comparison to docetaxel, both in squamous and non-squamous NSCLC[1-4]. In particular, Keynote-10[3] was the first to select patients with a programmed death cell protein ligand 1 (PD-L1) expression in tumor cells ≥ 1%, showing that a higher expression of PD-L1 tends to produce better responses.

In the following years, ICI were tested as first-line treatments. Keynote-024 was the first study to evidence that those patients with advanced NSCLC and PD-L1 > 50% receiving pembrolizumab obtained an OS significantly longer than those treated with a platinum doublet. In the updated analysis, with a median follow-up of 25.2 mo (mo), the median OS was 30.0 mo with pembrolizumab and 14.2 mo with chemotherapy [Hazard ratio (HR), 0.63; 95%CI: 0.47 to 0.86][5,6].

Moreover, the addition of pembrolizumab to platinum plus paclitaxel/nab-paclitaxel *vs* CT alone was assessed in two trials: Keynote-189 (for non-squamous) and Keynote-407 (for squamous NSCLC). A benefit in the pembrolizumab arm was observed in both trials: Progression-free survival (PFS) was 9 mo *vs* 4.9 mo (HR 0.48) and 8 mo *vs* 5.1 mo (HR 0.57), respectively. OS was 22 mo *vs* 10.7 mo (HR 0.56) and 17.1 mo *vs* 11.6 mo (HR 0.71), respectively[7-10]. These benefits were evidenced in all subgroups and were independent of PD-L1 status.

Atezolizumab has also shown good results in the first-line setting. In the IMpower 150 trial, patients with advanced non-squamous NSCLC who received a combination of carboplatin, paclitaxel, bevacizumab and atezolizumab presented higher PFS (8.3 mo *vs* 6.8 mo, HR 0.62) and OS (19.8 mo *vs* 14.9 mo, HR 0.62) when compared to carboplatin plus paclitaxel plus bevacizumab[11]. This benefit was also independent of PD-L1 expression. Interestingly, this has been the only study at this point that included patients with epidermal growth factor receptor and anaplastic lymphoma kinase mutations that had progressed to a tyrosine kinase inhibitor, although OS was not significant in this subgroup. In squamous NSCLC, the IMpower 130 study evidenced that the combination of atezolizumab, carboplatin and nab-paclitaxel improves PFS (7 mo *vs* 5.5 mo, HR 0.64) and OS (13.9 mo *vs* 8.6 mo, HR 0.79) compared to CT alone[12].

In unresectable stage III NSCLC, ICI have also changed the SoC. The results of the PACIFIC trial have led to the approval of one year of consolidative durvalumab in patients who have not progressed after definitive CRT and have a PD-L1 ≥ 1%[13,14].

Finally, in small-cell lung cancer, atezolizumab and durvalumab in combination with a doublet of platinum and etoposide have been recently approved after showing a modest improvement in PFS and OS[15,16].

INTERACTION BETWEEN RADIOTHERAPY AND THE IMMUNE SYSTEM

RT plays a role in all stages of NSCLC, both in the radical and palliative settings[17]. Even though RT has traditionally been considered as an exclusively local treatment, limited to the tissues involved in the radiation field, a number of cases reporting the "abscopal effect" (AE) of RT have been published since its first definition by Mole in 1953, who described it as an antitumor effect taking place outside the radiation field [18]. Recent investigations on this matter have shown that the AE might have an immunological explanation. Several preclinical data have evidenced that RT induces immunogenic cell death through the interaction of tumor-associated antigens (TAAs), damage-associated molecular patterns, high mobility group box 1, heat shock proteins, interferon type I (IFN-I), IFN-γ and other immune mediators[19]. This microenvironment favors the incorporation of TAAs by dendritic cells, which transport these to the lymph nodes in order to present them to naïve T cells through the major histocompatibility complex I. This causes the activation of T cells into cytotoxic T cells, which can then be distributed through the bloodstream and reach distant tumor locations[20,21]. This process is summarized in Figure 1.

For many years, this preclinical data has been difficult to translate into the clinical setting, as reports of the AE have been extremely rare[22]. However, since the introduction of ICI, abscopal responses have become much more frequent, with studies reporting up to 65% rates of AE in patients with metastatic NSCLC and melanoma[23]. This is due to the fact that RT and ICI seem to have a synergistic effect: while ICI "take the brakes off" the immune system by blocking inhibitory signals [such as upregulation of PD-1 and cytotoxic T-lymphocyte antigen 4 (CTLA4)-CD28 inhibition of T cell activation], RT serves as an in-situ vaccination that drives immune cells towards the tumor[24,25].

It must be noted, however, that RT can also unleash immunosupressive effects in certain conditions. A prime example is transforming growth factor beta, which participates in regulatory T cell differentiation. Studies have shown that high levels of this substance are associated with diminished antitumor responses, and its blockade is currently being investigated as a way of improving outcomes[26,27]. Although it is considered that RT generally favors a more immunostimulatory state, more data on various treatment variables that might have an influence on this balance (dose, fractionation, treatment sequence) are still required[28,29].

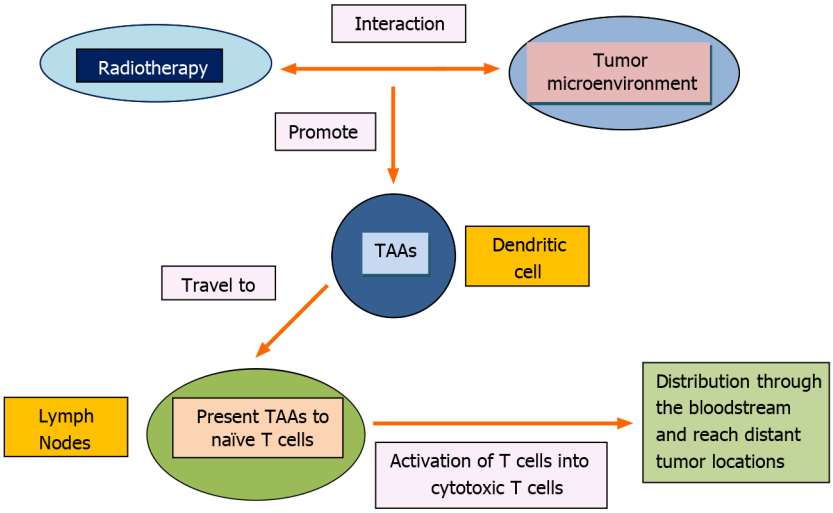

Figure 1 Interaction between radiotherapy and the immune system - Abscopal effect. TAAs: Tumor-associated antigens.

RADIO-IMMUNOTHERAPY IN EARLY-STAGE NSCLC

In the last few years, the results of translational and clinical studies have evidenced the synergistic effects obtainable through the combination of immunotherapy with radiotherapy (iRT) in NSCLC[30,31]. Most of these studies are focused on advanced disease. For instance, this combination has been a paradigm shift in the treatment of unresectable stage III NSCLC following the results of the PACIFIC trial, where an improvement in OS and PFS was observed[13,30].

The management of early-stage NSCLC is generating considerable interest in this setting of combined therapies. Although surgery and stereotactic ablative radiotherapy (SABR) have reported good local control rates (70%-92%) in stage I tumors[32], distant failures can represent up to 30%-60% of cases[33,34]. Moreover, many patients at this stage are inoperable due to comorbidities or refuse surgery. In this scenario, ICI may be an alternative to CT given their comparatively better toxicity profile[31]. The main problem, however, is the poor overall response rate (ORR) of ICI in monotherapy in NSCLC (19% for anti-PD-1 and 4.8% for anti-CTLA-4). For this reason, ICI are being combined with other treatments to achieve better results[35]. Forde *et al*[36] reported a pathological down-staging rate of 40% in patients receiving nivolumab prior to surgical resection (stages I-III). Furthermore, pathological response rates were approximately 10% and no grade ≥ 4 toxicities were observed.

In stage IV NSCLC, iRT in the form of SABR has already achieved an ORR of 36%-41.7% and PFS of 9 mo with a good safety profile[37]. Currently, there are several ongoing clinical trials evaluating iRT in stage I-II NSCLC (Table 1)[38-45]. Although there is still no consensus on the optimal fractionation, ICI agent and treatment sequence, most studies prescribe doses ≥ 6.5 Gy per fraction (fx). The ICI agents include nivolumab, durvalumab, atezolizumab and avelumab. Almost 50% of the registered studies are randomized and evaluate similar primary objectives, such as PFS, local control and toxicity. Among the studies that are already recruiting patients, two of them are randomized phase III studies. The NCT03833159 (PACIFIC-004) trial evaluates sequential durvalumab and SABR in patients with stage I-II NSCLC who are not candidates for surgery. Patients in this study will receive either durvalumab or placebo every four weeks for two years or until treatment discontinuation is necessary [38]. In the NCT04214262, patients will be treated with atezolizumab concurrently with SABR[39]. The exact SABR doses are not specified in either study, but a range of 1-8 fractions will be administered. Great expectations have been placed on these phase III studies, as they could set a new standard in inoperable stage I-II NSCLC.

RADIO-IMMUNOTHERAPY IN STAGE III NSCLC

Stage III NSCLC represents a heterogeneous group of patients with variable prognosis. It includes both resectable tumors in which surgery is the primary curative treatment and CT and RT are administered with neoadjuvant/adjuvant intent, and unresectable tumors in which the SoC is definitive CRT. The suboptimal results of these available

Table 1 Ongoing clinical trials of stereotactic ablative radiotherapy and immune checkpoint inhibitors combination in early-stage non-small cell lung cancer

Ref.	Phase	*n*	Stage	SABR dose	ICI agent	ICI sequence	Status
NCT03833154[38]	III randomized	706	I-II	NM; 3-8 fx	Durvalumab	Sequential	Recruiting
NCT04214262[39]	III randomized	460	I-II	NM; 3-5 fx	Atezolizumab	Concurrent	Recruiting
NCT03110978[40]	II randomized	140	I-IIA	50 Gy/4 fx; 70 Gy/10 fx	Nivolumab	Concurrent	Recruiting
NCT03446547[41]	II randomized	216	I	NM; 3-4 fx	Durvalumab	Sequential	Recruiting
NCT03148327[42]	I-II randomized	105	I-IIA	54 Gy/3 fx; 50 Gy/4 fx; 65 Gy/10 fx	Durvalumab	Concurrent	Recruiting
NCT03050554[43]	I-II	56	I	48 Gy/4 fx; 50 Gy/5 fx	Avelumab	Concurrent	Not recruiting
NCT03383302[44]	I-II	31	I-II	54 Gy/3 fx; 55 Gy/5 fx	Nivolumab	Sequential	Recruiting
NCT02599454[45]	I	33	I	50 Gy/4 fx; 50 Gy/5 fx	Atezolizumab	Induction	Not recruiting

SABR: Stereotactic ablative body radiotherapy; ICI: Immune checkpoint inhibitor; Gy: Gray; NM: Not mentioned.

treatments have led to the investigation of new therapeutic approaches, such as induction/consolidation CT, RT dose escalation, vaccines or targeted therapies. However, none of these have demonstrated significant improvements over standard treatments. For this reason, recent research is evaluating if the incorporation of ICI could improve results, both as consolidation therapy after CRT or surgery, as well as definitive treatment and neoadjuvant therapy.

Neoadjuvant setting

Even though there is currently no evidence on its clinical efficacy, the results of ongoing trials combining ICI with RT prior to surgery in resectable tumors could potentially change clinical practice in the years to come (Table 2). At the moment, there are some data on the combination of ICI with CT. For instance, Forde *et al*[36] reported a 45% of pathological responses in 23 patients with stage I-IIIA NSCLC receiving nivolumab monotherapy, independent of PD-L1 expression. Moreover, the recent NADIM study has observed even higher rates of major pathological response (84.6%) and complete pathological response (71%) with the combination of neoadjuvant nivolumab plus CT[46].

Adjuvant or consolidation setting

The PACIFIC trial was the first randomized double-blinded phase III study to evaluate maintenance durvalumab for 12 mo after definitive CRT in unresectable stage III NSCLC in patients who had not progressed to CRT. A significant increase in PFS (16.8 mo *vs* 5.6 mo) and a manageable toxicity profile (G3-4 30.5% *vs* 26.1%) made this approach the new SoC[13]. Its most recent update in February 2020 reported, with a median follow-up of 33 mo, a 3-year OS of 57% *vs* 43.5% and a 31% reduction in mortality risk[14]. These results were independent of PD-L1 expression, CT regimen and RT dose. In Europe, durvalumab was approved in September 2018, but only in patients with PD-L1 ≥ 1% based on a post-hoc analysis. This debate on PD-L1 status will be addressed in the PACIFIC 5 trial, as the original trial was not designed with this issue in mind[47]. In contrast, the sequence of administration does seem to be relevant, as an improvement in PFS and OS was reported in those patients that started durvalumab within 14 d after CRT.

On the other hand, the LUN 14-179 study, testing consolidative pembrolizumab 4-8 wk after CRT in 93 patients, showed that ICI can also be effective in delivered with a certain delay after concomitant definitive therapy[48]. With a median follow-up of 18.6 mo, the median time to metastatic disease or death was 22.4 mo, while PFS was 17 mo, with a 2-year OS of 61.9%. In regard to toxicity, only 5.4% of patients developed G3-4 pneumonitis.

Consolidative therapy with nivolumab was also being studied in the RTOG 3505 trial (NCT02768558), a randomized phase III study that was prematurely closed after the results of the PACIFIC trial were published[49]. Among the ongoing clinical trials (Table 3), some are investigating dual ICI and the potential side effects of this combination. An interim analysis of the first 20 patients of the NCT03285321 study has reported higher G ≥ 3 toxicity rates in the nivolumab plus ipilimumab arm, but still

Table 2 Ongoing clinical trials of radiotherapy and immune checkpoint inhibitors combination in locally advanced stage non-small-cell lung cancer in the neoadjuvant setting

Ref.	Phase	Design	No.ofpatients	Tumor stage	RT	ICI agent	Sequence	Status
CASE4516, NCT02987998[72]	1	Neoadjuvant CRT (CDDP-etoposide) + ICI followed by surgery and consolidative ICI	20	Resectable IIIA	45 Gy/25 fx (1.8 Gy/fx)	Pembroli zumab	Concomitant (neoadjuvant) + adjuvant ICI	Active, not recruiting
NCT03237377[73]	2	Neoadjuvant RT-ICI followed by surgery +/-adjuvant CT	32	Resectable IIIA	45 Gy/25 fx (1.8-2 Gy/fx)	Durvalumab ± tremelimumab	Concomitant(neoadjuvant)	Recruiting
NCT04245514, SAKK 16/18[74]	2 3 RT arms	Neoadjuvant RT-ICI followed by surgery	90	Resectable IIIA	Randomized 1:1:1; A: 20 × 2 Gy; B: 5 × 5 Gy; C: 3 × 8 Gy (non - consecutive days)	Durvalumab	Concomitant (neoadjuvant)	Recruiting
INCREASE, NL8435[75]	2 single arm	Neoadjuvant CRT (platinum doublet) + ICI followed by surgery	29	Resectable IIB-III (T3-4 N0-1)	50 Gy/25 fx	Ipilimumab + Nivolumab	Concomitant (neoadjuvant)	Recruiting
NCT02904954[76]	2 randomized	Neoadjuvant ICI +/- SBRT followed by surgery and adjuvant maintenance ICI	60	Resectable I-IIIA	SBRT 24 Gy/3 fx	Durvalumab	Concomitantneoadjuvant + adjuvant ICI	Active, not recruiting
NCT03871153[77]	2 single arm	Neoadjuvant CRT (Carbo-taxol) + ICI followed by surgery and adjuvant ICI	25	Resectable IIIA N2	45-61.2 Gy (25-34 fx a 1.8-2 Gy/fx)	Durvalumab	Concomitant (neoadjuvant) + adjuvant ICI	Recruiting
CHIO3, NCT04062708[78]	2single arm	Concomitant neoadjuvant CT (platinum doublet + ICI followed by surgery + adjuvant RT followed by ICI	55	Resectable IIIA-IIIB	54 Gy	Durvalumab	Concomitant CT-ICI (neoadjuvant) + adjuvant ICI (after adjuvant RT)	Not yet recruiting
NCT03102242[79]	2singlearm	Induction ICI followed by definitive CRT (Carbo-Taxol followed by consolidation CT-ICI	63	Unresectable IIIA-IIIB	60 Gy/30 fx	Atezolizumab	Neoadjuvant + consolidative ICI	Active, notrecruiting
NCT02572843[80]	2	Neoadjuvant CT (platinum + docetaxel) + ICI followed by surgery +/-RT + ICI	68	Resectable IIIA N2	Convenional RT if R1-R2 and before adjuvant ICI	Durvalumab	Neoadjuvant + adjuvant	Active, not recruiting

RT: Radiotherapy; CRT: Chemoradiotherapy; CT: Chemotherapy; ICI: Immune checkpoint inhibitor; Gy: Gray.

manageable according to the authors[50].

Definitive setting

Given the good results as consolidation therapy, concomitant ICI with definitive CRT is being investigated in order to further improve clinical outcomes while maintaining an adequate toxicity profile. This has been the case for nivolumab and atezolizumab in the ETOP NICOLAS and DETERRED trials, respectively.

The PACIFIC2 phase III study with durvalumab and the KEYNOTE-799 study with pembrolizumab (Table 4) put a focus on toxicity after the previous studies with nivolumab[51] and pembrolizumab[52], which offered promising outcomes but with an increased risk of pneumonitis. In the first one, the ETOP NICOLAS phase II trial [51], nivolumab is added to standard CRT both as concomitant and consolidation therapy. An interim analysis of the initial 21 patients showed a 1-year OS of 79% with

Table 3 Ongoing clinical trials of radiotherapy and immune checkpoint inhibitor combination in locally advanced stage non-small cell lung cancer in the adjuvant/consolidation setting

Ref.	Phase	Design	No.of patients	Tumor stage	RT	ICI agent	Sequence	Status
BTCRC-LUN16-081, NCT03285321[50]	2 randomized	Concomitant definitive CRT followed by consolidative ICI (3 CT regimens: CDDP-VP16 *vs* Carbo-Taxol *vs* Cisplatin- Pemetrexed)	108	Unresectable IIIA-IIIB	59.4-66.6 Gy	Nivolumab +/- Ipilimumab	Consolidation afterdefinitive treatment	Recruiting
NCT03589547[81]	2	CRT followed by consolidative ICI and SABR	25	III	60 Gy followed by SBRT 20 Gy/2-3 fx	Durvalumab	Consolidation after definitive treatment (ICI prior to SABR)	Recruiting
PACIFIC 6, NCT03693300[82]	2	ICI after sequential CRT	150	Unresectable III	Conventional RT; 60 Gy/30 fx	Durvalumab	Consolidation after definitive treatment (within 28 d after RT)	Active, not recruiting
MK-3475, NCT03379441[83]	2	Maintenance ICI after definitive CRT	126	Unresectable IIIA-IIIB	Conventional RT	Pembrolizumab	Consolidation afterdefinitive treatment	Not recrutiing
DUART,NCT 04249362[84]	2 single arm	RT followed by ICI	150	Unresectable III	Conventional RT 60 Gy Hypofractionated RT 40-54 Gy	Durvalumab	Consolidation after RT (no CT)	Recruiting
PACIFIC 5, NCT03706690[47]	3 randomized, doube-blinded	Consolidative ICI *vs* placebo after definitive CRT radical (concomitant or sequential)	360	Unresectable III	Conventional RT	Durvalumab	Consolidation after definitive treatment	Recruiting

RT: Radiotherapy; CRT: Chemoradiotherapy; CT: Chemotherapy; ICI: Immune checkpoint inhibitor; Gy: Gray.

no G ≥ 3 pneumonitis, which led to the recruitment of additional patients up to a total number of 80. In this case, the analysis of these 80 patients evidenced 10% G ≥ 3 pneumonitis. 1-year OS in this new cohort has not been published yet.

The phase II trial DETERRED[53] with concomitant atezolizumab has completed recruitment and reported better PFS in the ICI arm (57% *vs* 50%), with no significant increase in toxicity but with no benefit in OS at this point (79% in both arms).

In addition, several ongoing studies are investigating if CT can be excluded from radical treatment by combining RT and ICI. The SPRINT trial[54] is evaluating the efficacy of induction pembrolizumab in monotherapy and RT in patients with PD-L1 ≥ 50%. Moreover, the DART study[55] is testing the safety and efficacy of concomitant RT and durvalumab followed by consolidative durvalumab in patients who are not candidates for CT. Other strategies include combinations of ICI with different mechanisms, such as anti-CTLA-4 in the NCT03663166 study (Table 4).

RADIO-IMMUNOTHERAPY IN STAGE IV NSCLC

As mentioned above, the irruption of ICI has been shifted the treatment paradigm in metastatic NSCLC by increasing survival both as first and second-line therapy[2,3,5,7,

Table 4 Ongoing clinical trials of radiotherapy and immune checkpoint inhibitor combination in locally advanced stage non-small cell lung cancer in the concomitant setting

Ref.	Phase	Design	No.of patients	Tumor stage	RT	ICI agent	Sequence	Status
ARCHON-1, NCT03801902[85]	1; 2 RT arms	ICI + RT	24	Unresectable II-III	Conventional RT (60 Gy/30 fx); Hypofractionated RT (60 Gy/15 fx)	Durvalumab	Concomitant with definitive RT	Recruiting
PARTICLE-D, NCT03818776[86]	1; 2 RT arms (proton beam therapy	ICI + RT	27	Unresectable III	RT 60 Gy/20 fx; RT 63 Gy/23 fx	Durvalumab	Concomitant with definitive RT	Recruiting
NCT04013542[87]	1	ICI + RT	20	II-III	Conventional RT	Ipilimumab + Nivolumab	Concomitant with definitive RT and consolidation (nivolumab)	Recruiting
NCT03663166[88]	1; 2	Concomitant CRT + ICI +/- consolidative ICI	50	Unresectable III	60 Gy/30 fx	Ipilimumab +/- Nivolumab	Concomitant definitive treatment +/- consolidative ICI	Recruiting
SPRINT,NCT03523702 [54]	2	ICI + RT (if PD-L1 ≥ 50%) ; CRT (if PD-L1 < 50%)	63	Unresectable III	Conventional RT	Pembrolizumab	Concomitant with definitive RT	Recruiting
KEYNOTE-799, NCT03631784[89]	2	Concomitant ICI + CRT (platinum doublet) followed by ICI	216	Unresectable III	60 Gy/30 fx	Pembrolizumab	Concomitante and consolidative	Active, not recruiting
NCT04092283[90]	3 randomized	Concomitant CRT + ICI *vs* CRT followed by ICI (CT: Cisplatin + VP16/ Taxol + Carboplatin/ Cisplatin + Pemetrexed)	660	Unresectable III	60 Gy/30 fx	Durvalumab	Concomitant with definitive treatment *vs* adjuvant ICI	Recruiting
PACIFIC 2, NCT03519971[91]	3 randomized, double-blinded	ICI *vs* placebo concomitant to CRT (CDDP-VP16 *vs* Carbo-Taxol *vs* Cisplatin or Carbo + Pemetrexed)	328	Unresectable III	Conventional RT (60 Gy in 30 fx)	Durvalumab	Concomitant +/- consolidative	Active, not recruiting
NCT04026412[92]	3 randomized	ICI (nivolumab) + CRT followed by ICI (nivolumab + ipilimumab) *vs* ICI (nivolumab) + CRT followed by ICI (nivolumab) *vs* CRT followed by durvalumab	1400	Unresectable/inoperable III	Conventional RT	Nivolumab; Ipilimumab; Durvalumab	Concomitant + 2 consolidation regimens *vs* consolidation after CRT	Recruiting

RT: Radiotherapy; CRT: Chemoradiotherapy; CT: Chemotherapy; ICI: Immune checkpoint inhibitor; Gy: Gray.

11,56,57]. Furthermore, RT in stage IV has evolved from a merely palliative intent to having a key role when associated with ICI. Reports of objective responses in distant locations not included in the radiation field (AE) have multiplied in the era of immunotherapy[31,58].

Preclinical and clinical data suggest that the antitumor efficacy of ICI increases when combined with RT, with a possible impact in survival, which could be the base for designing new combinations that can maximize this synergistic effect[58-65]. Even though most published studies on the combination of RT and ICI in stage IV NSCLC

are phase I/II trials with a limited number of patients (Table 5), they have laid the foundation for the possible benefits of this strategy that are being determined in ongoing phase III studies.

Although retrospective data had been the only evidence available for years, phase I studies evaluating the safety of the combination recently started to surface. For instance, Tang *et al*[66] treated 21 patients with pembrolizumab and RT (SABR or hypofractionated RT) and reported an ORR of 32% while maintaining a good toxicity profile (14% G ≥ 3).

The safety of anti-CTLA-4 agents has also been addressed. Formentiet al[67] designed a phase I/II study with 39 patients treated with ipilimumab plus SABR (28.5 Gy in 3 fx or 30 Gy in 5 fx). ORR was 31%, PFS was 7.1 mo and OS was 13 mo, with only 10.3% G ≥ 3 toxicity[67]. The safety of multisite irradiation was evaluated in the oligometastatic setting by Bauml *et al*[68], who included 45 patients with oligometastatic NSCLC and delivered local ablative therapy (surgery or SABR) followed by sequential pembrolizumab, showing promising results in terms of PFS (19.1 mo) and OS (41.6 mo), with low toxicity rates.

With the safety of the combination established and the promising survival data reported in these initial studies, randomized evidence on the combination of ICI and RT (mainly in the form of SABR, also known as I-SABR) is finally starting to emerge. At the moment, three randomized trials have published their results. Not only are these reinforcing the idea that a benefit in survival exists, but they are also starting to contemplate some questions regarding the optimal treatment delivery. For instance, the COSINR study by Patel *et al*[69] is a phase I trial that randomized 35 patients to receive dual ICI (ipilimumab plus nivolumab) and either concurrent or sequential SABR. Global ORR was 68%, while PFS was 6.2 mo in the concomitant arm and 5.9 mo in the sequential arm. Welsh *et al*[70] recently reported the results of a phase II study that randomized 72 patients to receive RT plus pembrolizumab *vs* pembrolizumab monotherapy. In the experimental arm, patients received either SABR (50 Gy in 4 fx or 70 Gy in 10 fx) or conventional RT (45 Gy in 15 fx). Globally, there were no significant differences in response or PFS between the combination arm and the pembrolizumab arm, with an ORR of 22% *vs* 25 and PFS of 9.1 *vs* 5.1 (P = 1.00). However, in the subanalysis of patients treated in the combination arm, ORR was higher in the SABR group than in the conventional RT group (38% *vs* 10%), as well as PFS (20.8 mo *vs* 6.8 mo, P = 0.03)[70]. Finally, the PEMBRO-RT phase II study included 76 patients and randomized them in two arms: sequential pembrolizumab after SABR to a single lesion (24 Gy in 3 fx) *vs* pembrolizumab monotherapy. ORR was 36% and 18%, respectively. Furthermore, PFS favored the I-SABR arm (6.6 mo *vs* 1.9 mo), as well as OS (15.6 mo *vs* 7.6 mo), even though these were not statistically significant[71].

At present, a great number of clinical trials combining RT and ICI in stage IV NSCLC are ongoing (Table 5). These include multiple ICI agents (atezolizumab, avelumab, nivolumab, pembrolizumab, sintilimab, tremelimumab), different combinations, various treatment sequences (induction, sequential or concomitant) and several fractionations and RT techniques such as conventional RT, hypofractionation, SABR, intensity-modulated RT and proton beam RT.

CONCLUSION

Radio-immunotherapy represents a dynamic area of preclinical and clinical investigation in lung cancer. The synergy between RT and ICI to achieve a greater tumor response has been shown to be a promising option for the treatment of NSCLC. The positive experiences reported with the combination of RT and ICI in early stage, unresectable stage III and stage IV NSCLC have reinforced the interest in the association of these two treatments. In the years to come, the results of ongoing clinical trials will continue to evolve clinical practice in NSCLC.

Table 5 Ongoing clinical trials involving radiotherapy and immunotherapy in stage IV non-small cell lung cancer

Ref.	Phase	ICI agent	RT dose	Design	Primary endpoints
NCT03158883[93]	I	Avelumab	50 Gy/5 fx	ICI + SABR	ORR
NCT03224871[94]	I	Nivolumab; Pembrolizumab; Intratumor IL-2	8 Gy/3 fx	ICI + IL-2 + RT	MTD
NCT03436056, PRIMING [95]	I	Pembrolizumab	SABR 30 Gy-3 fx SABR 54 Gy/3 fx	ICI + SABR	MTD
NCT03812549[96]	I	Sintilimab	SABR 30 Gy/3 fx; LD (low dose)-RT: 2 Gy/1 fx or 4 Gy/2 fx or 10 Gy/5 fx	ICI + SABR; ICI + LD-RT	MTD
NCT03223155, COSINR [69]	I	Nivolumab; Ipilimumab	SABR 3-5 fx, 2-4 sites	ICI + SABR	MTD
NCT02639026[97]	I	Durvalumab; Tremelimumab	HFRT 24 Gy/3 fx, 17 Gy/1 fx	ICI + HFRT	MTD
NCT03275597[98]	I	Durvalumab; Tremelimumab	SABR 30-50 Gy/5 fx	ICI + SABR	MTD
NCT03168464[99]	I-II	Nivolumab; Ipilimumab	RT 30 Gy/5 fx	ICI + RT	ORR
NCT02239900[100]	I-IIR	Ipilimumab	SABR 50 Gy/4 fx or 60 Gy/10 fx; 1-4 lesions	ICI + SABR	MTD
NCT02444741[101]	I-IIR	Pembrolizumab	SABR 4 fx or IMRT, PBRT, 3D-CRT 15 fx	ICI + SABR or IMRT, PBRT, 3D-CRT	MTD, ORR
NCT03176173, RRADICAL [102]	II	Nivolumab; Pembrolizumab; Atezolizumab	SABR 1-10 fx	ICI +/- SABR	PFS
NCT03965468, CHESS[103]	II	Durvalumab	SABR 1-10 fx	ICI + SABR + CT	PFS
NCT03044626, FORCE [104]	II	Nivolumab	RT 20 Gy/5 fx	ICI + RT	ORR
NCT02221739[105]	II	Ipilimumab	IMRT or 3D-CRT 30 Gy/5 fx	ICI + RT	ORR
NCT02658097[106]	II	Pembrolizumab	RT 8 Gy/1 fx	ICI + RT	ORR
NCT03391869, LONESTAR [107]	III	Nivolumab; Ipilimumab	LCT	ICI +/- SABR	OS
NCT03867175[108]	III	Pembrolizumab	SABR 3-10 fx	ICI +/- SABR	PFS
NCT03774732, NIRVANA-LUNG[109]	III	Pembrolizumab	SABR or 3D-CRT 18 Gy/3 fx	ICI + RT + CT	OS

ICI: Immune checkpoint inhibitors; Fx: Fraction; SABR: Stereotactic ablative radiotherapy; RT: Radiotherapy; LD-RT: Low dose radiotherapy; HFRT: Hypofractionated radiotherapy; IMRT: Intensity modulated radiotherapy; PBRT: Proton beam radiation therapy; 3D-CRT: 3D conformal radiation therapy; LCT: Local consolidation therapy; CT: Chemotherapy; ORR: Overall response rate; MTD: Maximum tolerated dose.

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MINIREVIEWS

Consensus molecular subtypes of colorectal cancer in clinical practice: A translational approach

Guillermo Valenzuela, Joaquín Canepa, Carolina Simonetti, Loreto Solo de Zaldívar, Katherine Marcelain, Jaime González-Montero

ORCID number: Guillermo Valenzuela 0000-0002-8711-729X; Joaquín Canepa 0000-0003-2329-0293; Carolina Simonetti 0000-0002-2102-0000; Loreto Solo de Zaldívar 0000-0002-6364-7595; Katherine Marcelain 0000-0003-4018-6623; Jaime González-Montero 0000-0003-0324-2948.

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Guillermo Valenzuela, Joaquín Canepa, Carolina Simonetti, Loreto Solo de Zaldívar, Katherine Marcelain, Jaime González-Montero, Basic and Clinical Oncology Department, University of Chile, Santiago 8380453, Chile

Corresponding author: Jaime González-Montero, MD, PhD, Assistant Professor, Doctor, Basic and Clinical Oncology Department, University of Chile, Independencia 1027, Casilla 70058, Santiago 8380453, Chile. jagonzalez@ug.uchile.cl

Abstract

The identification of several genetic mutations in colorectal cancer (CRC) has allowed a better comprehension of the prognosis and response to different antineoplastic treatments. Recently, through a systematic process, consensus molecular subtypes (CMS) have been described to characterize genetic and molecular mutations in CRC patients. Through CMS, CRC patients can be categorized into four molecular subtypes of CRC by wide transcriptional genome analysis. CMS1 has microsatellite instability and mutations in CIMP and BRAF pathways. CMS2, distinguished by mutations in specific pathways linked to cellular metabolism, also has a better prognosis. CMS3 has a KRAS mutation as a hallmark. CMS4 presents mutations in fibrogenesis pathways and mesenchymal-epithelial transition, associated with a worse prognosis. CMS classification can be a meaningful step in providing possible answers to important issues in CRC, such as the use of adjuvant chemotherapy in stage II, personalized first-line chemotherapy for metastasic CRC, and possible new target treatments that address specific pathways in each molecular subtype. Understanding CMS is a crucial step in personalized medicine, although prospective clinical trials selecting patients by CMS are required to pass proof-of-concept before becoming a routine clinical tool in oncology routine care.

Key Words: Colorectal neoplasms; Precision medicine; Microsatellite instability; Next-generation sequencing

Core Tip: Colorectal cancer has a variable response to different treatments that could be

quality classification
Grade A (Excellent): A
Grade B (Very good): 0
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

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explained by genetic and molecular heterogeneity in the neoplasm. Recently, a novel classification according to consensus molecular subtype has been proposed to explain this neoplasm heterogeneity. From a clinical oncology perspective, this classification opens opportunities to resolve some current clinical questions in the treatment of colorectal cancer.

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INTRODUCTION

Colorectal cancer (CRC) is the second leading cause of death by cancer worldwide[1]. Despite important advances in early diagnosis and management, 25% of patients debut in metastatic stages and 50% localized stages, later presenting disseminated disease[2]. Currently, CRC management is based on tumor-node-metastasis (TNM) system staging, and in recent years, on several genetic mutations such as microsatellite instability (MSI), KRAS/NRAS, and BRAF. These mutations have a role in selecting better candidates for certain systemic therapies[3,4]. Improvements in classic systemic therapies for CRC have allowed more effective and tolerable chemotherapy regimens, mainly based on fluoropyrimidines with oxaliplatin and/or irinotecan. Proposing novel target therapies is also possible for selected patients[5,6].

A new paradigm has resulted from the problem of heterogeneity of CRC[7], which explains the significant impact of variable responses to classic systemic therapies. Thus, some patients present satisfactory and sustained responses. In contrast, other patients with CRC present low response rates to standard therapies, with rapidly progressive disease and high mortality. It has been argued that one way to approach this paradigm is through the characterization and creation of a framework based on genetic and molecular characteristics to explain the heterogeneity of colon cancer. Recently, a major initiative has emerged to describe CRC heterogeneity. The consensus molecular subtypes (CMS) provide a systematic way to classify CRC into four molecular subtypes according to their molecular and genetic profile[8].

Characterizing molecular subtypes in the CRC could optimize the management of these patients. Through knowledge of the biology of the disease, we could better predict the response to therapeutic alternatives to select the most appropriate therapy for each patient[9,10]. This approach is a crucial step in the development of personalized therapies in this disease. In this context, the current review aims to present a translational approach for routine oncology clinical practice regarding the implications of CMS classification with a focus on prognosis and promising novel antineoplastic agents in different stages of CRC.

CHARACTERISTICS OF EACH CMS

In recent years, different models have been proposed based on genetic, molecular, epigenetic, and phenotypic profiles to explain the heterogeneity of CRC[11-15], obtaining different molecular classifications with different clinical outcomes. A major collaborative effort to integrate all CRC classifications into a single model was identified by experts from the CRC Subtyping Consortium through the analysis of six independent classification studies, obtaining a CRC classification of four CMS[8]. This presents an integrated framework to capture the heterogeneity of CRC at the gene expression and molecular level through transcriptome-wide analysis[9]. The methodology of the consensus assessed redundant pathways and upregulation of signaling pathways that are independent of DNA mutations to provide a characterization of the molecular status[16].

CRC classification based on genome-wide transcriptional profiles has seen important research developments during the last decade; no single genetic defect can be unequivocally assigned to a specific molecular profile. CMS classifications have certain

hallmarks characterizing each subtype[9,17,18]. In brief, each CMS is characterized as follows.

CMS1 (immune) is characterized by MSI, with high mutations of CIMP and BRAF and a low prevalence of SNCA. It is associated with lymphocyte infiltration and immune activation, in addition to hypermethylation and decreased signaling through the WNT pathway[19].

CMS2 (canonical) has epithelial characteristics. It is characterized by high chromosomal instability, high somatic copy number alterations (SCNA) counts, and WNT and MYC mutations, causing high activity of these intracellular signaling pathways [18,19]. It also features increased expression of EGFR, its ligands AREG and EREG, and TP53, APC, and RAS mutation[20]. These can be distinguished from other CRC subtypes by marked upregulation of the downstream targets of WNT and MYC and increased expression of EGFR oncogenes, ERBB2 (also known as HER2), insulin-like growth factor 2, insulin receptor substrate 2, hepatocyte nuclear factor transcription factor 4, and cyclins[19].

CMS3 (metabolic) has a distinctive global genomic and epigenomic profile with mixed characteristics, metabolic reprogramming, and dysregulated pathways, with increased activity in glutaminolysis and lipidogenesis[20], enriched with KRAS-activating mutations. It presents a moderate or low mixed state of MSI and intermediate CIMP, and moderate activation of WNT and MYC, with PIK3CA mutation and IGBP3 overexpression, without BRAF mutations[19].

CMS4 (mesenchymal) has positive gene regulation and overexpression of proteins involved in stromal infiltration, mesenchymal activation, extracellular matrix remodeling, neoangiogenesis, prominent TGF-β activation, and complement pathways. These are characteristic of mesenchymal epithelial transition, overexpressing EMT genes, evidence of prominent EMT gene TGF-β activation, and high SCNA counts. Six immune genes (PROK1, THBS1, FGF11, CRP, S100A14, and CCL19) have been identified as the key factors of CMS4 and can potentially be applied for risk assessment of CRC patients[19,21]. The main hallmarks of CMS are briefly described in Figure 1.

IDENTIFYING THE PATIENT MOLECULAR SUBTYPE

Classification by CMS in real clinical settings, outside clinical trials, is challenging. In recent years, certain genetic hallmarks have been routinely determined. For example, MSI mutations are involved in advanced stages of CRC and are highly predictive of CMS1. MSI can be detected by polymerase chain reaction based on a panel of different microsatellite loci or applying immunohistochemistry (IHC) with antibodies against mismatch repair (MMR) proteins[22]. For the other subtypes, heterogeneous groups of genetic and molecular conditions are commonly found in pathogenic mutations in CRC, such as KRAS, BRAF, and APC[9,22]. For these mutations, in clinical settings, a commercial genetic panel that includes genes contained in CMS are the NanoString nCounter®, Almac Xcel microarray assay, and Affymetrix GeneChip® Human Transcriptome Array 2.0 (HTA).

Several research groups have aimed to obtain a practical and robust CMS classifier that works on formalin-fixed, paraffin-embedded primary CRC tissues, based on gene expression or IHC[23]. Categorizing patients relies fundamentally on mutational, transcriptomic, and proteomic data analysis[24]. A novel CMS classifier based on a filtered set of cancer cell-intrinsic, subtype-enriched gene expression markers, referred to as CMS caller[25], provides robust classification of CMS groups in datasets generated on different gene expression platforms and biological sample types, readily available for its purpose. A 40-gene ColoType signature has recently been developed, which uses genome-wide assays, frozen tissue-specific RNA sequences, or FFPE. The results correlate highly with those reported by the other two systems, in addition to allowing accurate and reproducible CMS subtype analysis for clinical applications[26].

Routinely practicing CMS classification for patients with CRC is challenging due to the difficult applicability and costs of this method[27]. However, an IHC approach has been proposed, which could represent a reasonable option for the molecular classification of CRC through morphological phenotype and a simpler way to guide case management[23,28]. Several IHC protocols have been proposed, such as a phenotypic subtyping method based on immune infiltrate, stromal invasion, and proliferation rate [27]. Another protocol proposed to correlate specifically with CMS is the IHC detection of MSI with antibodies against MSH1-2 MMR proteins, allocating samples with high-level MSI to CMS1, then classifying the remaining subtypes through staining for four

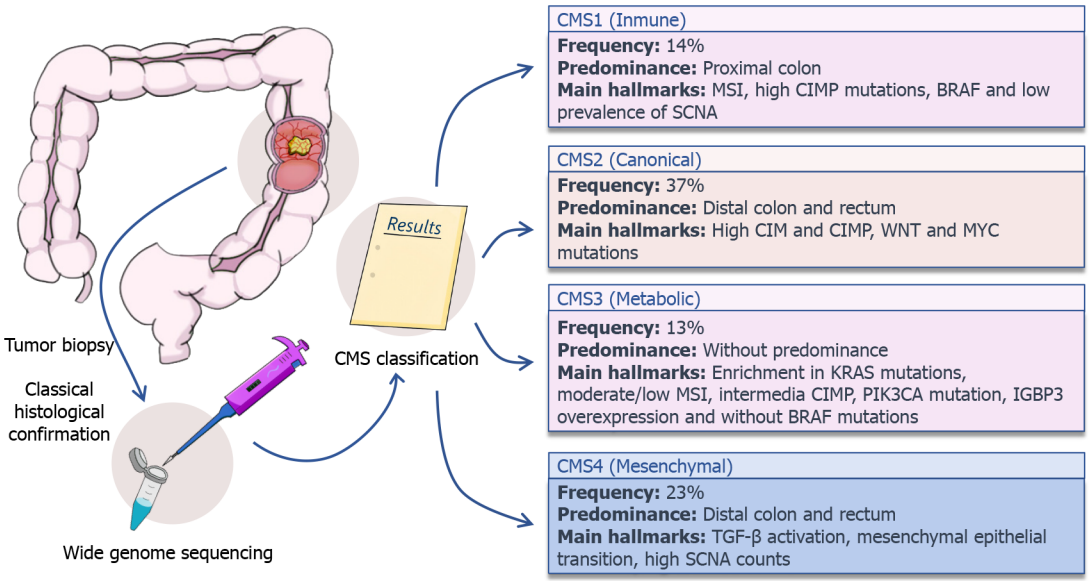

Figure 1 Main characteristics of consensus molecular subtypes in colorectal cancers. After the patient undergoes a biopsy, the diagnosis of colorectal cancer is made and subsequent stratification by tumor-node-metastasis is performed. Samples can be obtained to allow wide genome sequencing analysis with the objective of characterization into one of four consensus molecular subtypes. CMS: Consensus molecular subtypes; SCNA: Somatic copy number alterations.

gene product proteins (CDX2, FRD6, HTR2B, and ZEBI), allowing differentiation between CMS2/3 with CMS4[22]. This method, complemented with an IHC-based classifier, has demonstrated 87% concordance with transcriptome-based classification [23], indicating that IHC can be used to categorize CRC molecular subtypes, although not with 100% concordance. However, it has the disadvantage of being unable to distinguish between CMS2 and 3 because both subtypes share similar epithelial features. Recently, an improvement to this protocol has been proposed, adding IHQ for β-catenin to differentiate between CMS2 and 3, with 71.4% concordance compared to an RNA-sequencing-based classifier. This is based on CMS2 activating WNT pathway-regulated β-catenin expression[29].

However, the translation of CMS by genome-wide transcriptional profiles into clinical practice is subject to several obstacles[16], such as the complexity, difficulties of translation to routine pathology, and costs of this method of classification[24,27]. Until genomic profiling becomes more widespread in clinical practice, the molecular subtypes of CRC can be assessed by IHC but with less accuracy compared to the transcriptome gold standard[23]. Nevertheless, CMS is expected to be able to be used in routine clinical practice by overcoming these obstacles and becoming widely available in the near future for the classification of CRC through genome-wide transcriptional profiles.

CMS AND PROGNOSIS

Traditionally, the prognosis and treatment selection of patients with CRC has been based on the clinical pathological classification of TNM[30]. However, morphologically similar tumors can have different genetic expression and molecular profiles[9] with the capacity to determine different prognoses[31]. Currently, the main international clinical guidelines recommend determining certain biomarkers in specific clinical contexts, such as dMMR/MSI, BRAF, and RAS in metastatic CRC (mCRC) to select the optimal chemotherapy treatment[3,4]. In particular, the CMS classification was designed to categorize CRC heterogeneity in a transcriptional profile, although each subgroup has also been reported to have a different prognosis. In an analysis of 4151 patients with CRC[8], the overall survival (OS) in CMS4 was worse compared to CMS1–3, and a better OS was found in patients with CMS2. Notably, the OS calculation included patients in all TNM stages. In addition, CMS1 patients have a worse survival rate after relapse, and CMS2 patients have a longer survival after relapse.

Despite the important contribution of CMS classification to understanding the oncogenesis of CRC, whether this classification can better predict the prognosis of CRC patients is still uncertain[32]. In particular, in patients with stage II CRC, contro-

versies exist about the clinical benefits of chemotherapy[33]. Stage II patients are selected for chemotherapy if they have a pathological or clinical risk factor such as T4 status, suboptimal lymph node resection, perineural and perivascular invasion, or colon perforation[4]. In this context, it has been proposed that better markers such as CMS could provide a better selection of patients to undergo chemotherapy. Studies that shown that in stages II–III, patients with CMS 4 have a worse prognosis[34]. One study hypothesized that this is a consequence of resistance to fluorouracil–leucovorin regimens commonly used in these stages[35]. Likewise, in low-risk stage II CRC patients who did not undergo adjuvant chemotherapy, CMS4 had significantly worse outcomes in relapse-free survival (RFS) compared to other CMS groups[36]. Using IHQ CMS classification, Li *et al*[37] described a worse OS and disease-free survival in CMS4 and a better OS with adjuvant chemotherapy for stage II CRC in CMS2-3. Furthermore, it has been suggested that certain gene mutations in each CMS can modify outcomes. For instance, BRAF mutations were associated with metastasis in patients with MSS and CM1(OS 22% in BRAF mutated *vs* 81% in wild-type BRAF, P = 0.001). In CMS2-3 patients, mutated KRAS had worse outcomes (OS 59% in KRAS mutated *vs* 75% in wild-type KRAS)[38]. Moreover, patients with MSI and CMS1 have a better OS and RFS compared to CMS2-4. Contrary to previous results, Purcell *et al* [39] reported that stage II patients with CMS3 had a worse prognosis in OS than patients in CMS1-2, although an imbalance between CMS groups, with few CMS4 patients, could explain this result. Besides the possibility for CMS to determine CRC subtypes with worse prognosis for proposing personalized treatments, CMS still needs more studies to define the differences in the prognosis of patients through the different TNM stages of CRC.

In recent years, a special interest has emerged in defining molecular characteristics in patients with mCRC to select the best chemotherapy regimen[40]. In particular, the applicability of CMS has been studied most in this subgroup of patients. An analysis of the CALGB/SWOG 80405[16] trial determined the CMS of 664 patients using a genetic panel (NanoString). It found a positive relationship between OS and progression-free survival (PFS) and each CMS, determining a mean survival (months) of 15 for CMS1, 40.3 for CMS2, 24.3 for CMS3, and 31.4 for CM4, independent of assigned first-line chemotherapy treatment. In a sub-analysis of the AGITG MAX trial, 237 patients with mCRC were classified by CMS using an Almac Xcel microarray assay. A statistically significant association was found between CMS and OS, but not with PFS, independent of assigned first-line chemotherapy treatment. Similar OS were reported: CMS2 had the larger OS (median 24.2 mo), CMS1 had the worst (8.8 mo), and CMS3 (17.6 mo) and CMS4 (21.4 mo) had intermediate OS[41]. Similarly, the FIRE-3 trial[20] that included 438 patients categorized by CMS using the Almac Xcel microarray showed a correlation with OS and PFS independent of assigned treatment, with a worse mean OS in CMS1 (15.9 mo) and better OS in CM2 (29.0 mo). Whilst CM3 (18.6 mo) and CMS4 (24.8 mo) had a medium OS. Similar results were also reported by a retrospective analysis finding a worse OS in CMS1 and a better OS in CMS2[42]. Finally, a retrospective analysis of the TRIBE2 trial found better PFS and OS outcomes in CMS2 and CMS4 compared to CMS1 and CMS3[43]. A summary of the main prognoses in published reports of CMS is shown in Table 1. Questions remain in the prognosis of each CMS, especially when analyzing the results at each stage measured by TNM. However, encouraging results have been seen when predicting the subtypes of patients with worse prognoses in mCRC and stage II, opening possibilities to propose personalized treatments based on the molecular landscape of the CRC of each patient.

IMPORTANCE OF CONSIDERING CMS FOR FUTURE CLINICAL TRIALS

Considering the significant recent advances in the molecular and genetic profile of CRC through CMS classification, this knowledge must be projected using a proof-of-concept approach, applying it in clinical trials[17]. Patient selection by CMS characterization could be a crucial step in cancer staging and personalized treatment guided by biomarker selection. However, CMS interpretation in the context of clinical trials has some factors that need to be considered when interpreting the results, such as the sample collection site (colon *vs*. rectum), the trial inclusion and exclusion criteria, the first-line chemotherapy scheme used, specific mutations that alone produce different outcomes, and the method used to predict the CMS[44]. Despite these limitations, the identification of CMS in future clinical trials is projected to allow better precision in selecting specific treatments for each patient, especially in the use of immunotherapy

Table 1 Outcomes in four consensus molecular subtype profiles

Ref.	*n*	Outcomes	CMS1, mean (95%CI)	CMS2, mean (95%CI)	CMS3, mean (95%CI)	CMS4, mean (95%CI)
Stages I-IV						
Purcell *et al*[39], 2019	257	5-yr OS (%)	63.7 (51.1-79.4)	64.4 (56.6-73.4)	52.8 (37.1-75.1)	42.8 (23.8-76.8)
		5-yr PFS (%)	61.2 (48.8-76.8)	59.8 (51.8-68.9)	52.7 (47.5-74.0)	38.8 (21.0-71.9)
Guinney *et al*[8], 2015	2129	5-yr OS (%)	74 (70-75)	77 (74-80)	75 (70-80)	62 (58-66)
		5-yr DFS (%)	75 (70-80)	73 (70-77)	73 (68-80)	60 (55-65)
Stage II						
Shinto *et al*[36], 2020	232	5-yr DFS (%)	100	85.5	92.3	73
Stage IV						
Borelli *et al*[43], 2021	426	OS (mo)	13.7 (6.1-27.9)	27.0 (23.9-30.1)	18.3 (16.1-24.0)	26.2 (21.4-29.9)
		PFS (mo)	5.4 (3.8-9.9)	12.9 (11.0-14.3)	8.3 (7.4-10.1)	10.7 (9.8-13.1)
Stintzing *et al*[20], 2019	438	OS (mo)	15.9 (11.0-20.8)	29.0 (26.7-31.4)	18.6 (15.4-21.7)	24.8 (22.6-27.1)
		PFS (mo)	8.2 (6.7-9.6)	11.7 (10.8-12.6)	8.5 (6.8-10.3)	9.6 (8.6-10.6)
Lenz *et al*[16], 2019	581	OS (mo)	15.0 (11.7-22.4)	40.3 (36.1-43.1)	24.3 (16.4-29.0)	31.4 (26.3-36.9)
		PFS (mo)	7.1 (5.7-8.6)	13.4 (12.8-15.4)	8.7 (7.2-9.8)	11.0 (9.7-12.0)
Mooi *et al*[41], 2018	237	OS (mo)	8.8 (6.5-16.0)	24.2 (19.1-27.4)	17.6 (11.3-24.6)	21.4 (15.8-23.1)
		PFS (mo)	No statistical differences in this cohort			
Okita *et al*[42], 2018	193	OS (mo)	21.4 (13.3-35.5)	48.1 (34.8-65.6)	38.7 (30.6-45.6)	44.0 (33.0-50.5)

OS: Overall survival; DFS: Disease-free survival; PFS: Progression-free survival.

for mCRC[10,45]. In the case of immunotherapy, ongoing trials (NCT03436563) are testing M7824 treatment, an anti-PD-L1/TGF-β Trap fusion protein. This treatment has demonstrated an anti-tumor response by TGF-βand PD-L1 immunosuppressive pathways with successful results in murine CRC models[46,47]. It has been proposed as a possible treatment for CMS4 because it activates the TGF-pathway[9,48]. In addition, CMS identification could allow selecting a personalized first-line chemotherapy regimen in mCRC. For instance, a possible hypothesis has recently been proposed after analysis through CMS classification in two important clinical trials, FIRE-3[20] and CALGB/SWOG 80405[16], which both compared the response to first-line chemotherapy in addition to cetuximab or bevacizumab. The authors theorized that the combination of irinotecan and cetuximab in all CMS classification, when patients have received oxaliplatin, has a synergic effect in CMS2 and CMS3, but in CMS1 and CMS4 it has an antagonistic effect due to the poor efficacy of oxaliplatin in a fibroblast-rich microenvironment[49]. Recently, different retrospective studies of clinical trials have shown associations between CMS and the prognosis of different chemotherapy regimens[43,50]. However, these results must be confirmed using clinical trials with prospective designs that include different CMS patients.

CONCLUSION

The CMS provides an interesting opportunity to explore the heterogeneity of CRC. CMS classification can approximate research in frequently unsolved daily clinical practice problems. For instance, in patients with stage II colon cancer, where the benefit of chemotherapy is still unclear, CMS classification could determine which patients would benefit from adjuvant chemotherapy. Likewise, CMS will allow defining the best first-line chemotherapy regimen in mCRC. Understanding the genetic profile of tumors could allow developing new interventions to target treatments that address specific pathways to each molecular subtype. Therefore, CMS comprehension is a crucial step towards personalized medicine, though any interesting perspective must be proven through prospective clinical trials selecting patients by CMS.

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ORIGINAL ARTICLE

Retrospective Cohort Study

Real-world evaluation of upfront docetaxel in metastatic castration-sensitive prostate cancer

Jenny Isaksson, Henrik Green, Dimitrios Papantoniou, Linn Pettersson, Mats Anden, Johan Rosell, Elisabeth Åvall-Lundqvist, Nils Oskar Elander

ORCID number: Jenny Isaksson 0000-0002-8640-350X; Henrik Green 0000-0002-8015-5728; Dimitrios Papantoniou 0000-0001-5472-2322; Linn Pettersson 0000-0001-9253-5245; Mats Anden 0000-0002-9298-7724; Johan Rosell 0000-0002-2342-1348; Elisabeth Åvall-Lundqvist 0000-0001-7274-1770; Nils Oskar Elander 0000-0001-9345-0278.

Author contributions: Isaksson J, Green H, Åvall-Lundqvist E and Elander NO designed the study; Isaksson J acquired the patient data with the help of Papantoniou D, Pettersson L and Anden M at the respective sites; Isaksson J, Green H, Rosell J and Elander NO analyzed the data; Isaksson J, Green H and Elander NO drafted the first version of the manuscript; all authors helped develop the methodology and perform the investigation, and all read and approved the final manuscript.

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Informed consent statement: Based on the retrospective and

Jenny Isaksson, Elisabeth Åvall-Lundqvist, Nils Oskar Elander, Department of Oncology, Department of Biomedical and Clinical Sciences, Linköping University, Linköping 58185, Sweden

Henrik Green, Division of Drug Research, Department of Biomedical and Clinical Sciences, Linköping University, Linköping 58185, Sweden

Dimitrios Papantoniou, Linn Pettersson, Department of Oncology, Ryhov County Hospital, Jönköping 55305, Sweden

Mats Anden, Department of Oncology, Kalmar County Hospital, Kalmar 39244, Sweden

Johan Rosell, Regional Cancer Center Southeast Sweden, Linköping University, Linköping 58185, Sweden

Corresponding author: Nils Oskar Elander, MD, PhD, Doctor, Department of Oncology, Department of Biomedical and Clinical Sciences, Linköping University, Linköping University Hospital, Linköping 58185, Sweden. nils.elander@liu.se

Abstract

BACKGROUND

The majority of patients with newly diagnosed metastatic prostate cancer (PC) initially respond to androgen deprivation therapy (ADT) and are classified as metastatic castration-sensitive PC (mCSPC). Following months to years of ADT, the disease tends to become resistant to ADT. Recent randomized phase-III trials demonstrated a survival benefit with the addition of upfront docetaxel to ADT in mCSPC. Following its implementation in routine care, this combined treatment strategy requires more detailed evaluation in a real-world setting.

AIM

To assess the real-world outcome and safety of upfront docetaxel treatment in mCSPC.

METHODS

A multicenter retrospective cohort study in the Southeast Health Care Region of Sweden was performed. This region includes approximately 1.1 million citizens and the oncology departments of Linköping, Jönköping, and Kalmar. All patients

noninterventional nature of the study and the absence of publication of individual data, the ethics board did not consider it possible or necessary to obtain written informed consent.

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given upfront docetaxel for mCSPC from July 2015 until December 2017 were included. The primary endpoint was progression-free survival (PFS) at 12 mo, and the secondary endpoints were PFS at 24 mo, overall survival (OS), treatment intensity, adverse events, and unplanned hospitalizations. Exploratory analyses on potential prognostic parameters were performed.

RESULTS

Ninety-four patients were eligible and formed the study cohort. PFS at 12 and 24 mo was 75% (95%CI: 66–84) and 58% (46–70), respectively. OS at 12 and 24 mo was 93% (87–99) and 86% (76–96). A total of 91% of patients (n = 86) were given docetaxel according to the standard protocol of 75 mg/m^2 every 3 wk (6 cycles), while 9% (n = 8) received a modified protocol of 50 mg/m^2 every 2 wk (9 cycles). The average overall dose intensity for those commencing standard treatment was 91%. Univariate Cox regression analyses show that baseline PSA > 180 *vs* < 180 and the presence of distant metastases *vs* locoregional lymph node metastases were only negative prognostic factors (HR 2.86, 95%CI: 1.39–5.87, P = 0.0041 and 3.36, 95%CI: 1.03–10.96, P = 0.045). Following multivariate analysis, statistical significance remained for PSA (2.51, 95%CI: 1.21–5.19, P = 0.013) but not for metastatic status (2.60, 95%CI: 0.78–8.65, P = 0.12). Febrile neutropenia was recorded in 21% (n = 20) of patients, and 26% (n = 24) had at least one episode of unplanned hospitalization under and up to 30 d after the treatment course.

CONCLUSION

Results from this study support the implementation of upfront docetaxel plus ADT as part of the standard of care treatment strategy in mCSPC.

Key Words: Prostate cancer; Chemotherapy; Docetaxel; Castration sensitive; Metastatic; Real world

Core Tip: Two recent trials reported impressive outcomes when upfront docetaxel is added to androgen deprivation therapy in metastatic castration-sensitive prostate cancer (mCSPC). This study presents the outcome and safety of this treatment strategy in a real-world context of all eligible patients in the southeast region of Sweden. While the treatment is toxic in terms of febrile neutropenia and unplanned hospitalizations, the outcome and long-term prognosis appear similar in real life and randomized controlled trial contexts. Further implementation of upfront docetaxel in mCSPC in routine care is encouraged.

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INTRODUCTION

Prostate cancer (PC) is the second most common malignancy in men. In 2018, more than 1.2 million new cases were reported worldwide, which corresponds to approximately 7% of all cancers[1]. In Sweden, the annual incidence is approximately 10500, with a median age of onset of 68 years[2]. While the 5-year overall survival (OS) (for all stages combined) is continuously improving and now exceeds 90%, the prognosis for patients presenting with upfront metastases remains less optimistic, with expected OS in the range of 30–36 mo and 5-year survival of approximately 30%[3-9].

The majority of patients with newly diagnosed metastatic PC will initially respond to androgen deprivation therapy (ADT) and are classified as castration sensitive (mCSPC). Following months to years of ADT, the disease will tend to become resistant to ADT and thus be defined as metastatic castration refractory prostate cancer

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(mCRPC). In mCRPC, palliative chemotherapy with docetaxel may offer temporary relief, but survival benefits are usually limited to a few months[4]. However, two recent multicenter trials demonstrated a considerable benefit for docetaxel when this drug was introduced early (*i.e.*, in the initial castration-sensitive phase of the disease) [10,11].

In the CHAARTED study, 790 men were randomized into six cycles of docetaxel plus ADT *vs* ADT alone. Patients were stratified according to high (visceral metastases or ≥ 4 bone lesions with ≥ 1 beyond the vertebral bodies and pelvis) or low-volume disease. The median OS was 58 mo for men treated with ADT plus docetaxel and 44 mo for men treated with ADT alone. In men with high-volume disease, the additive effect of docetaxel was even better, with a median OS benefit of 17 mo (49 mo *vs* 32 mo)[11].

STAMPEDE was a multiarmed, multistage trial that included 2962 men with both metastatic and nonmetastatic PC. Stratified randomization (2:1:1:1) allocated men to a standard of care (SOC): ADT with or without radiotherapy, SOC plus docetaxel, SOC plus zoledronic acid, and SOC plus docetaxel plus zoledronic acid. Sixty-one percent had distant metastasis, and 15% had node-positive disease. The remaining 24% presented with nonmetastatic high-risk locally advanced disease [T3/4, PSA ≥ 40 ng/mL, and/or Gleason score (GS) 8–10]. In the STAMPEDE trial, median OS was improved by 10 mo for SOC plus docetaxel compared with SOC alone (81 mo *vs* 71 mo). For the group with metastatic disease, the OS benefit was 15 mo for SOC plus docetaxel *vs* SOC alone (60 mo *vs* 45 mo)[10,12,13].

A smaller French study, GETUG-AFU 15, including approximately 400 patients who were randomized to receive ADT alone or ADT plus docetaxel[14], could not confirm the findings of CHAARTED and STAMPEDE. The French study did not reveal any statistically significant survival benefit with upfront docetaxel treatment (median OS 59 mo in the ADT plus docetaxel group *vs* 54 mo in the ADT alone group). The different outcomes of the various trials may depend on discrepancies in study populations. In the STAMPEDE and CHAARTED trials, the median PSA levels were nearly twice as high as the median PSA reported in the GETUG-15 population, indicating that the disease stage was generally more advanced in the former cohorts than in the latter. While 66% of CHAARTED patients were reported to have a high volume of metastases, only 48% were classified as such in GETUG-15. Differences were also observed in the GS, with a GS ≥ 8 reported for nearly 61% of the population in CHAARTED and 74% in STAMPEDE compared to 55% in GETUG-15[10,11,14]. Together, these findings suggest that the CHAARTED and STAMPEDE trials included patients with worse prognosis than the subjects enrolled in the GETUG-15 study.

Based on the promising results of STAMPEDE and CHAARTED, the addition of docetaxel to ADT in early mCSPC was introduced in international and national (including Swedish) guidelines, particularly for patients with high-volume disease, in 2015-2016. To be eligible for this therapy, patients should be in good general condition and without significant comorbidities[15]. The eligibility conditions in the Swedish national guidelines were used from the reported characteristics of the STAMPEDE and CHAARTED populations.

Since its introduction in routine care, it remains largely unknown to what extent the outcomes observed in the STAMPEDE and CHAARTED trials are evident in patients treated outside the frame of a randomized controlled trial. This study was therefore designed to assess the real-world outcome and safety of early docetaxel treatment for patients with mCSPC. To completely describe the real-world situation with patients of all ages and with or without concomitant comorbidities, all consecutive patients who received this treatment in the Southeast Health Care Region of Sweden since 2015 were included.

MATERIALS AND METHODS

A retrospective multicenter cohort study of all men diagnosed with primary mCSPC in the Southeast Health Care Region of Sweden was designed. This region covers approximately 1.1 million citizens and includes the oncology departments of Linköping, Jönköping, and Kalmar. These three centers provide all oncological treatments in the region. The study was conducted in accordance with the Declaration of Helsinki and was approved by the Regional Ethics Review board in Linköping, Region Östergötland, Sweden (diary number 2018/139–31). Based on the retrospective and noninterventional nature of the study and the absence of publication of individual data, the ethics board did not consider it possible or necessary to obtain written

informed consent.

Inclusion criteria were as follows: Male sex, age 18 years or older, evidence of newly diagnosed mCSPC between July 2015 and December 2017 (ICD-10 code C61.x), defined as either node positive (N+) and/or distant metastatic (M+) disease, and administration of at least one cycle of upfront docetaxel chemotherapy in addition to ADT. ADT was initiated before the start of docetaxel, either in conjunction with the diagnosis of mCSPC or earlier (*i.e.*, for patients already receiving ADT in an earlier nonmetastatic disease setting). The exclusion criteria were recurrent disease, castration refractory disease, and patient refusal to undergo ADT. Otherwise, to completely describe the real world situation, no exclusion criteria were applied.

The Swedish Cancer Registry (SCR) was used to identify eligible patients (https://www.socialstyrelsen.se/statistik-och-data/register/alla-register/cancerregistret/). Reporting to the SCR is mandatory, and the registry achieves over 95% coverage for all malignant tumors. The CSAM Cytodos software system (CSAM Health AS, Oslo, Norway), a software program being used for the prescription and administration of chemotherapy at all participating centers, was used to identify those treated with docetaxel.

Medical records were reviewed, and data were registered in a standardized case report form where patient and tumor characteristics, baseline biochemistry, Eastern Cooperative Oncology Group (ECOG) performance status, treatment regimens, toxicity parameters, PSA levels, relapse, and vital status were recorded. Patient and tumor characteristics were recorded according to the TMN classification (8th edition by Union for International Cancer Control 2017), GS according to International Society of Urological Pathology 2014, and histology according to WHO 2004.

The patients included had received docetaxel according to any of two different regimens, either by intravenous infusion every three weeks at doses of 75 mg/m^2 for a total of six cycles according to the CHAARTED and STAMPEDE treatment protocols or at a dose of 50 mg/m^2 in two-week cycles for a total of nine cycles according to local guidelines. The latter was used by one site for patients who, for any reason and at the treating oncologist's discretion, were deemed unfit to receive the 75 mg/m^2 regimen.

Bone marrow toxicity was evaluated by blood cell counts in addition to other standard biochemical parameters prior to each dose. In general, treatment response was evaluated with PSA levels at days 18–20 in every cycle and, for most patients, with X-ray computed tomography at the end of the sixth cycle (or at the ninth cycle of the 50 mg/m^2 two-week cycles).

The primary endpoint was progression-free survival (PFS) at 12 mo. PFS was defined as the time to biochemical progression in accordance with the CHAARTED protocol, where a serologic increase of the PSA level of more than 50% above nadir, reached after initiation of ADT and with two consecutive increases at least two weeks apart, clinical progression due to increasing symptoms, or deterioration or disease progression according to RECIST 1.0 were considered progression. If the PSA nadir was less than 2 μg/L, a minimum increase of more than 2 μg/L was required[10,11]. In addition, an alternative definition of progression according to the Swedish national guidelines, which stipulate serologic increase ≥ 25% from lowest PSA value after start of latest given treatment (and a minimum absolute increase of ≥ 2 μg/L), worsening of clinical symptoms, or radiological disease progression according to RECIST 1.0, was similarly applied[15].

Secondary endpoints were PFS at 24 mo, OS and treatment intensity included dose reductions, premature termination and protocol modifications, and safety of docetaxel treatment in terms of registered bone marrow toxicity and unplanned hospitalizations under and within 30 d after the last docetaxel treatment cycle. Patients were followed until death or May 18, 2018, whichever occurred first.

Statistical analysis

All statistical analyses were performed in the per-protocol population, defined as all patients who received at least one dose of docetaxel. Patient characteristics and tumor and treatment data were reported as numbers and percentages for categorical variables and medians and ranges for continuous variables. PFS at 12 and 24 mo was estimated according to the CHAARTED[11] and Swedish national guidelines[15] definitions of progressive disease (PD), respectively. Median PFS and OS for the entire cohort and subgroups defined by age over and under median (68); PSA over and under median (180); comorbidities; and presence of distant metastases or locoregional lymph node metastases only were estimated using Kaplan–Meier survival analyses, and the significance of the differences in estimates of median survival was calculated using log rank test. Cox regression analysis with a 95% confidence interval was used to evaluate hazard ratios for the same subgroups. P values below 0.05 were considered

statistically significant. Analyses were performed using IBM SPSS statistics software (IBM, version 25). Any missing data are reported in the respective Table.

RESULTS

Patients and baseline characteristics

A total of 94 eligible patients with primary mCSPC treated with docetaxel and ADT were identified and included. Baseline characteristics are shown in Table 1. For comparison, published data from CHAARTED[11] and STAMPEDE[10] are also shown in Table 1. Median age was 68 years (range 49–79). Comorbidities were present in 53% (n = 50) of patients, of which hypertension was the most prevalent. Regarding ECOG PS, data were only available in 64 (70%) of the cases, of which an overwhelming majority were ECOG PS 0–1 (n = 61, 95%). Median PSA at diagnosis was 180 (range 2–7367). Clinical TNM staging was recorded in 84 (90%) of the subjects, with T3N1M1 being the most common staging. Of those with distant metastases, bone metastases were most prevalent (n = 74, 79%), followed by lymph node metastases (n = 54, 57%). Most tumors (n = 60, 64%) were classified as GS 8–10.

Treatment data

Eighty-two (87%) of the patients received a combination of gonadotropin releasing hormone (GnRH) and a nonsteroidal antiandrogen as the castration method, nine (10%) were treated with GnRH alone, and three (3%) were surgically orchidectomized. The median time from the start of ADT until the start of docetaxel was 63 d (range 8–400). The median duration of ADT was 331 d (range 5–1038) (Table 2). Seventy-seven patients (82%) received docetaxel according to the 75 mg/m^2 every six weeks schedule, and eight (8%) received docetaxel according to the modified schedule of 50 mg/m^2 every two weeks.

Of those 77 patients commencing the 75 mg/m^2 regimen, 63 (81%) completed all 6 cycles. The mean administered dose (of 75 mg/m^2 full dose) was 91%, corresponding to 139 mg docetaxel (Table 2).

Of those eight patients commencing the 50 mg/m^2 schedule, four (50%) completed all 9 planned cycles. For this regimen, the mean administered dose was 83% of the full dose, corresponding to 86 mg of docetaxel.

Nine patients started with the 75 mg/m^2 schedule but switched to the 50 mg/m^2 regimen during treatment. In this subgroup of patients, all nine fulfilled the expected 6 cycles.

In total, 33 (35%) underwent at least one dose reduction, 13 (14%) had a dose escalation, and 47 (50%) received the initially prescribed dose throughout the treatment period (Table 2).

Progression free and OS

PFS and OS in the entire cohort are shown in Figures 1 and 2. PFS at 12 mo in the total cohort of 94 patients was 75% (95%CI: 66%-84%) or 71% (95%CI: 61%-81%), depending on whether the definition of CHAARTED/STAMPEDE or the Swedish national guidelines was used. The corresponding proportions at 24 mo were 58% (95%CI: 46%-70%) and 55% (95%CI: 43%-67%) (Table 2). The OS rates at 12 and 24 mo were 93% (95%CI: 87%-99%) and 86% (95%CI: 76%-96%), respectively. Median PFS and median OS were not reached by the data cutoff date. At the time of analysis, 65 patients had evidence of disease (69%), and 14 had died (15%) (Table 1). The best response at the end of docetaxel treatment was complete response for six subjects (6%), partial response (n = 50, 53%), stable disease (n = 15, 16%), and PD (n = 11, 12%). Twelve (13%) of the patients were non-evaluable (NE) for PFS (Table 2). Median follow-up was 20 mo.

Univariate and multivariate regression analyses of progression-free and OS in subgroups

Cox regression analyses were performed to compare PFS and OS in the following subgroups: Age older than 68 years *vs* 68 years or younger, PSA higher than 180 μg/L *vs* less than 180 μg/L, comorbidities (yes/no) and absence of distant metastases vs. presence of any distant metastases. For continuous variables (age and PSA), patients were dichotomized according to their below or above the median value of the respective parameter. Univariate Cox regression analyses showed that baseline PSA higher than 180 and the presence of distant metastases were negative prognostic

Table 1 Baseline characteristics of the first 94 patients with metastatic castration-sensitive prostate cancer treated with docetaxel and androgen deprivation therapy between July 2015 and December 2017 in the Southeast Health Care region of Sweden

	Total, *n* = 94 (%)	CHAARTED, ADT + Docetaxel	STAMPEDE, Standard of care + Docetaxel
Age, yr			
Median	68.0	64	65
Range	49-79	36-88	40-81
Prostate-specific antigen (μg/L), at diagnosis			
Median	180	50.9	70
Range	2-7367	0.2-8540.1	1-9999
Comorbidities, *n* (%)	50 (53)		
Diabetes mellitus I and II	16 (17)		56 (9)
Hyperlipidemia	23 (24)		208 (35)
Hypertension	38 (40)		
Previous malignant disease[1]	11 (11)		
Performance status (ECOG)[2], *n* (%)			
0	46 (72)	277 (69.8)	
1	15 (23)	114 (28.7)	
2	3 (5)	6 (1.5)	
T category at diagnosis[3], *n* (%)			
T1	6 (6)		0
T2	17 (18)		60 (10)
T3	46 (49)		390 (66)
T4	11 (12)		105 (18)
TX	4 (4)		35 (6)
Not assessed	10 (11)		
N category at diagnosis[3], *n* (%)			
N0	29 (31)		260 (44)
N1	42 (45)		298 (50)
NX	23 (24)		34 (6)
Metastases[3], *n* (%)			
Non-distant metastasis[4]	19 (20)		
Distant metastases	75 (80)		362 (61)
Location, *n* (%)			
Bone metastases	74 (79)		307 (52)
Liver metastases	2 (2)		6 (1)
Lung metastases	12 (13)		13 (2)
Lymph node metastases	54 (57)		102 (17)
Gleason sum score, *n* (%)			
≤ 6	2 (2)	21 (5.3)	≤ 7
7	27 (29)	96 (24.2)	110 (19%)
8-10	60 (64)	241 (60.7)	436 (74%)
Unknown	5 (5)	39 (9.8)	46 (8%)

Histology (WHO 2004), *n* (%)	
Acinar adenocarcinoma	86 (92)
Ductal carcinoma	1 (1)
Mixed type	2 (2)
Unknown	5 (5)
Follow-up, months	20
Median (IQR)	13-28
Status last follow-up, *n* (%)	
Alive, no disease progression	15 (16)
Alive, disease progression	65 (69)
Dead of disease	14 (15)

[1]Previous non-prostate cancer: Not specified (*n* = 6), basal cell carcinoma (*n* = 1), malignant melanoma (*n* = 2), pancreatic cancer (*n* = 1), thyroid cancer (*n* = 1).
[2]ECOG: Eastern Cooperative Oncology Group performance status. This information was available for 64 of 94 patients (68%).
[3]Staging according to TNM classification (8th edition UICC 2017); clinical staging *n* = 85, pathological staging *n* = 7. No information was found for *n* = 2. X means that a substage was not defined.
[4]Locoregional lymph node metastases are referred to as non-distant metastases. Corresponding data from the CHAARTED and STAMPEDE randomized trials[10,11] are shown for comparison.
ADT: Androgen deprivation therapy; PFS: Progression-free survival.

factors (HR 2.86, 95%CI: 1.39–5.87, P = 0.0041 and 3.36, 95%CI: 1.03–10.96, P = 0.045). Following multivariate analysis, statistical significance remained for PSA (2.51, 95%CI: 1.21–5.19, P = 0.013) but not for metastatic status (2.60, 95%CI: 0.78–8.65, P = 0.12) (Table 3). Similar and statistically significant findings on baseline PSA and PFS were evident when the Swedish national guidelines criteria for progressive disease were used (Table 4).

Safety

Table 5 shows registered side effects and bone marrow toxicity according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE version 4). Most strikingly, 20 (21%) of the patients experienced febrile neutropenia, and 24 (26%) had at least one episode of unplanned hospitalization under and up to 30 d after the docetaxel treatment course. Other reported adverse events, as well as reasons for early termination of the treatment, are shown in detail in Table 5.

DISCUSSION

This population-based study explored the outcome and safety of combined upfront docetaxel and ADT in mCSPC in a real-world cohort including the first 94 patients undergoing this treatment strategy in the Southeast Health Care Region of Sweden, reporting outcome and safety measures that were similar to previous findings in pivotal randomized controlled trials on the topic[10,11].

In the last few years, treatment of mCSPC with upfront docetaxel in addition to ADT has been widely implemented in routine care in Sweden and elsewhere. This significant change in practice was primarily based on the results of two major randomized controlled trials, CHAARTED and STAMPEDE[10,11]. While the results of these trials were promising, less is known about the outcome and safety of this treatment in a real-world context (*i.e.*, among patients who are treated outside the frame of a randomized controlled trial).

Based on the CHAARTED/STAMPEDE definition of progressive disease, the cohort investigated in this study exhibited PFS rates of 75% and 58% at 12 and 24 mo, respectively, closely corresponding to the outcomes displayed in the CHAARTED and STAMPEDE publications[10,11]. Similarly, OS estimates at 12 and 24 mo of 93% and 86% mirror the Kaplan–Meier curves of the two trial populations. Taken together, these results indicate that the value of upfront docetaxel added to ADT in mCSPC appears similar in randomized controlled populations and this Swedish real-world cohort.

Table 2 Treatment data

	Total, *n* = 94 (%)
ADT	
GnRH and nonsteroidal antiandrogen	82 (87)
GnRH alone	9 (10)
Orchidectomy	3 (3)
ADT	
Time from ADT start to Docetaxel start, days	
Median (range)	63 (8-400)
ADT duration, days	
Median (range)	331 (5-1038)
Docetaxel	
75[1] mg/m²	77
Adm mean dose % of full dose	91
Mean adm dose, mg	139
Mean acc dose, mg	758
Completed all cycles	63 (67)
50[2] mg/m²	8
Adm mean dose % of full dose	83
Mean adm dose, mg	86
Mean acc dose, mg	610
Completed all cycles	4 (50)
Switch	9
Adm mean dose % of full dose	87
Mean adm dose, mg	107
Mean acc dose, mg	641
Completed all cycles	9 (100)
Dose reduction	33 (35)
Dose escalation	13 (14)
Unchanged	47 (50)
Missing	1 (1)
Best response at end of Docetaxel[3]	
CR	6 (6)
PR	50 (53)
SD	15 (16)
PD	11 (12)
NE	12 (13)
Est. PFS	**Mean (95%CI)**
12 mo	
CHAARTED/STAMPEDE	75% (66-84)
Swedish national guidelines	71% (61-81)
24 mo	
CHAARTED/STAMPEDE	58% (46-70)

Swedish national guidelines	55% (43-67)
OS	
12 mo	93% (87-99)
24 mo	86% (76-96)

[1]75 mg/m^2 is given in 6 cycles every 21 d.
[2]50 mg/m^2 is given in 9 cycles every 14 d.
[3]CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. (PD definition CHAARTED: Serologic increase of PSA level of more than 50% above nadir reached after initiation of androgen deprivation therapy, two consecutive increases at least 2 wk apart. If the nadir was less than 2 μg/L, a minimum increase of more than 2 μg/L was required. STAMPEDE: Biochemical progression rose by 50% above the within 24-wk nadir and above 4 μg/L. Radiologic according to RECIST version 1.0 Swedish national guidelines: Clinical: Increasing symptoms or deterioration of general condition. Serologic ≥ 25 percent from lowest PSA value after start of latest given treatment an augmentation of at least ≥ 2 μg/L is required. Radiologic progression of existing or new metastasis).
NE: Nonevaluable; ADT: Androgen deprivation therapy; PFS: Progression-free survival.

Table 3 Progression-free survival (according to the CHAARTED and STAMPEDE definitions of progressive disease) age, PSA, comorbidities and bone metastases

	Number of patients	Number of events	HR, 95%CI, *P* value (univariate)	HR, 95%CI, *P* value (multivariate)
Age, yr (median)				
≤ 68	48	21	1.00	1.00
> 68	46	15	0.78, 0.40-1.51, 0.45	0.83, 0.42-1.67, 0.61
PSA (median)				
≤ 180	48	12	1.00	1.00
> 180	46	24	2.86, 1.39-5.87, 0.0041	2.51, 1.21-5.19, 0.013
Comorbidities				
No	44	15	1.00	1.00
Yes	50	21	1.15, 0.59-2.23, 0.68	1.19, 0.60-2.36, 0.63
Distant metastases				
No	19	3	1.00	1.00
Yes	75	33	3.36, 1.03-10.96, 0.045	2.60, 0.78-8.65, 0.12

There are some similarities and differences between the real-world population investigated in this study and the patient populations of CHAARTED and STAMPEDE. In this cohort, patients were marginally older with a median of 68 years compared to a median of 64 (CHAARTED) and 65 (STAMPEDE) in the randomized controlled trials. The vast majority of patients (95%–99%) in the real-world cohort as well as the phase-III trial populations exhibited ECOG PS 0–1. Conversely, baseline PSA levels were considerably higher in the real-world cohort (median 180) than in the controlled trial populations, which exhibited median PSA levels of 51 (CHAARTED) and 70 (STAMPEDE), potentially indicating a higher disease burden in the real-world cohort at the start of the treatment. Patients with PSA above the median also had a significantly higher risk of progressive disease, which was reflected in both univariate and multivariable regression analyses (Figure 2).

Also, the extent of metastatic disease was different in the two phase-III trials and this real-world cohort. The STAMPEDE trial reported that 61% of the total study population had metastatic disease, and the CHAARTED trial, which only included patients with evidence of metastatic disease, reported 65% with high volume disease; these latter numbers were not available from the STAMPEDE publication. In this real-world cohort, 80% had distant metastases, while 20% had non-distant metastases only. While metastatic burden was a negative prognostic factor in univariate regression analysis of this cohort, the statistical significance did not remain in multivariable analysis.

Taken together, these findings indicate that the outcome of docetaxel in mCSPC is comparable in real life, where patients are generally older and often present with more

Table 4 Progression-free survival (according to Swedish national guidelines) age, PSA, comorbidities and bone metastases

	Number of patients	Number of events	HR, 95%CI, *P* value (univariate)	HR, 95%CI, *P* value (multivariate)
Age, yr (median)				
≤ 68	48	22	1.00	1.00
> 68	46	17	0.83, 0.44-1.56, 0.55	0.88, 0.46-1.71, 0.71
PSA (median)				
≤ 180	48	13	1.00	1.00
> 180	46	26	2.86, 1.44-5.69, 0.0028	2.57, 1.28-5.16, 0.0081
Comorbidities				
No	44	17	1.00	1.00
Yes	50	22	1.06, 0.56-2.00, 0.85	1.08, 0.56-2.07, 0.83
Distant metastases				
No	19	4	1.00	1.00
Yes	75	35	2.69, 0.96-7.59, 0.061	2.11, 0.73-6.06, 0.17

advanced disease in terms of baseline PSA levels, and phase-III trial populations with more beneficial baseline characteristics.

Completion of all planned cycles was reported in 86% of the CHAARTED and 76% of the STAMPEDE trial populations. Similar figures were found in this cohort: 81% completed the entire treatment course, and 35% (n = 33) underwent dose reductions. Eight (8%) also received a modified 50 mg/m^2 every-two-weeks schedule from the start, and nine (10%) converted from the standard 75 mg/m^2 every-three-weeks to this modified 50 mg/m^2 protocol (switch). There is currently little evidence for this 50 mg/m^2 protocol in mCSPC, and the deviation from SOC probably reflects an eagerness to provide the treatment to frail and/or comorbid patients who otherwise would be considered not eligible for docetaxel. The low number of patients in this subgroup together with the finding that only 50% of the patients who began with 50 mg/m^2 were able to fulfil all planned cycles mean that the efficacy and safety for this adapted treatment schedule remain unproven.

Safety data of this study reveal that 21% of the patients experienced febrile neutropenia and, in total, 26% had at least one episode of unplanned hospitalization under or shortly after the docetaxel treatment course. While only 4% had their treatments prematurely terminated due to febrile neutropenia, these findings still emphasize that the docetaxel 75 mg/m^2 every-three-weeks regimen is a particularly toxic treatment. This result might be particularly important when upfront docetaxel is considered for older and/or frail patients who would not be eligible for the STAMPEDE and CHAARTED trials.

To our knowledge, this is the first study that systematically reports the real-world outcome of upfront docetaxel in a Scandinavian context. Other real-world studies conducted in other countries and/or ethnic groups corroborate the results of this study. Lavoie *et al*[16] assessed the clinical effectiveness of upfront docetaxel in a Canadian setting, showing a similar outcome and safety data to those of this study, with 12-mo OS of 91% and 26% experiencing grade 3–4 febrile neutropenia[16], and comparable outcomes were also reported in a German study[17] and in Northern American non-white populations[18].

The primary strengths of this study include the truly real-world setup, covering all eligible patients in a reasonably large geographical region. Because there are no nongovernmental health care providers that offer cancer chemotherapy in the Southeast Region in Sweden, every patient who was given the therapy and met the inclusion criteria was included. Another additional value is that Swedish health care is generally available and publicly funded, meaning that all individuals, regardless of socioeconomic status, are offered similar treatment and follow-up programs. In the current era of novel therapeutic options in the early and late stages of PC, including targeted treatments such as radium 223[19] and lutetium-177 [^{177}Lu]-PSMA-617[20], it becomes increasingly important to assess the efficacy and tolerability of treatments already established in standard practice.

Table 5 Side-effects reported

	Total, *n* = 94 (%)
Reason for termination of treatment	
Completed as planned	74 (79)
Adverse event	11 (12)
Fatigue	5 (5)
Tumor progression	2 (2)
Patient preference	1 (1)
Other	1 (1)
Bone marrow toxicity	
Hemoglobin	
Any grade	16 (17)
≥ grade 3-4	0
White blood cell count	
Any grade	20 (21)
≥ grade 3-4	15 (16)
Neutrophil count	
Any grade	19 (20)
≥ grade 3-4	19 (20)
Grade missing	1
Platelet count	
Any grade	2 (2)
≥ grade 3-4	0
Unplanned hospitalization under and within 30 d after chemotherapy	24 (26)
Febrile neutropenia	20 (21)

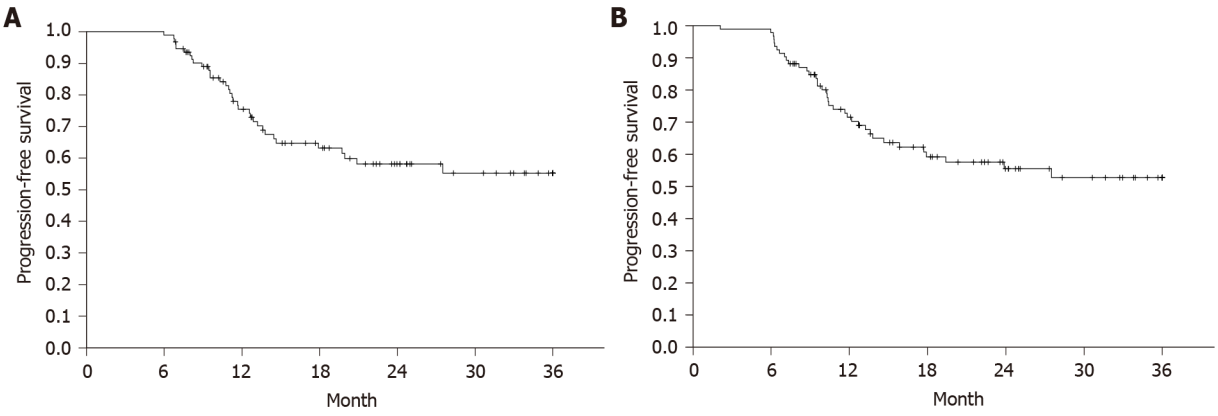

Figure 1 Progression-free survival according to the CHAARTED and STAMPEDE definitions of progressive disease and Swedish national guidelines. Time from date of diagnosis to last follow-up/death. Censored at 36 mo. A: CHAARTED and STAMPEDE; B: Swedish national guidelines.

The study's primary weakness mirrors its primary strength: The retrospective inclusion and, to some extent, different treatment regimens prescribed make it more difficult to define the efficacy and toxicity of the treatment schedule evaluated in the STAMPEDE and CHAARTED trials. The limited sample size means that subgroup analyses should be considered exploratory, and that their results should be interpreted with care.

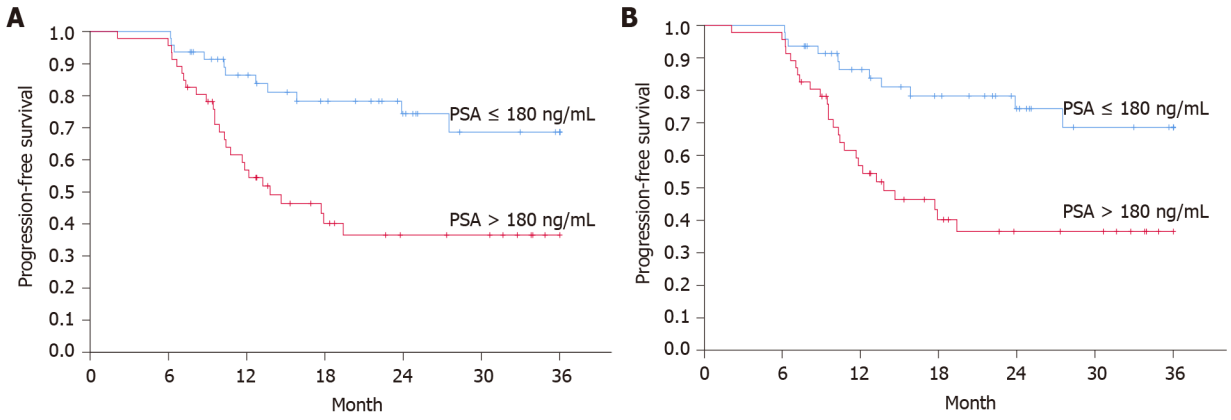

Figure 2 Progression-free survival for subgroups defined by PSA over/under median. A: Progression-free survival (PFS) according to the CHAARTED and STAMPEDE definitions of progressive disease (log-rank: $P = 0.0027$); B: PFS according to the Swedish national guidelines (log-rank: $P = 0.0018$). Time from date of diagnosis to last follow-up/death. Censored at 36 mo.

CONCLUSION

This study provides additional evidence on the efficacy and safety of upfront docetaxel in a real-world context of mCSPC. Progression-free and OS appear similar in real-world and randomized controlled trial settings. Febrile neutropenia remains a frequent and severe adverse event, and unplanned hospitalizations are common in patients undergoing this treatment. High baseline PSA indicates worse prognosis. In conclusion, results support the implementation of upfront docetaxel plus ADT as part of the SOC treatment strategy in mCSPC.

ARTICLE HIGHLIGHTS

Research background

Randomized phase-III trials indicate that upfront treatment with docetaxel, in addition to androgen deprivation therapy (ADT), improves survival in metastatic castration-sensitive prostate cancer (mCSPC). Less is known about the outcome of such treatment in real-world patients treated outside the frames of a clinical trial.

Research motivation

It is important to assess the outcome and safety of upfront docetaxel and ADT combination therapy following its implementation in real-world patients with mCSPC.

Research objectives

To evaluate the outcome of docetaxel and ADT combination therapy in real-world patients with mCSPC in terms of progression-free survival (PFS), overall survival (OS), and safety.

Research methods

A multicenter retrospective noninterventional study was performed and included 94 first consecutive real-world patients with mCSPC receiving upfront docetaxel and ADT in the Southeast Health Care Region of Sweden. Univariate and multivariate regression analyses were performed to identify prognostic parameters. Adverse events and unplanned hospitalizations were thoroughly reviewed.

Research results

PFS at 12 and 24 mo was 75% and 58%, while OS was 93% and 86% concurrently points, respectively. High baseline PSA levels were associated with worse prognosis in multivariate regression analysis. Twenty-one percent of the patients experienced febrile neutropenia, and 26% had at least one episode of unplanned hospitalization.

Research conclusions

The outcome and safety of docetaxel and ADT combination therapy in mCSPC appear

similar in real-world and randomized controlled trial populations. This study supports further implementation of this treatment strategy in standard of care.

Research perspectives

Future studies must identify clinically useful biomarkers and tools for tailored treatment strategies in patients with mCSPC.

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ORIGINAL ARTICLE

Retrospective Cohort Study

Uptake and outcomes of small intestinal and urinary tract cancer surveillance in Lynch syndrome

Jeshua DeJesse, Ravy K Vajravelu, Christina Dudzik, Gillain Constantino, Jessica M Long, Kirk J Wangensteen, Kathleen D Valverde, Bryson W Katona

ORCID number: Jeshua DeJesse 0000-0002-2658-4628; Ravy K Vajravelu 0000-0002-6557-3307; Christina Dudzik 0000-0001-5485-9804; Gillain Constantino 0000-0002-7997-7572; Jessica M Long 0000-0003-0382-7890; Kirk J Wangensteen 0000-0001-6042-6490; Kathleen D Valverde 0000-0001-6515-8982; Bryson W Katona 0000-0001-8186-9119.

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Jeshua DeJesse, Kathleen D Valverde, Department of Genetics, University of Pennsylvania, Philadelphia, PA 19104, United States

Ravy K Vajravelu, Christina Dudzik, Gillain Constantino, Kirk J Wangensteen, Bryson W Katona, Division of Gastroenterology and Hepatology, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA 19104, United States

Jessica M Long, Division of Hematology and Oncology, University of Pennsylvania, Philadelphia, PA 19104, United States

Corresponding author: Bryson W Katona, MD, PhD, Assistant Professor, Division of Gastroenterology and Hepatology, University of Pennsylvania Perelman School of Medicine, 3400 Civic Center Blvd, 751 South Pavilion, Philadelphia, PA 19104, United States. bryson.katona@pennmedicine.upenn.edu

Abstract

BACKGROUND

Lynch syndrome (LS) is a hereditary cancer predisposition syndrome associated with increased risk of multiple cancers. While colorectal cancer surveillance decreases mortality in LS and is recommended by guidelines, there is lack of evidence for the efficacy of surveillance for extra-colonic cancers associated with LS, including small intestinal cancer (SIC) and urinary tract cancer (UTC). Given the limited evidence, guidelines do not consistently recommend surveillance for SIC and UTC, and it remains unclear how often individuals will choose to undergo and follow through with extra-colonic surveillance recommendations.

AIM

To study factors associated with SIC and UTC surveillance uptake and outcomes in LS.

METHODS

This is an IRB-approved retrospective analysis of individuals with LS seen at a tertiary care referral center. Included individuals had a pathogenic or likely pathogenic variant in *MLH1*, *MSH2*, *MSH6*, *PMS2*, or *EPCAM*, or were a confirmed obligate carrier, and had at least one documented visit to our center. Information regarding SIC and UTC surveillance was captured for each individual, and detailed personal and family history was obtained for individuals

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who had an initial LS management visit in our center's dedicated high-risk LS clinic between January 1, 2017 and October 29, 2020. During these initial management visits, all patients had in-depth discussions of SIC and UTC surveillance with 1 of 3 providers experienced in LS management to promote informed decision-making about whether to pursue SIC and/or UTC surveillance. Statistical analysis using Pearson's chi-squared test and Wilcoxon rank-sum test was completed to understand the factors associated with pursuit and completion of SIC and UTC surveillance, and a *P* value below 0.05 was deemed statistically significant.

RESULTS
Of 317 individuals with LS, 86 (27%) underwent a total of 105 SIC surveillance examinations, with 5 leading to additional work-up and no SICs diagnosed. Additionally, 99 (31%) patients underwent a total of 303 UTC surveillance examinations, with 19 requiring further evaluation and 1 UTC identified. Of 155 individuals who had an initial LS management visit between January 1, 2017 and October 29, 2020, 63 (41%) chose to undergo SIC surveillance and 58 (37%) chose to undergo UTC surveillance. However, only 26 (41%) and 32 (55%) of those who initially chose to undergo SIC or UTC surveillance, respectively, successfully completed their surveillance examinations. Individuals with a pathogenic variant in *MSH2* or *EPCAM* were more likely to initially choose to undergo SIC surveillance ($P = 0.034$), and older individuals were more likely to complete SIC surveillance ($P = 0.007$). Choosing to pursue UTC surveillance was more frequent among older individuals ($P = 0.018$), and females more frequently completed UTC surveillance ($P = 0.002$). Personal history of cancer and family history of SIC or UTC were not significantly associated with electing nor completing surveillance. Lastly, the provider discussing SIC/UTC surveillance was significantly associated with subsequent surveillance choices.

CONCLUSION
Pursuing and completing SIC/UTC surveillance in LS is influenced by several factors, however broad incorporation in LS management is likely unhelpful due to low yield and frequent false positive results.

Key Words: Lynch syndrome; Urinary tract cancer; Intestinal neoplasms; Early diagnosis of cancer; Patient preference; Gastrointestinal surgical procedure

Core Tip: This retrospective study of a Lynch syndrome (LS) cohort measured the uptake and outcome of small intestinal cancer (SIC) and urinary tract cancer (UTC) surveillance. When given the option of surveillance, a minority of patients elected surveillance, and patient completion of surveillance exams was suboptimal. Completed surveillance exams rarely detected SIC/UTC and resulted in multiple false positives that led to additional follow-up procedures. Pursuing and completing SIC/UTC surveillance in LS was influenced by several factors, however given the low yield and positive predictive value, broad incorporation of SIC/UTC surveillance in LS management is unlikely to be helpful.

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INTRODUCTION

Lynch syndrome (LS) is an autosomal dominant cancer predisposition syndrome

resulting from a disease-causing variant in the *MLH1*, *MSH2*, *MSH6*, *PMS2*, or *EPCAM* gene. LS is primarily associated with increased colorectal and endometrial cancer risk but is also associated with increased risk of gastric, small intestinal, hepatobiliary, ovarian, urinary tract, brain, and skin cancers[1-3]. Colorectal cancer surveillance has proven effective in LS, with colonoscopy decreasing colorectal cancer mortality in LS by approximately 65%, which has led to inclusion of frequent colonoscopy in all LS management guidelines[4-8]. There is less agreement about the utility of surveillance for extra-colonic cancers in LS. Although recent reports show upper gastrointestinal cancer surveillance could detect gastric and duodenal cancers in LS[9,10], differences remain in recommended upper gastrointestinal cancer surveillance[5,11]. There is a paucity of evidence supporting efficacy of other types of extra-colonic cancer surveillance in LS, including small intestinal cancer (SIC) and urinary tract cancer (UTC) surveillance, as well as a lack of data addressing provider recommendation and patient uptake of SIC and UTC surveillance.

The cumulative risk of small intestinal adenocarcinoma in LS is up to 11%, markedly higher than the general population risk of 0.3%[5,7,12-14]. Options for SIC surveillance include small bowel follow through (SBFT), video capsule endoscopy (VCE), or CT/MRI enterography, with VCE being considered the most sensitive for small intestinal pathology[15,16]. However, there are limitations to the use of VCE, including cost and possible capsule retention in those with a history of prior abdominal surgery[17]. A study of SIC surveillance with VCE in 35 asymptomatic LS patients identified 2 adenomas and 1 adenocarcinoma, all distal to the duodenum[18]. A separate study of VCE performed on 200 asymptomatic LS patients led to the discovery of a small intestinal adenoma and a small intestinal adenocarcinoma[19]; this same group performed follow-up VCE on 155 patients of the same cohort a mean interval of 2 years after the first VCE which led to no additional small intestinal neoplasms being detected[20]. Other prospective and retrospective studies of LS cohorts concluded that the low frequency of SIC in LS prevented surveillance from being cost effective[20,21]. Given the limited data on SIC surveillance, there is currently no consensus recommendation regarding dedicated SIC surveillance for individuals with LS.

Individuals with LS are also at increased risk of UTC, including cancer of the renal pelvis, bladder, and ureters[21-23]. Cumulative risk of UTC in LS is up to 28%, a 20-fold increase in risk compared to the general population, with the highest risk seen in males with pathogenic *MSH2* variants[5,13,21,24,25]. Options for UTC surveillance include urinalysis, urine cytology, CT urogram, or cystoscopy. A study of the Danish HNPCC Registry found that only 2 (0.1%) of 1,868 urine cytology screens in 977 patients led to a diagnosis of an asymptomatic tumor, and 22 screens (1.2%) led to a false positive result, leading the authors to conclude that urine cytology is not an ideal surveillance method in LS[23]. Another study of the same registry found that 78% of UTCs in the cohort occurred in patients without a family history of UTC, and 73% of UTCs were in individuals with a pathogenic *MSH2* variant or a first degree relative of a *MSH2* carrier, leading the authors to suggest that UTC surveillance should not be limited to patients with a family history of UTC and should be focused on patients with pathogenic *MSH2* variants[25]. There has been disagreement amongst LS guidelines regarding the utility of UTC surveillance as some groups, like the U.S. Multi-Society Task Force, have recommended considering routine surveillance[6,26-29], while others, including the Mallorca group, have deemed there is not sufficient evidence to recommend regular surveillance[5,7,23,30].

Apart from whether SIC or UTC surveillance is recommended, it is equally important to understand whether individuals with LS will undergo surveillance if recommended, especially given the already intensive surveillance recommendations often mandated as part of a comprehensive LS surveillance program. Data characterizing extra-colonic cancer surveillance compliance in LS are limited, however a large study of annual UTC surveillance in LS found a compliance rate of only 29%[23]. This compliance is substantially lower than colonoscopy compliance (68%-85%)[31,32]. Furthermore, it remains uncertain what factors influence a patient's decision to pursue SIC or UTC surveillance in the presence of variable guidelines and recommendations.Herein, we aim to characterize the uptake and outcomes of SIC and UTC surveillance in LS, including patients' decisions about whether to pursue surveillance despite the limited evidence on efficacy and varying guideline recommendations, whether these individuals successfully complete surveillance, and the yield of the surveillance examinations.

MATERIALS AND METHODS

This is a retrospective study of individuals with LS seen at Penn Medicine, approved by the University of Pennsylvania Institutional Review Board. Individuals with LS had a confirmed pathogenic or likely pathogenic variant in *MLH1*, *MSH2*, *MSH6*, *PMS2*, or *EPCAM*, or were an obligate carrier of a familial pathogenic or likely pathogenic variant in one of these genes, and had at least one visit to the health system.

The electronic medical records of all LS patients were reviewed for pertinent details regarding demographics, medical history, family history, and surveillance examination results. Data were captured and entered into a REDCap database hosted at the University of Pennsylvania to facilitate statistical analysis. SIC surveillance was defined as a VCE or SBFT ordered in the absence of symptoms concerning for small intestinal pathology. Abnormal SIC surveillance results included any finding that was suspicious for a polyp or neoplastic process. UTC surveillance was defined as a urinalysis or urine cytology ordered in the absence of symptoms concerning for urinary tract pathology. Abnormal UTC surveillance results included a urine dipstick positive for blood, microscopic detection of red blood cells above the upper limit of normal, or atypical/abnormal urothelial cells found on urine cytology.

In an effort to further characterize recent SIC and UTC surveillance decisions, this study reviewed data from individuals who had their initial office visit for LS management in the Penn Medicine Gastrointestinal Cancer Genetics Program between January 1, 2017 and October 29, 2020 and were seen by 1 of 3 providers experienced in LS management. During the initial office visit to formulate the LS surveillance plan, each patient was engaged in detailed discussion about SIC and UTC surveillance covering the risks of surveillance (including false positive results generating additional evaluations), potential benefits, lack of robust data showing surveillance prevents cancer and/or reduces mortality, and lack of consistent guideline recommendations. If after this in-depth discussion a patient decides to pursue SIC and/or UTC surveillance, the provider orders appropriate testing and notes the patient's decision in their chart. If no evidence of a completed surveillance examination was in the patient's electronic medical record, the surveillance examination was noted as incomplete.

Statistical analysis using Pearson's chi-squared test for categorical variables and Wilcoxon rank-sum test for continuous variables was completed with a Type I error rate of 0.05 using Stata software version 16.1.

RESULTS

Three hundred seventeen individuals with LS had a visit to the health system and were included as part to the cohort; the cohort was mostly white (86%), non-Hispanic (98%), and female (59%), with a median age of 49 years (IQR: 38-61 years) (Supplementary Table 1). Distribution of LS genes in the cohort was relatively uniform as the percentage of pathogenic/likely pathogenic variants in *MLH1*, *MSH2*/*EPCAM*, *MSH6*, and *PMS2* was 23%, 35%, 22%, and 20% respectively. Of the 317 individuals with LS, 86 (27%) underwent a total of 105 SIC surveillance examinations with the majority (55%) being VCEs. There were no SICs diagnosed. However, 5 of these surveillance VCEs were suspicious for a small bowel polyp, which led to further work-up with invasive procedures (Table 1). None of the follow-up procedures led to the identification of any neoplastic small intestinal lesions. The positive predictive value (PPV) for VCE was 0% with a one-sided 97.5% confidence interval of 0%-52%. Of this same cohort of 317 individuals with LS, 99 (31%) underwent a total of 303 UTC surveillance examinations, the majority (65%) of which were urinalysis, with 19 of these surveillance tests showing abnormal findings that prompted further evaluation (Table 1). Of the 19 abnormal surveillance results leading to further work up, 10 (53%) were urine cytologies, and 1 surveillance urine cytology led to a single UTC diagnosis of a non-invasive high grade urothelial papillary carcinoma in a 64 year-old male individual with a pathogenic variant in *MSH2*. This patient had localized disease that was treated with nephroureterectomy and retroperitoneal/pelvic lymph node dissection and is subsequently followed by regular cystoscopy and MRI without reoccurrence. Urinalysis had a PPV of 0% with a one-sided 97.5% confidence interval of 0%-34%, and urine cytology had a PPV of 10% with a 95% confidence interval of 0.25%-45%.

To understand the factors influencing uptake of SIC and UTC surveillance in LS, we further analyzed those individuals with LS who had an initial LS management visit with our program between January 1, 2017 and October 29, 2020. This cohort was

Table 1 Small intestinal cancer and urinary tract cancer surveillance outcomes in Lynch syndrome

	***n* = 317**
Individuals who underwent SIC surveillance	86 (27%)
SIC surveillance exams completed per individual, median (IQR)	1 (1-1)
Total completed SIC surveillance exams	105
VCE	58 (55%)
SBFT	47 (45%)
Abnormal SIC surveillance exams leading to further work-up	5 (5%)
VCE	5 (100%)
SBFT	0 (0%)
Abnormal SIC surveillance exams leading to a SIC diagnosis	0 (0%)
Individuals who underwent UTC surveillance	99 (31%)
UTC surveillance exams completed per individual, median (IQR)	2 (1-3)
Total completed UTC surveillance exams	303
Urinalysis	197 (65%)
Urine cytology	106 (35%)
Abnormal UTC surveillance exams leading to further work-up	19 (6%)
Urinalysis	9 (47%)
Urine Cytology	10 (53%)
Abnormal UTC surveillance exams leading to a UTC diagnosis	1 (5%)

SIC: Small intestinal cancer; UTC: Urinary tract cancer; VCE: Video capsule endoscopy; SBFT: Small bowel follow through.

comprised of 155 individuals who were primarily white (90%) and female (65%), and the majority had private insurance (86%) (Table 2). There was a near equal distribution of patients across all LS genes, with 70 (45%) of these individuals having a personal history of cancer, including 2 (1%) with SIC and 6 (4%) with UTC. Almost all (97%) of these individuals had a family history of cancer, with 8 (5%) having a family history of SIC, and 35 (23%) having a family history of UTC. A majority of the cohort (78%) was treated by a single provider.

At their initial LS management visit, during which the risks and benefits of SIC and UTC surveillance were reviewed to allow patients to make an informed decision, 63 (41%) patients chose to undergo SIC surveillance and 58 (37%) chose to undergo UTC surveillance (Figure 1). However, of those who chose to undergo SIC and UTC surveillance at their initial management visit, only 26 (41%) and 32 (55%) completed their SIC or UTC surveillance examinations, respectively.

We next assessed for factors associated with choosing to undergo SIC and/or UTC surveillance as well as successfully completing surveillance tests. Individuals with a pathogenic variant in *MSH2* or *EPCAM* were more likely to initially choose to undergo SIC surveillance compared to those with other mutations as this group accounted for 24 (38%) of the individuals who chose SIC surveillance (Table 3, $P = 0.034$). Older age was associated with completion of SIC surveillance ($P = 0.007$), as the median age of those who completed SIC surveillance was 56 years—14 years higher than the median age of those who did not complete surveillance. Additionally, there were statistically significant differences in choosing and completing SIC surveillance in a provider-dependent manner.

For UTC surveillance, older age was associated with choosing to undergo surveillance; the median age of those who chose to undergo surveillance was 48 years, 8 years higher than those who chose no surveillance (Table 4, $P = 0.018$). Female sex was associated with UTC surveillance completion ($P = 0.002$) as 26 (81%) individuals who completed UTC surveillance were female. Ashkenazi Jewish ancestry was also associated with completion of UTC surveillance ($P = 0.006$). The individuals who were treated by Provider 1 chose UTC surveillance less frequently ($P = 0.000$) but were more likely to complete surveillance exams if they chose to pursue them ($P = 0.000$).

Table 2 Characteristics of patients with an initial Lynch syndrome management visit between January 1, 2017 and October 29, 2020

	***n* = 155**
Age (yr), median (IQR)	46 (33-58)
Female sex	100 (65%)
Race	
White	139 (90%)
Black	3 (2%)
Asian	7 (5%)
Other	2 (1%)
Unknown	4 (3%)
Hispanic ethnicity	2 (1%)
Ashkenazi Jewish ancestry	16 (10%)
Lynch syndrome gene	
MLH1	29 (19%)
MSH2 or *EPCAM*	40 (26%)
MSH6	45 (29%)
PMS2	41 (26%)
Personal history of cancer	70 (45%)
Small intestinal	2 (1%)
Urinary tract	6 (4%)
Colorectal	30 (19%)
Family history of cancer	151 (97%)
Small intestinal	8 (5%)
Urinary tract	35 (23%)
Colorectal	113 (73%)
Type of insurance	
Private insurance	134 (86%)
Medicare insurance	16 (10%)
Medicaid insurance	5 (3%)
Provider	
Provider 1	121 (78%)
Provider 2	17 (11%)
Provider 3	17 (11%)

Personal history of cancer and family history of SIC or UTC were not associated with initially choosing to undergo surveillance or surveillance completion (Tables 3-4). Race, Hispanic ethnicity, and insurance status were also not associated with choosing nor completing surveillance (Tables 3-4).

DISCUSSION

Lynch syndrome is a high-risk cancer predisposition syndrome, with affected individuals requiring lifelong cancer risk management. Whereas some surveillance, such as colorectal cancer surveillance, is strongly recommended in LS, there is a lack of consistent recommendations for SIC and UTC surveillance due to the limited data showing this extra-colonic surveillance is effective. In this study, we investigated uptake of SIC and UTC surveillance in LS and the outcomes of the associated

Table 3 Characteristics of individuals with Lynch syndrome who chose to undergo and/or completed small intestinal cancer surveillance

	Surveillance chosen (*n* = 63)	Surveillance not chosen (*n* = 92)	*P* value	Surveillance completed (*n* = 26)	Surveillance not completed (*n* = 37)	*P* value
Age (yr), median (IQR)	48 (37-59)	42 (32-57)	0.114	56 (46-62)	42 (33-54)	0.007[a]
Female	44 (70%)	56 (61%)	0.252	21 (81%)	23 (62%)	0.113
Race			0.750			0.531
White	58 (92%)	81 (88%)		24 (92%)	34 (92%)	
Black	1 (2%)	2 (2%)		0 (0%)	1 (3%)	
Asian	3 (5%)	4 (4%)		2 (8%)	1 (3%)	
Other	0 (0%)	2 (2%)		-	-	
Unknown	1 (2%)	3 (3%)		0 (0%)	1 (3%)	
Hispanic ethnicity	1 (2%)	1 (1%)	0.912	0 (0%)	1 (3%)	0.211
AJ ancestry	5 (8%)	11 (12%)	0.687	1 (4%)	4 (11%)	0.489
Lynch syndrome gene			0.034[a]			0.357
MLH1	10 (16%)	19 (21%)		5 (19%)	5 (14%)	
MSH2 or *EPCAM*	24 (38%)	16 (17%)		7 (27%)	17 (46%)	
MSH6	14 (22%)	31 (34%)		8 (31%)	6 (16%)	
PMS2	15 (24%)	26 (28%)		6 (23%)	9 (24%)	
Personal history of cancer	33 (52%)	37 (40%)	0.135	17 (65%)	16 (43%)	0.083
Family history of SIC	5 (8%)	3 (3%)	0.182	1 (4%)	4 (11%)	0.340
Insurance			0.111			0.314
Private	58 (92%)	76 (83%)		25 (96%)	33 (89%)	
Medicare	5 (8%)	11 (12%)		1 (4%)	4 (11%)	
Medicaid	0 (0%)	5 (5%)		-	-	
Provider			0.000[a]			0.030[a]
Provider 1	39 (62%)	82 (89%)		17 (65%)	22 (59%)	
Provider 2	13 (21%)	4 (4%)		8 (31%)	5 (14%)	
Provider 3	11 (17%)	6 (7%)		1 (4%)	10 (27%)	

[a]$P < 0.05$. SIC: Small intestinal cancer; AJ: Ashkenazi Jewish.

surveillance examinations. Our data shows that after engagement in an in-depth discussion on the potential benefits, risks, and limitations of SIC and UTC surveillance, a majority of patients decided to forgo surveillance, and those that initially chose to pursue surveillance had low completion rates. Additionally, we show a low PPV with frequent false positive results for both SIC and UTC surveillance, and the overall yield of cancer diagnoses was low for all surveillance methods. Taken together, our results do not support regular incorporation of SIC and UTC surveillance into standard LS cancer risk management care.

Effective cancer surveillance in LS should ideally utilize testing that is cost-effective and low risk, and surveillance should ultimately increase survival[7]. An ideal test must also have a high level of sensitivity and specificity, as false positive cancer surveillance results not only lead to further work-up but also lead to emotional distress for the patient as well as decreased compliance rates and follow-up with subsequent surveillance exams[33,34]. Additionally, false positive results can expose patients to possible harms resulting from superfluous follow-up procedures as well as

Table 4 Characteristics of individuals with Lynch syndrome who chose to undergo and/or completed urinary tract cancer surveillance

	Surveillance chosen (*n* = 58)	Surveillance not chosen(*n* = 97)	*P* value	Surveillance completed (*n* = 32)	Surveillance not completed (*n* = 26)	*P* value
Age (yr), median (IQR)	48 (39-60)	40 (32-55)	0.018[a]	45 (40-61)	50 (37-60)	0.772
Female	37 (64%)	63 (65%)	0.884	26 (81%)	11 (42%)	0.002[a]
Race			0.431			0.498
White	54 (93%)	85 (88%)		30 (94%)	24 (92%)	
Black	1 (2%)	2 (2%)		0 (0%)	1 (4%)	
Asian	3 (5%)	4 (4%)		2 (6%)	1 (4%)	
Other	0 (0%)	2 (2%)		-	-	
Unknown	0 (0%)	4 (4%)		-	-	
Hispanic ethnicity	0 (0%)	2 (2%)	0.336	-	-	-
AJ ancestry	3 (5%)	13 (13%)	0.229	3 (9%)	0 (0%)	0.006[a]
Lynch syndrome gene			0.640			0.171
MLH1	8 (14%)	21 (22%)		3 (9%)	5 (19%)	
MSH2 or *EPCAM*	17 (29%)	23 (24%)		9 (28%)	8 (31%)	
MSH6	17 (29%)	28 (29%)		13 (41%)	4 (15%)	
PMS2	16 (28%)	25 (26%)		7 (22%)	9 (35%)	
Personal history of cancer	29 (50%)	41 (42%)	0.349	17 (53%)	12 (46 %)	0.597
Family history of UTC	15 (26%)	20 (21%)	0.477	11 (34%)	4 (15%)	0.118
Insurance			0.631			0.402
Private	50 (86%)	84 (87%)		29 (91%)	21 (81%)	
Medicare	7 (12%)	9 (9%)		3 (9%)	4 (15%)	
Medicaid	1 (2%)	4 (4%)		0 (0%)	1 (4%)	
Provider						
Provider 1	36 (62%)	85 (88%)	0.001[a]	28 (88%)	8 (31%)	0.000[a]
Provider 2	12 (21%)	5 (5%)		2 (6%)	10 (38%)	
Provider 3	10 (17%)	7 (7%)		2 (6%)	8 (31%)	

[a]$P < 0.05$. UTC: Urinary tract cancer; AJ: Ashkenazi Jewish.

additional medical costs related to these procedures. Our data showed that both SIC and UTC surveillance had a low PPV, with 24 positive surveillance studies leading to the diagnosis of only 1 neoplastic lesion. These data are consistent with a previous study of SIC screening in asymptomatic LS patients that observed 13 VCE results suspicious for SIC, none of which led to the confirmation of a SIC through follow-up testing[20]. While VCE is the most sensitive test for picking up small intestinal pathology[15,16], it may have a downside of being less specific, leading to high rates of false positive test results that require patients to undergo unnecessary invasive procedures. In addition to this observed low specificity, the sensitivity of urine cytology in asymptomatic LS patients has also been previously reported to be poor (29%)[23]. Effective cancer surveillance should also result in improved survival. With only one individual in our study having a surveillance-detected UTC or SIC, we are unable to meaningfully comment on the impact of surveillance on cancer survival, however at this time it remains unclear if early diagnosis of UTC or SIC leads to higher survival rates[7,35]. Together, the low yield and low PPV of SIC and UTC surveillance described in this study do not provide support for broad inclusion of SIC and/or UTC surveillance in LS management; however, whether this surveillance should be

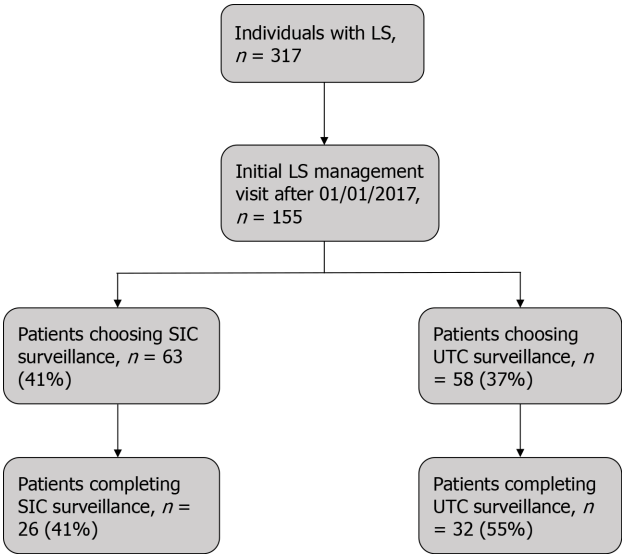

Figure 1 Schematic representation of small intestinal cancer and urinary tract cancer surveillance uptake among individuals with LS. SIC: Small intestinal cancer; UTC: Urinary tract cancer; LS: Lynch syndrome.

considered for certain sub-groups of patients with LS will require future larger studies.

The majority of the patients in our cohort chose not to pursue SIC or UTC surveillance after having an in-depth discussion with their provider about the risks, benefits, and limitations of surveillance. It is likely that this discussion and the provider involved influenced the patients' decision making; accurate risk perception has previously been observed to impact LS patients' behaviors towards cancer surveillance[36]. The difference in cancer surveillance behaviors between patients of different providers could result from differing manners in which the providers discussed surveillance options in an individual's initial LS management visit. In this study, individuals with pathogenic variants in *MSH2* or *EPCAM* chose to pursue SIC surveillance more frequently, while older individuals chose to pursue UTC surveillance more often. In a study of colorectal cancer survivors with Lynch-like syndrome, increased cancer worry was associated with a stronger belief that extra-colonic cancer surveillance was necessary[37]; perhaps learning of the increased cancer risk that comes with age and pathogenic *MSH2* or *EPCAM* variants compelled patients in this study to opt for additional surveillance. The observation that individuals with *MSH2* or *EPCAM* pathogenic variants were more likely to choose to undergo SIC surveillance, but not UTC surveillance, compared to individuals with pathogenic variants in other genes may be due to a Type I error or may also be influenced by other factors that were not captured in this study. The choice to initially pursue surveillance was likely also influenced by other factors not examined in this study. Some individuals may have decided to forgo surveillance due to the emotional distress that comes with the increased surveillance burden and the requirement to navigate potentially challenging health care system infrastructures, factors that have been shown to influence other cancer surveillance in LS[36]. Other variables such as associated costs and familial obligations may also have affected patient decision making. A future prospective study surveying the attitudes and perceptions of individuals with LS about low-evidence surveillance tests would be important to help answer this question.

The completion rate of SIC and UTC surveillance in this cohort was 41% and 55%, respectively, which is higher than a previous study of compliance with UTC surveillance in LS finding a rate of 29%[23]. Our increased completion rate may have resulted from the in-depth discussion on this surveillance between the patient and provider. However, our observed completion rate was lower than the reported compliance rate for colonoscopy within the LS population (68-85%)[31,32]. Colorectal cancer risk is well-recognized as one of the highest cancer risks in LS, and therefore, the lower completion rate compared to colorectal cancer surveillance may be due to the individuals' perception of the decreased risk of extra-colonic cancers[36]. The discrepancy could also be due to provider emphasis on the effectiveness of colonoscopy to decrease mortality and morbidity. In this study, we observed that providers may influence an individual's choices towards SIC and UTC surveillance, both in terms of choosing to undergo surveillance and completing surveillance.

Additionally, we found completion of SIC surveillance was more frequent among older individuals, and completion of UTC surveillance was more frequent among those of female sex and Ashkenazi Jewish ancestry. These findings present a contrast to another study of a LS cohort which observed that cancer surveillance completion was associated with younger age[38]. This other study also ascertained that surveillance completion was influenced by occupation status, a factor not captured by this study. Other unexamined factors could have played a role in surveillance completion, as well; for instance, the completion of surveillance may have been put on hold due to the management of other ongoing health issues.

Considering the limited information available on the effectiveness of SIC and UTC surveillance in LS, which was further obfuscated by the findings of this study, we do not believe that SIC and UTC surveillance should be broadly performed in all individuals with LS. Instead, we advocate for the individualized incorporation of these surveillance methods in a patient-dependent manner after a detailed discussion of the risks, limitations, benefits, and uncertainties. A larger prospective study would be better equipped to assess the true benefits and risks of SIC and UTC surveillance as well as to understand patients' interest in and concerns with extra-colonic surveillance. Additionally, the low PPV of the surveillance methods observed in this study emphasize the need for further research on the cost of this surveillance and the effect of early detection of SIC and UTC on patient morbidity and mortality. Qualitative studies could also elucidate patient perspectives as individuals with LS may have negative psychological effects if multiple extra-colonic cancer surveillance studies are incorporated into their management.

Limitations of this study include that the LS cohort is from a single tertiary care center and lacks racial diversity; therefore, the results observed may not be representative of more geographically and racially diverse cohorts. Another limitation is that individuals may have completed SIC or UTC surveillance outside of our medical center, with these completed surveillance tests neither appearing in the individual's electronic medical record nor being captured by this study. Finally, this study has a relatively small sample size, which may prevent recognition of other significant associations.

CONCLUSION

This cohort study describes outcomes of SIC and UTC surveillance in LS and identifies factors influencing the SIC and UTC surveillance practices of individuals with LS. This study highlights problems with incorporation of SIC and UTC surveillance into LS care, as illustrated by the low PPV and low overall yields of these tests. The study also shows that the pursuit and completion of these surveillance examinations may depend on the affected individual's age, sex, genotype, and provider; however at this time, there is insufficient evidence to support widespread use of SIC/UTC surveillance in all individuals with LS. Further large-scale studies on SIC and UTC surveillance are needed to better understand the utility of available surveillance tests as well as their cost effectiveness and impact on patient survival.

ARTICLE HIGHLIGHTS

Research background

Lynch syndrome (LS) is an autosomal dominant cancer predisposition syndrome resulting from a disease-causing variant in the *MLH1*, *MSH2*, *MSH6*, *PMS2*, or *EPCAM* gene. LS is primarily associated with increased colorectal and endometrial cancer risk, but it is also associated with increased risk of small intestinal cancer (SIC) and urinary tract cancer (UTC). Cancer surveillance management for SIC and UTC has yet to be standardized for LS patients due to a lack of proven efficacy for current surveillance methods, and data regarding provider and patient interest in the current SIC and UTC surveillance methods are also lacking.

Research motivation

This study was interested in describing the efficacy and impact of completed SIC and UTC surveillance exams in a cohort of 317 LS patients. In addition, we were interested in patients' decisions about whether to pursue surveillance despite the limited evidence on efficacy and varying guideline recommendations and whether these

individuals successfully completed surveillance.

Research objectives

To characterize the uptake and outcomes of SIC and UTC surveillance among LS patients at a tertiary care referral center. We intended to analyze the factors influencing individuals' surveillance behaviors and to calculate the yield of completed surveillance exams.

Research methods

This was a retrospective study of individuals with LS seen at a tertiary care referral center. Information regarding SIC and UTC surveillance was captured for each individual. Additional demographic information and medical history was collected for individuals who had an initial LS management visit in our center's dedicated high-risk LS clinic between January 1, 2017 and October 29, 2020 to allow for analysis of individuals' behaviors after engaging in an in-depth conversation regarding surveillance with a provider in the clinic. Statistical analysis using Pearson's chi-squared test and Wilcoxon rank-sum test was completed, and a *P* value below 0.05 was deemed statistically significant.

Research results

Of the 317 individuals with LS in our cohort, 27% underwent a total of 105 SIC surveillance exams, and 31% underwent a total of 303 UTC surveillance exams. Each surveillance method was found to have a low positive predictive value and yield. A single UTC was diagnosed, and 0 SICs were diagnosed. Of 155 individuals who had an initial LS management visit between January 1, 2017 and October 29, 2020, a minority of individuals chose to undergo either SIC (41%) or UTC (37%) surveillance. Only 41% of individuals completed SIC surveillance, and 55% completed UTC surveillance when ordered. Several factors were found to be significantly associated with surveillance pursuit and completion, including age, sex, genotype, and provider.

Research conclusions

This study observed a low positive predictive value and yield for completed SIC and UTC surveillance exams, and after an in-depth conversation on the limitations and benefits of SIC and UTC surveillance, there was limited interest for this surveillance among individuals with LS. At this time, there continues to be insufficient evidence to support widespread SIC and UTC surveillance in LS.

Research perspectives

This study highlights the need for further research in SIC and UTC surveillance in LS. More data is needed on the cost of SIC and UTC surveillance and the effect of early detection of SIC and UTC on patient morbidity and mortality. Qualitative studies are also needed to elucidate patient perspectives regarding the addition of low-evidence surveillance exams to their cancer surveillance management.

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ORIGINAL ARTICLE

Retrospective Study

First-line pazopanib in patients with advanced non-clear cell renal carcinoma: An Italian case series

Sebastiano Buti, Melissa Bersanelli, Francesco Massari, Ugo De Giorgi, Orazio Caffo, Gaetano Aurilio, Umberto Basso, Giacomo Carteni, Claudia Caserta, Luca Galli, Francesco Boccardo, Giuseppe Procopio, Gaetano Facchini, Giuseppe Fornarini, Alfredo Berruti, Elena Fea, Emanuele Naglieri, Fausto Petrelli, Roberto Iacovelli, Camillo Porta, Alessandra Mosca

ORCID number: Sebastiano Buti 0000-0003-0876-0226; Melissa Bersanelli 0000-0002-6527-6281; Francesco Massari 0000-0001-6476-6871; Ugo De Giorgi 0000-0001-7520-2908; Orazio Caffo 0000-0001-7968-2531; Gaetano Aurilio 0000-0002-9879-6486; Umberto Basso 0000-0002-5075-2177; Giacomo Carteni 0000-0003-1441-6376; Claudia Caserta 0000-0002-3337-9120; Luca Galli 0000-0003-0147-7807; Francesco Boccardo 0000-0002-5369-6852; Giuseppe Procopio 0000-0002-2498-402X; Gaetano Facchini 0000-0002-7430-001X; Giuseppe Fornarini 0000-0002-3180-5843; Alfredo Berruti 0000-0002-3956-0043; Elena Fea 0000-0003-4629-8992; Emanuele Naglieri 0000-0002-9761-7431; Fausto Petrelli 0000-0001-9639-4486; Roberto Iacovelli 0000-0002-1750-2117; Camillo Porta 0000-0003-2412-1563; Alessandra Mosca 0000-0002-2660-1299.

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Informed consent statement: All

Sebastiano Buti, Melissa Bersanelli, Medical Oncology Unit, University Hospital of Parma, Parma 43126, Italy

Melissa Bersanelli, Medicine and Surgery Department, University of Parma, Parma 43126, Italy

Francesco Massari, Division of Oncology, Policlinico Sant'Orsola-Malpighi Hospital, Bologna 40138, Italy

Ugo De Giorgi, Department of Oncology, IRCCS Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori (I.R.S.T.), Meldola 47014, Italy

Orazio Caffo, Department of Medical Oncology, Santa Chiara Hospital, Trento 38122, Italy

Gaetano Aurilio, Department of Medical Oncology, Division of Urogenital and Head and Neck Tumours, European Institute of Oncology IRCCS, Milan 20141, Italy

Umberto Basso, Medical Oncology Unit 3, Istituto Oncologico Veneto IOV IRCCS, Castelfranco Veneto, Padova 31033, Italy

Giacomo Carteni, Division of Oncology, Azienda Ospedaliera di Rilievo Nazionale A. Cardarelli, Napoli 80131, Italy

Claudia Caserta, Medical Oncology Unit, Azienda Ospedaliera S. Maria, Terni 05100, Italy

Luca Galli, Oncology Unit 2, University Hospital of Pisa, Pisa 56126, Italy

Francesco Boccardo, Academic Unit of Medical Oncology, IRCCS San Martino Polyclinic Hospital, Genova 16132, Italy

Giuseppe Procopio, Medical Oncology Genitourinary Section, Fondazione IRCCS Istituto Nazionale Dei Tumori, Milan 20133, Italy

Gaetano Facchini, Departmental Unit of Clinical and Experimental Uro-Andrologic Oncology, Istituto Nazionale Tumori IRCCS Fondazione G. Pascale, Napoli 80131, Italy

Giuseppe Fornarini, Medical Oncology Unit, Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS) Ospedale Policlinico San Martino, Genova 16132, Italy

study participants provided informed written consent prior to study enrollment.

Conflict-of-interest statement: Melissa Bersanelli received honoraria as a speaker at scientific events by Bristol-Myers Squibb (BMS), Novartis, Astra Zeneca, Pierre Fabre, and Pfizer and as a consultant for advisory role by Novartis, BMS, IPSEN, and Pfizer; she also received fees for copyright transfer by Sciclone Pharmaceuticals and research funding by Roche S.p.A., Seqirus UK, Pfizer, Novartis, BMS, Astra Zeneca, and Sanofi Genzyme. Sebastiano Buti received honoraria as a speaker at scientific events and advisory role by Bristol-Myers Squibb (BMS), Pfizer; MSD, Ipsen, Roche, Eli-Lilly, AstraZeneca, and Novartis; he also received research funding from Novartis. Orazio Caffo received honoraria as a speaker by Astellas, Bayer, Astra Zeneca, Janssen, Pfizer, Sanofi, and a consultant for advisory role by Astellas, Janssen, MSD. Camillo Porta received honoraria a Consultant or Speaker for Angelini, Astra Zeneca, BMS, Eisai, EUSA, General Electric, Ipsen, Janssen, Merck, MSD, Novartis and Pfizer, acted as an Expert Testimony for EUSA and Pfizer and was a Protocol Steering Committee Member ofr BMS, Eisai, and EUSA. Finally, he did receive travel support from Roche. All other authors have no conflict of interest to declare.

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Alfredo Berruti, University of Brescia, ASST-Spedali Civili, Brescia, Brescia 25123, Italy

Elena Fea, Medical Oncology Unit, S Croce and Carle Teaching Hospital, Cuneo 12100, Italy

Emanuele Naglieri, Division of Medical Oncology, Istituto Tumori G Paolo II, IRCCS, Bari 70124, Italy

Fausto Petrelli, Medical Oncology Unit, ASST Bergamo Ovest, Treviglio, Bergamo 24047, Italy

Roberto Iacovelli, Medical Oncology Unit, Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Rome 00161, Italy

Camillo Porta, Division of Oncology, AOU Consorziale Policlinico di Bari, Bari 70124, Italy

Camillo Porta, Department of Biomedical Sciences and Human Oncology, University of Bari "A.Moro", Bari 70124, Italy

Alessandra Mosca, Multidisciplinary Outpatient Oncology Clinic, Candiolo Cancer Institute, FPO-IRCCS, Candiolo, Turin 10060, Italy

Corresponding author: Melissa Bersanelli, MD, Adjunct Professor, Postdoctoral Fellow, Staff Physician, Medical Oncology Unit, University Hospital of Parma, Via Gramsci 14, Parma 43126, Italy. bersamel@libero.it

Abstract

BACKGROUND

Non-clear cell (ncc) metastatic renal-cell carcinoma (RCC) has dismal results with standard systemic therapies and a generally worse prognosis when compared to its clear-cell counterpart. New systemic combination therapies have emerged for metastatic RCC (mRCC), but the pivotal phase III trials excluded patients with nccRCC, which constitute about 30% of metastatic RCC cases.

AIM

To provide a piece of real-life evidence on the use of pazopanib in this patient subgroup.

METHODS

The present study is a multicenter retrospective observational analysis aiming to assess the activity, efficacy, and safety of pazopanib as first-line therapy for advanced nccRCC patients treated in a real-life setting.

RESULTS

Overall, 48 patients were included. At the median follow-up of 40.6 mo, the objective response rate was 27.1%, the disease control rate was 83.3%, and the median progression-free survival and overall survival were 12.3 (95% confidence interval [CI]: 3.6-20.9) and 27.7 (95%CI: 18.2-37.1) mo, respectively. Grade 3 adverse events occurred in 20% of patients, and no grade 4 or 5 toxicities were found.

CONCLUSION

Pazopanib should be considered as a good first-line option for metastatic RCC with variant histology.

Key Words: Pazopanib; Non-clear cell; Kidney cancer; Renal-cell carcinoma; Variant histology; Tyrosine kinase inhibitors

Core Tip: Non-clear cell metastatic renal-cell carcinoma (nccRCC) has dismal results with standard systemic therapies and a poor prognosis. Few therapeutic molecules have

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been explicitly tested in nccRCC patients. We retrospectively collected 48 advanced nccRCC patients treated with pazopanib in the first-line setting, offering promising findings of quite good response rate (27%), progression-free survival around 12 mo, and overall survival around 28 mo. In light of these results, we suggest that pazopanib can be a good treatment choice in this subgroup of patients, pending the results of ongoing clinical trials with new therapeutic combinations.

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INTRODUCTION

Non-clear cell renal-cell carcinoma (nccRCC) represents a heterogeneous group of tumors with distinct genomic and metabolic features. Therefore, its clinical behavior can be benign to indolent and even highly malignant with high metastatic potential[1].

Of note, non-clear mRCC has dismal results with standard systemic therapies and a generally worse prognosis when compared to its clear-cell counterpart, as demonstrated in a large study by the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC), showing a worse overall survival (OS) for patients with nccRCC compared to ccRCC patients [12.8 mo (95%CI: 11.0-16.1) *vs* 22.3 mo (20.7-23.5)][2].

Recent advances have offered the availability of new systemic therapies for metastatic RCC (mRCC), such as immunotherapy-based combinations with the current recommendation in the first-line setting[3-6]. These combinations, all forecasting the use of anti-PD-1/PD-L1 immune checkpoint inhibitors (ICIs), have been investigated in phase III randomized clinical trials (RCTs) enrolling patients with clear-cell RCC (ccRCC) or at least a clear-cell component in the tumor histology. Nevertheless, conventional clear-cell RCC accounts for only 70% of renal cortical tumors that metastasize, preventing to provide evidence for 30% of mRCC patients still lacking indication for the most productive therapeutic solutions. About nccRCC, international guidelines still recommend that such patients should be preferentially referred to clinical trials.

The previous gold-standard first-line therapies for mRCC, represented by anti-vascular endothelial growth factor receptor tyrosine kinase inhibitors (TKIs) used as a single agent, have been in part investigated in nccRCC patients. In particular, sunitinib was tested in two prospective trials (the ESPN trial and the ASPEN trial) initially planned to show the superiority of the mammalian target of rapamycin inhibitor everolimus over sunitinib as first-line therapy. Both studies, on the contrary, finally supported the use of sunitinib as a primary systemic approach in this population of patients[7,8]. On the other hand, other TKIs have been approved in the first-line setting for all-mRCC histologies, including the alternative with pazopanib, which demonstrated similar efficacy and even better safety profile when compared to sunitinib in randomized trials[9,10]. Nevertheless, little evidence is available about using this drug in nccRCC patients, with a consequent reluctance to prescription in clinical practice, notwithstanding the drug's good profile, also suitable for frail and elderly patients[11,12].

Given the unmet oncological need for evidence for the systemic approach to nccRCC, the present report of a retrospective multicenter case series aims to provide a piece of real-life evidence on the use of pazopanib in this patient subgroup.

MATERIALS AND METHODS

Study population and setting

The present study is a retrospective, observational analysis aiming to assess the

activity, efficacy, and safety of pazopanib as first-line therapy for advanced nccRCC patients treated in a real-life setting at multiple Italian institutions. The principal inclusion criteria were the diagnosis of nccRCC, including papillary RCC (pRCC), chromophobe RCC (chRCC), RCC with Xp11 translocation, RCC with undefined histology, and mixed-histology RCC with mostly ncc component; receiving the first dose of pazopanib between June 2012 and June 2015; > 18 years old; measurable disease at the computed tomography (CT) scans performed according to clinical practice at the treating centers. Data were collected between February 2017 and February 2018.

Study endpoints

The primary objective was to assess the outcome of patients in terms of objective response rate (ORR), disease control rate (DCR), progression-free survival (PFS), OS, and tolerability as co-primary endpoints. PFS was defined as the time between pazopanib initiation and disease progression or death; OS was defined as the time between pazopanib initiation and death or the date of the last follow-up visit for alive patients; DCR as responses plus stable diseases. Objective responses (complete, CR; partial, PR; stable, SD; progressive disease, PD) were evaluated according to Response Evaluation Criteria in Solid Tumors (RECIST 1.1)[13] and assessed every 2-3 mo according to clinical practice.

Treatment-related adverse events (TRAEs) were recorded as clinical practice according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0 (in use at the time of the study conduct)[14].

The characteristics of patients were collected, and their correlation with the outcome was explored.

The study was reviewed and approved by the Local Ethics Committee of Parma (Italy). All study participants provided informed written consent before study enrollment.

Statistical analysis

Descriptive statistics are used to summarize the data. PFS and OS were estimated using the Kaplan-Meier method with 95% confidence intervals (CI) and compared using the log-rank test. Univariate and multivariate analyses were performed by using Cox proportional hazards models. The comparison between categorical endpoints was performed using the chi-square test. Significance levels were set at a 0.05 value, and all *P* values were two-sided. SPSS Statistics 24.0 software (IBM Corporation, Armonk, NY, United States) was used to conduct the statistical analyses.

RESULTS

From January 2011 to January 2017, 48 consecutive patients were included in 20 Italian centers. The median follow-up was 40.6 mo (95%CI: 22.3-58.9). The characteristics of patients are reported in Table 1. The median age was 70 (range, 27-86) years, and most patients were male (75.0%). Fifteen patients (31.3%) had distant metastases at disease onset. The majority of patients had pRCC (50.0%) or chRCC (18.8%) as histology. Most patients had previously received nephrectomy (85.4%), and seven (14.6%) had metastasectomy. Thirty-seven patients (77.1%) had an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0. All IMDC risk groups were represented in the study population.

The median duration of treatment was 9.1 (range, 0.6-52.5) mo, and eight patients (16.7%) were still receiving pazopanib at the time of the last follow-up. Twenty-eight patients (58.3%) received a second-line therapy (four received nivolumab and three cabozantinib).

In 17 cases (35.4%), the starting dose of pazopanib was primarily reduced because of the patient conditions (age and/or comorbidity): Ten patients started with 600 mg, and seven patients started with 400 mg. Secondary dose reductions or temporary treatment discontinuations due to TRAEs were required in 19 cases (39.6%), mainly due to grade (G) 3 hepatic toxicity, fatigue, and diarrhea. G3 TRAEs occurred in 20.8% of patients, G1-2 in 81.2%, and no G4 toxicity was observed (Table 2).

PR was achieved in 13 patients (27.1%), and no CR was observed. Twenty-seven patients (56.3%) obtained SD; the DCR was 83.3%, whereas six patients (12.5%) had PD as the best response (while 4.2% were not evaluable). Neither ORR nor DCR was significantly correlated with any of the following parameters: Sex, histology, grading, sarcomatoid component, initial pazopanib dose, ECOG PS, and IMDC risk group.

Table 1 Characteristics of patients, *n* (%)

Baseline characteristic	*n* = 48
Age, median (range)	70 (27-86)
Sex	
Males	36 (75)
Females	12 (25)
Histology	
Papillary	24 (50)
Chromophobe	9 (10.8)
Xp11 translocation	1 (2.1)
Unclassified	6 (12.5)
Mixed[1]	8 (16.7)
Grade (Fuhrman/ISUP)	
1-2	6 (12.5)
3	15 (31.3)
4	4 (8.3)
NA	23 (47.9)
Stage at diagnosis	
I-III	33 (68.8)
IV	15 (31.3)
Previous nephrectomy	
Yes	41 (85.4)
No	7 (14.6)
Metastasectomy	
Yes	7 (14.6)
No	41 (85.4)
ECOG PS	
0	37 (77.1)
1	11 (22.9)
IMDC score risk group	
Good	19 (39.6)
Intermediate	25 (52.1)
Poor	2 (4.2)
NA	2 (4.2)
Starting dose of pazopanib	
800 mg	31(64.6)
600 mg	10 (20.8)
400 mg	7 (14.6)

[1]Four tumors had mixed histology (clear-cell/papillary) with papillary histology prevalence and four tumors had mixed histology (clear-cell/chromophobe) with chromophobe histology prevalence.

NA: Not assessed/available; IMDC: International Metastatic Renal Cell Carcinoma Database Consortium; ECOG PS: Eastern Cooperative Oncology Group Performance Status; ISUP: International Society of Urological Pathology.

Table 2 Adverse events according to Common Terminology Criteria for Adverse Events (version 4.0)

Adverse event	Grade 1/2, *n* (%)	Grade 3, *n* (%)
Fatigue	24 (50.0)	
Diarrhea	15 (31.3)	2 (4.2)
Mucositis	9 (18.8)	
Hypertransaminasemia	7 (14.6)	4 (8.3)
Thrombocytopenia	6 (12.5)	
Anemia	15 (31.2)	2 (4.2)
Neutropenia	5 (10.4)	
Hypothyroidism	15 (31.3)	
Disgeusia	5 (10.4)	1 (2.1)
Cutaneous toxicity[1]	8 (16.7)	
Nausea/vomiting	14 (29.2)	
Heart failure	1 (2.1)	
Renal failure	5 (10.4)	1 (2.1)
Other[2]	16 (33.3)	

[1]Including discoloration of hairs and cutis, hand-foot syndrome, and dermatitis.
[2]Including bleeding, sleepiness, hypertrigliceridemia, hypophosphoremia, hyperbilirubinemia, loss of appetite/hyporexia, dyspepsia/epigastralgia, and hypertension.

Most cases of primary refractory (PD as best response) were pRCC. Table 3 shows the responses according to the histology.

Median PFS and OS were 12.3 (95%CI: 3.6-20.9) and 27.7 (95%CI: 18.2-37.1) mo, respectively (Figure 1, Table 3).

In the univariate analysis, no factors (among sex, previous nephrectomy, histology, grading, metastatic disease at diagnosis, previous metastasectomy, IMDC risk group, ECOG PS, and initial pazopanib dose) were significantly associated with PFS. Conversely, factors significantly associated with a better OS were IMDC group (P = 0.011), previous nephrectomy (P = 0.002), previous metastasectomy (P = 0.008), absence of metastatic disease at diagnosis (P = 0.014), and subsequent therapy with cabozantinib or nivolumab (P = 0.049).

Notwithstanding the limit of multivariate analysis in such a small sample size, it was performed for OS, and only the absence of metastatic disease at diagnosis (hazard ratio = 8.49, 95%CI: 1.76-40.90; P = 0.008) maintained a positive impact on OS.

DISCUSSION

The present analysis reported the most extensive case series, to our knowledge, treated with the TKI pazopanib as first-line systemic therapy for advanced nccRCC patients.

The activity and efficacy outcomes are in line with those reported by two prior series from the literature, with an ORR around 27%, a good DCR (over 80%), an mPFS over 1 year, and a good mOS of 27.7 mo. Compared to the other older reports, our study also included patients receiving new-generation drugs as second-line after pazopanib (*i.e.*, nivolumab or cabozantinib), suggesting (in the univariate analysis) this choice as significantly associated with improved survival and providing some evidence for these treatment sequences in nccRCC.

Regarding safety, pazopanib was generally well-tolerated, with G3 TRAEs occurring only in 20% of patients and no G4-5 toxicities. The AE-related discontinuations and the initial dose reductions were relatively frequent. Still, no impact on the outcome was evidenced for the latter choice, often preferable for frail patients with hepatic impairment or cardiovascular comorbidities.

The limitations of our report are represented by the retrospective nature, the heterogeneous follow-up time (with a wide range, but a good median value), the lack of central independent revision for the histological samples (nccRCC histology based on

Table 3 Objective response rate, progression-free survival, and overall survival outcomes

Effectiveness outcome	All patients (*n* = 48)	Papillary RCC (*n* = 24)	Chromophobe RCC (*n* = 9)
Response rate (RECIST 1.1), *n* (%)			
Partial responses	13 (27.1)	6 (25.0)	2 (22.2)
Complete responses	0 (0.0)	0 (0.0)	0 (0.0)
Stable disease	27 (56.3)	14 (58.3)	5 (55.5)
Progressions of disease	6 (12.5)	3 (12.5)	1 (11.1)
Not evaluable	2 (4.2)	1 (4.2)	1 (11.1)
Disease control rate	40 (83.3)	20 (83.3)	7 (77.8)
PFS			
Median (mo) (95%CI)	12.3 (3.6-20.9)	-	-
Rate of patients progression free at 6 mo	67.8%	-	-
Rate of patients progression free at 12 mo	49.0%	-	-
OS			
Median (mo) (95%CI)	27.6 (18.3-37.1)	-	-
Rate of patients alive at 12 mo	82.7%	-	-
Rate of patients alive at 24 mo	62.0%	-	-

RCC: Renal cell carcinoma; PFS: Progression free survival; OS: Overall survival; RECIST 1.1: Response Evaluation Criteria in Solid Tumours version 1.1.

the original diagnosis), and the limited number of patients receiving new-generation drugs (such as cabozantinib or nivolumab) in other treatment lines. On the other hand, the present analysis corroborates with the largest sample size two previous similar retrospective case series, providing herein clean data for pure first-line setting (as a difference *vs* Matrana *et al*[12]), and supporting the use of pazopanib as a single agent for nccRCC patients with advanced disease.

A further single-TKI alternative could be available in the next future as a primary choice for the subgroup of pRCC patients, represented by the third generation TKI cabozantinib. Currently approved as a first-line treatment option for ccRCC patients with poor- or intermediate-risk according to the IMDC model, this drug was investigated in a prospective study as a first- or second-line TKI for advanced pRCC. It demonstrated improved PFS (median 9.0 mo, 95%CI: 6-12) *vs* the comparator sunitinib (5.6 mo, 95%CI: 3-7; HR = 0.60, 95%CI: 0.37-0.97, $P = 0.019$) and ORR (23% *vs* 4% for sunitinib, $P = 0.010$), at the cost of quite manageable toxicity and a toxic death reported [15].

Beyond TKIs, the advent of immunotherapy has finally landed also in the field of nccRCC, reporting initial findings from prospective monotherapy trials. The single-arm phase II Keynote-427 trial investigated the efficacy and safety of single-agent pembrolizumab, a PD-1 inhibitor, in advanced nccRCC. In this study, 71.5% of patients had confirmed pRCC, 12.7% had chRCC, and 15.8% had unclassified RCC histology. Overall, the ORR was 26.7% (28.8% for papillary, 9.5% for chromophobe, and 30.8% for unclassified RCC); the mPFS was 4.2 mo (95%CI: 2.9-5.6), and the mOS was 28.9 mo. The toxicity was manageable, with 69.7% of patients reporting TRAEs; nevertheless, two deaths were reported as treatment-related[16]. These findings are pretty encouraging about the activity of immunotherapy in variant histologies. Anyway, the activity seems in line with those reported herein for pazopanib (similar ORR). In contrast, the efficacy appears relatively poor in terms of mPFS compared with that reported with TKIs in ours and similar populations. On the other hand, the OS outcome was similar.

Another first-line trial (Checkmate-920) recently investigated an immunotherapy combining ipilimumab and nivolumab (anti-CTLA-4 and anti-PD1 respectively) in a nccRCC treatment-naïve population. The first results reported relatively high rates of G3 (92.3%) and G4 (36.5%) toxicities (but without toxic deaths), ORR of 19.6%, and mPFS of 3.7 mo (95%CI: 2.7-4.6)[17]. The SUNNIFORECAST trial, a phase II randomized study currently ongoing with the same combination *vs* standard of care for previously untreated nccRCC patients, will provide further evidence about this

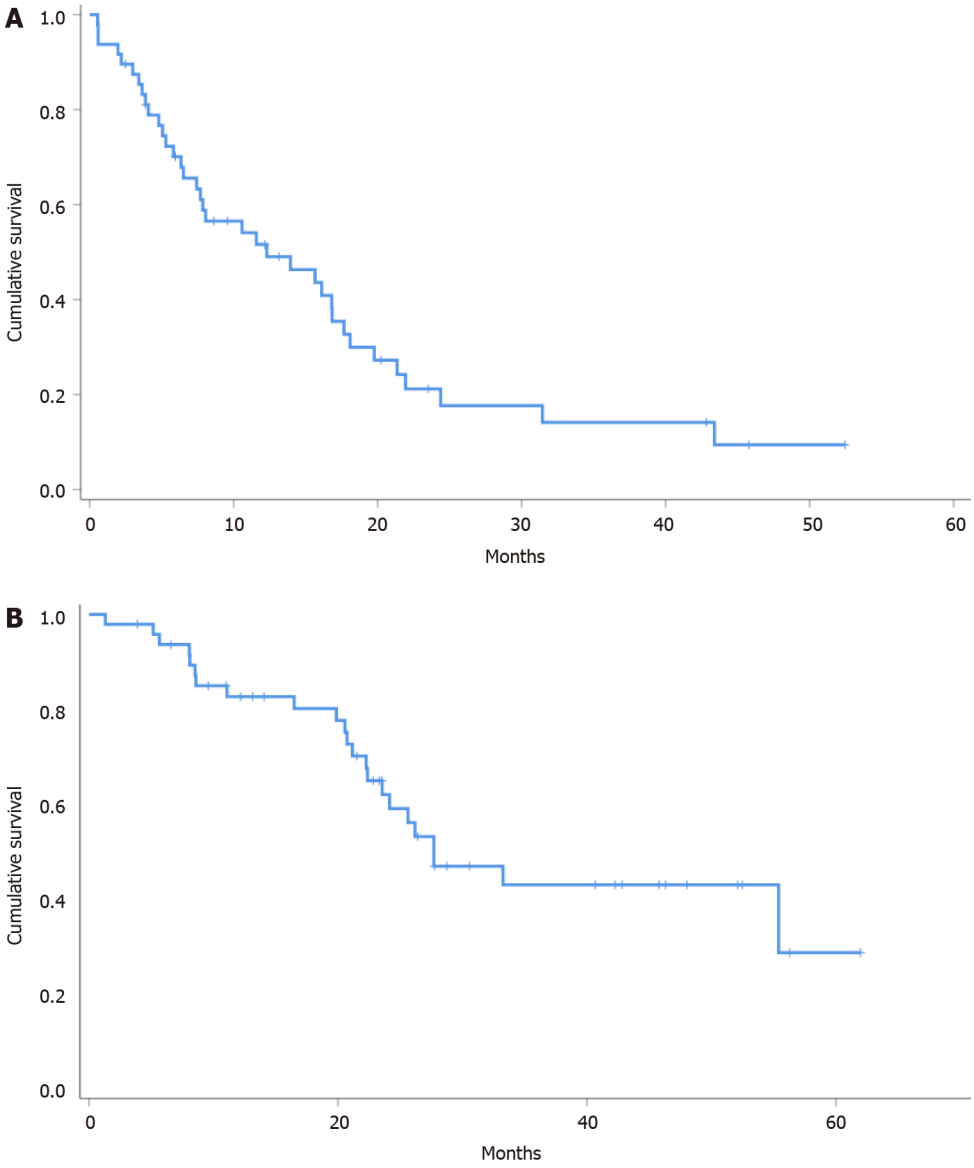

Figure 1 Progression-free survival (A) and overall survival (B) of the study population.

exclusive immunotherapy strategy (NCT03075423).

CONCLUSION

On the one hand, RCC with sarcomatoid features (irrespective of the primary histology) indeed gains excellent benefit from immunotherapy compared to TKIs[18]. On the other hand, RCC with variant histology still needs a TKI-based approach, with new generation TKIs, possibly combined with ICIs in future trials.

Meanwhile, the single-agent options should include pazopanib, favored by excellent manageability in terms of safety, and supported by high feasibility and excellent cost-effectiveness, especially for elderly patients.

ARTICLE HIGHLIGHTS

Research background

Non-clear cell metastatic renal-cell carcinoma (nccRCC) has dismal results with standard systemic therapies and a generally worse prognosis when compared to its clear-cell counterpart.

Research motivation
We aimed to provide a piece of real-life evidence on the use of pazopanib in this patient subgroup.

Research objectives
To assess the activity, efficacy, and safety of pazopanib as first-line therapy for advanced nccRCC patients treated in a real-life setting.

Research methods
This was a multicenter retrospective observational analysis.

Research results
The objective response rate with pazopanib was 27.1%, the disease control rate was 83.3%, and the median progression-free survival and overall survival were 12.3 (95%CI: 3.6-20.9) mo and 27.7 (95%CI: 18.2-37.1) mo, respectively. Grade 3 adverse events occurred in 20% of patients, and no grade 4 or 5 toxicities were found.

Research conclusions
Pazopanib should be considered as a good first-line option for metastatic RCC with variant histology.

Research perspectives
Pazopanib warrants further development in metastatic RCC with variant histology.

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ORIGINAL ARTICLE

Retrospective Study

Pathological response to neoadjuvant therapy with chemotherapy *vs* chemoradiotherapy in stage III NSCLC-contribution of IASLC recommendations

Diego Muñoz-Guglielmetti, David Sanchez-Lorente, Roxana Reyes, Daniel Martinez, Carmen Lucena, Marc Boada, Pilar Paredes, Marta Parera-Roig, Ivan Vollmer, Joel Mases, Roberto Martin-Deleon, Sergi Castillo, Mariana Benegas, Silvia Muñoz, Maria Mayoral, Carla Cases, Meritxell Mollà, Francesc Casas

ORCID number: Diego Muñoz-Guglielmetti 0000-0002-1857-8930; David Sanchez-Lorente 0000-0003-3308-4696; Roxana Reyes 0000-0001-9035-4491; Daniel Martinez 0000-0001-7492-5311; Carmen Lucena 0000-0001-8265-3918; Marc Boada 0000-0002-3801-4497; Pilar Paredes 0000-0002-8097-9217; Marta Parera-Roig 0000-0001-8571-4878; Ivan Vollmer 0000-0002-8051-3994; Joel Mases 0000-0002-7991-7932; Roberto Martin-Deleon 0000-0002-2786-1084; Sergi Castillo 0000-0003-0402-9612; Mariana Benegas 0000-0003-0585-5609; Silvia Muñoz 0000-0002-3265-5306; Maria Mayoral 0000-0003-0108-3226; Carla Cases 0000-0003-2110-9016; Meritxell Mollà 0000-0001-6215-2251; Francesc Casas 0000-0001-6464-0603.

Author contributions: Muñoz Guglielmetti D, Sanchez-Lorente D, Reyes R, Martinez D, Lucena C, Boada M, Paredes P, Parera-Roig M, Vollmer I, Mases J, Martin-Deleon R, Castillo S, Benegas M, Muñoz S, Mayoral M, Cases C, Mollà M and Casas F collaborated in the preparation of this manuscript; Statistical analyses and the final review were performed by Muñoz Guglielmetti D.

Diego Muñoz-Guglielmetti, Joel Mases, Carla Cases, Radiation Oncology Department, Hospital Clínic de Barcelona, Barcelona 08036, Cataluña, Spain

David Sanchez-Lorente, Marc Boada, Thoracic Surgery Department, Thoracic Unit, Hospital Clínic de Barcelona, Barcelona 08036, Cataluña, Spain

Roxana Reyes, Medical Oncology Department, Thoracic Unit, Hospital Clínic de Barcelona, Barcelona 08036, Cataluña, Spain

Daniel Martinez, Pathology Department, Thoracic Unit, Hospital Clínic de Barcelona, Barcelona 08036, Cataluña, Spain

Carmen Lucena, Pneumology Department, Thoracic Unit, Hospital Clínic de Barcelona, Barcelona 08036, Cataluña, Spain

Pilar Paredes, Nuclear Medicine Department, Faculty of Medicine of University of Barcelona, Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Barcelona 08036, Cataluña, Spain

Marta Parera-Roig, Medical Oncology Department, Hospital Comarcal de Vic, Vic 08500, Cataluña, Spain

Ivan Vollmer, Mariana Benegas, Radiology Department, Thoracic Unit, Hospital Clínic de Barcelona, Barcelona 08036, Cataluña, Spain

Roberto Martin-Deleon, Pneumology Department, Hospital Universitario Reina Sofía, Córdoba 14004, Andalucía, Spain

Sergi Castillo, Medical Oncology Department, Hospital de Mollet, Mollet 08100, Cataluña, Spain

Silvia Muñoz, Medical Oncology Department, Hospital General de Granollers, Granollers 08402, Cataluña, Spain

Maria Mayoral, Nuclear Medicine Department, Thoracic Unit, Hospital Clínic de Barcelona, Barcelona 08036, Cataluña, Spain

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Meritxell Mollà, Francesc Casas, Radiation Oncology Department, Thoracic Unit, Hospital Clínic de Barcelona, Barcelona 08036, Cataluña, Spain

Corresponding author: Diego Muñoz-Guglielmetti, MD, Doctor, Radiation Oncology, Hospital Clínic de Barcelona, Carrer de Villarroel 170, Barcelona 08036, Cataluña, Spain.
dimunoz@clinic.cat

Abstract

BACKGROUND

Neoadjuvant treatment (NT) with chemotherapy (Ch) is a standard option for resectable stage III (N2) NSCLC. Several studies have suggested benefits with the addition of radiotherapy (RT) to NT Ch. The International Association for the Study of Lung Cancer (IASLC) published recommendations for the pathological response (PHR) of NSCLC resection specimens after NT.

AIM

To contribute to the IASLC recommendations showing our results of PHR to NT Ch *vs* NT chemoradiotherapy (ChRT).

METHODS

We analyzed 67 consecutive patients with resectable stage III NSCLC with positive mediastinal nodes treated with surgery after NT Ch or NT ChRT between 2013 and 2020. After NT, all patients were evaluated for radiological response (RR) according to Response Evaluation Criteria in Solid Tumours criteria and evaluated for surgery by a specialized group of thoracic surgeons. All histological samples were examined by the same two pathologists. PHR was evaluated by the percentage of viable cells in the tumor and the resected lymph nodes.

RESULTS

Forty patients underwent NT ChRT and 27 NT Ch. Fifty-six (83.6%) patients underwent surgery (35 ChRT and 21 Ch). The median time from ChRT to surgery was 6 wk (3-19) and 8 wk (3-21) for Ch patients. We observed significant differences in RR, with disease progression in 2.5% and 14.8% of patients with ChRT and Ch, respectively, and partial response in 62.5% ChRT *vs* 29.6% Ch (P = 0.025). In PHR we observed ≤ 10% viable cells in the tumor in 19 (54.4%) and 2 cases (9.5%), and in the resected lymph nodes (RLN) 30 (85.7%) and 7 (33.3%) in ChRT and Ch, respectively (P = 0.001). Downstaging was greater in the ChRT compared to the Ch group (80% *vs* 33.3%; P = 0.002). In the univariate analysis, NT ChRT had a significant impact on partial RR [odds ratio (OR) 12.5; 95% confidence interval (CI): 1.21 - 128.61; P = 0.034], a decreased risk of persistence of cancer cells in the tumor and RLN and an 87.5% increased probability for achieving downstaging (OR 8; 95%CI: 2.34-27.32; P = 0.001).

CONCLUSION

We found significant benefits in RR and PHR by adding RT to Ch as NT. A longer follow-up is necessary to assess the impact on clinical outcomes.

Key Words: Non-small cell lung cancer; Chemotherapy; Chemoradiotherapy; Neoadjuvant treatment; Resectable stage III; Pathological response

Core Tip: Preoperative chemotherapy (Ch) has become a standard treatment option, especially in resectable stage III (primarily N2) non-small cell lung cancer (NSCLC). Phase II and phase III studies have raised the question as to whether preoperative Ch plus radiotherapy provides any additional benefits to preoperative Ch. The objective of our retrospective study was to contribute (with an experienced team of medical oncologists, radiation oncologists, thoracic surgeons, and pathologists) to the International Association for the Study of Lung Cancer recommendations in relation to

differences in the pathological evaluation of tumors and mediastinal and hilar nodes in resectable stage III NSCLC, comparing neoadjuvant Ch *vs* chemoradiotherapy.

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INTRODUCTION

The International Association for the Study of Lung Cancer (IASLC) recently published recommendations for the pathological evaluation of histological specimens from the resection of non-small cell lung cancer (NSCLC) after neoadjuvant therapy (NT)[1]. This article describes the lack of consensus in clinical practice regarding the evaluation of surgical specimens and in precise definitions of the degree of pathological response (PHR).

The seminal articles by both Junker *et al*[2] and Pataer *et al*[3] have been the main guide for the pathological evaluation of NT in recent decades. Although Junker *et al*[2] proposed that the lymph nodes of these patients be evaluated in the same way as the primary tumor (pT), the importance of the precise histological characteristics of these nodes has not been well established.

In relation to treatment, NT chemotherapy (Ch) has become a standard treatment option, especially in resectable stage III NSCLC[4]. However, later phase II and phase III studies raised the question as to whether NT Ch plus radiotherapy (RT) provides any additional benefit to NT Ch[5,6].

In 1996, the Lung Cancer Committee of our hospital (LCCHCB) initiated the first phase II trial of induction chemoradiotherapy (ChRT) in stage III NSCLC in Spain. We used the histological evaluation recommended by Junker *et al*[2] to describe the percentage of viable cells in resected neoplastic samples. The long follow-up of these results was presented at several international congresses[7].

In 2012, following the results of the Intergroup phase III trial[8], the LCCHCB and three other hospitals developed a new phase II trial with NT in resectable stage III NSCLC patients with exclusive lobectomy and a histologically proven single mediastinal lymph node level. In the Hospital Clínic de Barcelona (HCB), induction "per protocol" was with radical ChRT up to 60 Gy, and in the other hospitals the induction was performed with Ch alone (except for Pancoast tumors that also received induction of ChRT). After NT, all the patients were evaluated for radiological response (RR) according to Response Evaluation *Criteria* in Solid Tumours (RECIST) criteria and for surgery by a specialized group of thoracic surgeons. All the histological samples were examined by the same two pathologists.

The objective of this retrospective study was to contribute (with an experienced team of medical oncologists, radiation oncologists, thoracic surgeons, and pathologists) to the IASLC recommendations on differences in the pathological evaluation of tumor and mediastinal and hilar nodes in resectable stage III NSCLC comparing NT Ch *vs* ChRT.

MATERIALS AND METHODS

Patient selection

The population studied in this retrospective analysis were all patients consecutively diagnosed with resectable stage III NSCLC (AJCC, 8th edition) with pathologically proven single positive mediastinal lymph nodes treated between 2013 and 2020. NT treatment was followed by surgery with intention-to-cure according to the protocols of the four participating institutions and the decision of the respective Lung Cancer Committees. Some patients with N3 Level involvement and stage IV (single brain

metastasis previously treated with radiosurgery) were accepted for salvage thoracic surgery by decision of the LCCHCB. Patients with histologically demonstrated NSCLC but N2 Lymph nodes not accessible for biopsy were eligible, provided that the N2 node had a diameter greater than 1 cm and was positron emission tomography/computerized tomography (PET/CT) positive.

Patients who did not fully complete the curative treatment course were included in the study for intention-to-treat analysis.

Pre-treatment evaluation

All patients were evaluated by the multidisciplinary Lung Cancer Committee in each hospital which was composed of pulmonologists, radiologists, nuclear radiologists, medical oncologists, radiation oncologists and thoracic surgeons. The initial diagnostic study included radiological evaluation by chest CT, PET/CT, brain imaging [CT or brain magnetic resonance imaging (MRI)], and cardiopulmonary tests. Mediastinal and hilar involvement was confirmed by mediastinoscopy, endobronchial ultrasound (EBUS) and/or esophageal ultrasound (EUS). Before surgery, all patients were reassessed by the committee using chest CT to assess response to NT, and patients not demonstrating progression were considered for thoracic surgery.

Treatment

NT with ChRT or Ch was performed according to the protocol of each hospital and according to the clinical characteristics of each patient. All the patients included were considered for radical surgery by resection of the tumor and extensive resection of the hilar and mediastinal lymph nodes. RT was performed in the ChRT group concomitant with Ch, using 3 dimensional (D) conformal RT with standard fractionation of 2 Gy per fraction up to a total dose of 60 Gy (range 58-62 Gy). RT was administered to the pT and affected lymph nodes, with margins for microscopic disease and patient set up error. 4D assessment was not used, and involved-field of tumor and nodal treatment was exclusively adopted. Patients in both groups received platinum-based Ch without consolidation Ch after surgical resection. In the NT-Ch group, patients with R1 resection or persistence of viable cells in N2 Lymphadenectomy received postoperative RT (PORT) up to 54-60 Gy.

Post-NT evaluation and treatment

Chest CT scan was used to assess RR between 3 wk and 4 wk after NT according to the RECIST criteria. Operable patients who did not progress during NT were considered for radical surgical treatment. All patients were operated centrally in the same hospital (HCB). After surgery, PHR was evaluated by the same team of pathologists. Patients not considered for surgery after NT were treated with radical ChRT.

Histological assessment of pT and lymph nodes

PHR was defined according to the percentage of viable cells in the sample in both the pT and in the pathological lymph nodes (pN). It was categorized into five groups: 0%-10%; 11%-30%; 31%-50%, 51%-70%; > 70%, according to the literature. pN were taken into account to determine the downstaging rate.

Small volume samples (up to 2 cm) of pT and pN were completely sampled. In larger tumors, at least one paraffin block per cm of the largest diameter of the tumor was sampled in each specimen. The percentages of viable tumor cells, tumor necrosis, and fibrosis were evaluated in each slide, and the average of the percentages of viable tumor cells was reported for each patient. In specimens evaluated during 2020, PHR was evaluated following the IASCL recommendations[1]. In these cases, an entire cross-section of the tumor bed was sampled and photographed matching the areas on the specimen corresponding to the submitted blocks, and the percentage of necrosis, stromal tissue and viable tumor of the tumor bed was recorded. The components of the stromal tissue, fibrosis and inflammation were not specified.

Statistical analysis

Data were retrospectively analyzed after previous approval by the institutional review board. Two cohorts of patients were analyzed: NT ChRT plus surgery and NT Ch plus surgery. The parameters analyzed and compared in each group were: Mean age, sex, performance status, stage at diagnosis, TNM description, lung tumor location, N2-N3 confirmation, pathological distribution of the affected lymph node level, Ch scheme based on platinum doublet, acute RT or Ch toxicity, RR according to RECIST, and the median time from the end of NT to surgery. The type of surgery and complications of the intervention, levels of systematic lymph node dissection, the presence of DS, the

percentage of histological tumor viability (HTV) and lymph node histological viability (HLNV) were also analyzed. Both HTV and HLNV were also analyzed according to the histological type (adenocarcinoma *vs* squamous carcinoma) and NT type (ChRT *vs* Ch).

We performed a descriptive analysis comparing variables related to demographic, clinical, treatment and response data. The student's *t* test was used for quantitative variables, while the chi-square and Fisher exact test were applied for qualitative variables. Univariate analysis was carried out to assess the impact of ChRT on response using a logistic regression model. The statistical analyses were performed by a radiation oncologist with expertise in the IBM SPSS© version 25.0.

RESULTS

Between 2013 and 2020, 67 patients with resectable locally advanced NSCLC were evaluated (66 stage III and one stage IV with single brain metastasis, previously treated with radiosurgery); 65% were men, and the median age was 64 years (41-79). More than 90% of the patients had good functional status (ECOG PS ≤ 1). The most frequent histology was adenocarcinoma (62.5% ChRT and 74.1% Ch). Pathological nodal confirmation at diagnosis was made in most patients (87.5% ChRT and 92.6% Ch) by EBUS/EUS, mediastinoscopy or both. The clinical characteristics of the patients are summarized in Table 1.

In the ChRT group 47.5% of the patients simultaneously received Ch with cisplatin plus VP16 *vs* 0% in the Ch group, while 37% of the Ch group received the carboplatin-based doublet (with vinorelbine, taxol or gemcitabine) *vs* 7.5% in ChRT (with vinorelbine) (Table 2). Of the 40 ChRT patients, 28 (70%) started concomitant treatment within less than 7 d, 9 (22.5%) patients started at between 7 d and 14 d, and in 3 (7.5%) concomitant treatment was initiated after more than 14 d.

A total of 10 patients required hospitalization secondary to NT; 8 (20%) in the ChRT group *vs* 2 (7.4%) in the Ch group. Grade 2-3 esophagitis was observed in 10 (14.5%) patients with ChRT (only 2 grade 3) compared with no esophagitis in the Ch group.

Five patients in the ChRT group presented toxicity after surgery; 2 presented atrial fibrillation that was treated pharmacologically, 2 cases required surgical management due to bronchio-pleural fistula and cerebrospinal fluid fistula, and one patient presented grade 5 toxicity due to complicated bronchio-pleural fistula five months after surgery. No case of surgical toxicity was observed in the Ch group.

The RR showed a statistically significant difference (P = 0.025) in favor of NT with ChRT, with no case of local progression.

One patient (2.5%) in the ChRT group presented disease progression with brain metastases prior to surgery *vs* 4 patients (14.8%) in the Ch group who presented local progression during Ch.

Twenty-five (62.5%) ChRT patients showed partial RR compared to 8 (29.6%) in the Ch group (Table 3).

A total of 11 patients did not undergo surgery after committee reassessment. Of these, 5 (12.5%) were in the ChRT group, and surgery was not performed due to poor post-NT respiratory functionalism in 1, high risk of pneumonectomy in another, in 1 patient symptomatic brain metastasis was detected prior to surgery, 1 developed bilateral pneumonia secondary to influenza type A, and 1 patient presented poor respiratory functionalism prior to NT and stable radiological disease and suspicion of brain metastasis on MRI. The remaining 6 (22.2%) Ch patients did not undergo surgery: 1 for poor post-NT respiratory function and high risk of pneumonectomy, 3 for local disease progression during Ch, and 2 patients showed poor response after NT. The characteristics of the surgery according to NT group are shown in Table 4.

Lobectomy was the most frequent type of surgery (60% ChRT and 76% Ch), although this was more complex (due to vascular reconstruction, rib resection and / or vertebrectomy) in 25.7% *vs* 9.6% of patients receiving ChRT compared to Ch, respectively.

The median time from the end of NT with ChRT to surgery was 6 wk (3-19), and the median time from the end of the NT Ch to surgery was 8 wk (3-21).

In relation to PHR there was a statistically significant difference in favor of the ChRT group (Table 5). Maximum response (≤ 10% viable cells) was observed in the tumor in 54.5% *vs* 9.5% (P = 0.001) and at the lymph node level in 85.5% *vs* 33.3% (P = 0.001) with ChRT and Ch, respectively. Downstaging was achieved in 28 (80%) and 7 (33.3%) ChRT and Ch patients, respectively (P = 0.002). Two patients in the ChRT group showed lymph node involvement outside the RT field after surgery, but with

Table 1 Patient characteristics, *n* (%)

	RTCh (*n* = 40)	Ch (*n* = 27)	*P* value
Age	60 (54-67)	67 (62-73)	0.32
Gender			0.29
Male	26 (65)	21 (77.8)	
Performance status			0.21
ECOG 0	7 (17.5)	5 (18.5)	
ECOG 1	33 (82.5)	20 (74.1)	
ECOG 2	0	2 (7.4)	
Smoking habit			0.48
Yes	20 (50)	15 (55.6)	
No	2 (5)	3 (11.1)	
Former smoker	18 (45)	9 (33.3)	
Tumor localization			0.33
Apex	7 (17.5)	1 (3.7)	
Right upper lobe	13 (32.5)	13 (48.1)	
Right lower lobe	6 (15)	2 (7.4)	
Left upper lobe	12 (30)	9 (33.3)	
Left lower lobe	2 (5)	2 (7.4)	
Histology			0.28
Adenocarcinoma	25 (62.5)	20 (74.1)	
Squamous	13 (32.5)	6 (22.2)	
NSCLC[1]	0	1 (3.7)	
Large cell	2 (5)	0	
Stage			0.52
IIIA	27 (67.5)	21 (77.8)	
IIIB	12 (30)	6 (22.2)	
IV	1 (2.5)	0	
T			0.08
T1	4 (10)	9 (33.3)	
T2	16 (40)	9 (33.3)	
T3	10 (25)	7 (25.9)	
T4	10 (25)	2 (7.4)	
N			0.04
0	5 (12.5)	0	
2	34 (85)	27 (100)	
3	1 (2.5)	0	
Metastasis	1 (2.5)	0	0.59
Nodal station distribution			0.012
N0	6 (15)	0	
1N2	12 (30)	19 (70.4)	
2N2	2 (5)	1 (3.7)	

1N2 + 1N1	13 (32.5)	7 (25.9)	
2N2 + 1N1	5 (12.5)	0	
1N1 + 1N2 + 1N3	2 (5)	0	
Nodal staging method			0.68
EBUS	24 (60)	14 (51.9)	
Mediastinoscopy	2 (5)	3 (11.1)	
EBUS and mediastinoscopy	8 (20)	6 (22.2)	
EUS	1 (2.5)	2 (7.4)	
None	5 (12.5)	2 (7.4)	

[1]Specific histology could not be determined in one patient. Ch: Chemotherapy. ECOG: Eastern Cooperative Group. NSCLC: Non-Small Cell Lung Cancer. RTCh: Radiochemotherapy; EUS: Endoscopic ultrasound; EBUS: Endobronchial ultrasound

Table 2 Chemotherapy regimens, *n* (%)

	RTCh	Ch
	(*n* = 40)	(*n* = 27)
Cisplatin-Etoposide	19 (47.5)	0
Cisplatin-Vinorelbine	14 (35)	6 (22.2)
Cisplatin-Pemetrexed	4 (10)	3 (11.1)
Cisplatin-Docetaxel	0	6 (22.2)
Cisplatin-Gemcitabine	0	2 (7.4)
Carboplatin-Vinorelbine	3 (7.5)	1 (3.7)
Carboplatin-Paclitaxel	0	6 (22.2)
Carboplatin-Pemetrexed	0	1 (3.7)
Carboplatin-Gemcitabine	0	2 (7.4)

Ch: Chemotherapy. RTCh: Radiochemotherapy.

Table 3 Radiological response, *n* (%)

	RTCh	Ch	*P* value
	(*n* = 40)	(*n* = 27)	
Disease progression	1 (2.5)	4 (14.8)	0.025
Stable disease	14 (35)	14 (51.9)	
Partial response	25 (62.5)	8 (29.6)	
Complete response	0	1 (3.7)	

Ch: Chemotherapy. RTCh: Radiochemotherapy.

maximum PHR in the nodes within the RT field. Numerical but not significant differences were found in complete PHR (17.1% ChRT *vs* 4.8% Ch; $P = 0.23$).

In addition, the Ch group had a higher rate of "non-response" to NT in the tumor (> 70% viable cells pT) 38.1% *vs* 2.9% for ChRT ($P = 0.001$), being 42.9% Ch *vs* 5.7% ChRT ($P = 0.001$) at the lymph node level (> 70% viable pN cells).

In the univariate analysis, the use of NT ChRT had a significant impact on the RR with an increased probability of presenting partial response [odds ratio (OR) 12.5; 95% confidence interval (CI): 1.21-128.61; $P = 0.034$]. In addition, NT ChRT patients presented a decreased risk of persistence of cancer cells in the tumor and resected

Table 4 Surgery characteristics, *n* (%)

	RTCh (*n* = 40)	Ch (*n* = 27)	*P* value
No surgery	5 (12.5)	6 (22.2)	
Type of surgery			0.48
Lobectomy	21 (60)	16 (76)	
Bilobectomy	3 (8.6)	1 (4.8)	
Pneumonectomy	2 (5.7)	1 (4.8)	
Lobectomy and vascular reconstruction	1 (2.8)	1 (4.8)	
Lobectomy and rib resection	5 (14.3)	1 (4.8)	
Lobectomy with rib resection and vertebrectomy	3 (8.6)	0	
Segmentectomy with rib resection and vertebrectomy	0	1 (4.8)	
Node level dissection			0.26
2N2 + 1N1	4 (11.4)	3 (14.3)	
3N2	2 (5.7)	5 (23.7)	
3N2 + 1N1	12 (34.3)	7 (33.3)	
3N2 + 2N1	5 (14.3)	3 (14.3)	
4N2 + 1N1	8 (22.9)	1 (4.8)	
4N2 + 2N1	0	1 (4.8)	
4N2 + 1N3	2 (5.7)	0	
5N2 + 1N1	2 (5.7)	1 (4.8)	

Ch: Chemotherapy. RTCh: Radiochemotherapy.

lymph nodes (Table 6). Patients in the ChRT group presented an 87.5% increased probability of presenting lymph node downstaging (OR 8; 95%CI: 2.34-27.32; P = 0.001).

When analyzing both HTV and HLNV by histological (adenocarcinoma *vs* squamous carcinoma) and NT type, remarkable results were not obtained due to the limited number of patients in each group.

DISCUSSION

In this retrospective multi-institutional phase II study we compared NT Ch *vs* NT ChRT and present the RR and PHR following NT in patients with stage III NSCLC treated by lung cancer specialists from 4 experienced university centers.

Several randomized clinical trials (RCT) have compared NT Ch to NT ChRT, but the results of some of these studies have only been reported in abstract form[9,10], which precludes a real scientific analysis, especially at the level of PHR. Another phase II RCT was published comparing NT Ch *vs* NT ChRT[11], but no relevant information was obtained due to the small number of patients included (n = 46) which were further divided into three different groups. In addition, the main endpoint of this study was the feasibility of surgery, and PHR results were not provided.

Thomas *et al*[5] published a RCT that compared a control group undergoing induction Ch with 3 cycles of cisplatin and VP16 followed by surgery and PORT *vs* an intervention group that underwent NT Ch with the same regimen followed by twice-daily RT (45 Gy) concomitant with carboplatin and vindesine, followed by surgery. In the study, 54% and 59% of ChRT and Ch patients underwent surgery, respectively, and only 37% and 32% of each group, respectively achieved complete resection. This may be due to the inclusion of a proportion of locally advanced NSCLC not clearly resectable at first (15% with T4N2 and 22% with T4N3). It is also important to note that about 20% of the patients in each group progressed to induction Ch prior to NT ChRT

Table 5 Pathological response, *n* (%)

	RTCh (*n* = 40)	Ch (*n* = 27)	*P* value
No surgery	5 (12.5)	6 (22.2)	
Pathological complete response	6 (17.1)	1 (4.8)	0.23
Tumor response[1]			0.001
0%-10%	19 (54.4)	2 (9.5)	
11%-30%	9 (25.7)	2 (9.5)	
31%-50%	4 (11.4)	3 (14.3)	
51%-70%	2 (5.7)	6 (28.6)	
> 70%	1 (2.8)	8 (38.1)	
Nodal response[1]			0.001
0%-10%	30 (85.7)	7 (33.3)	
11%-30%	1 (2.8)	0	
31%-50%	2 (5.7)	3 (14.3)	
51%-70%	0	2 (9.5)	
> 70%	2 (5.7)	9 (42.9)	
Downstaging	28 (80)	7 (33.3)	0.002

[1]According to the percentage of viable cells in the histological study.
Ch: Chemotherapy. RTCh: Radiochemotherapy.

or surgery, and all patients with NT Ch received PORT.

Each endpoint favored NT ChRT with more complete resection (75% *vs* 60%; P = 0.008), nodal downstaging from N2 to N0-1 (46% *vs* 29%, P = 0.02) and PHR greater than 90% (60% *vs* 20%; $P < 0.0001$). Patients with complete resection and mediastinal downstaging presented a greater overall survival (OS), with no differences in progression-free survival (PFS) or OS in relation to the different types of NT.

Katakami *et al*[12] published an RCT of 60 pathologically proven N2 patients randomized to receive induction Ch with docetaxel and carboplatin plus concurrent RT (40 Gy) followed by surgery or NT Ch followed by surgery. Nodal downstaging was described in 20.8% and 40% in Ch and ChRT, respectively. The median OS in patients with and without downstaging in the ChRT arm was 72.1 mo and 31.2 mo, respectively (P = 0.018) and 32.6 mo and 29.0 mo, respectively (P = 0.542) in the Ch arm. The median PFS and OS in each study arm were not statistically significant due to the small sample size.

The next RCT comparing NT Ch *vs* NT ChRT was performed by Pless *et al*[13]. Similar to the trial by Thomas *et al*[5], this study was not a true and strict comparison between NT Ch and NT ChRT. Patients were randomized to 3 cycles of NT Ch (cisplatin and docetaxel) plus sequential RT *vs* NT Ch. All patients were scheduled for surgery. An additional difference with the Thomas trial was that PORT was only administered in the case of microscopic (R1) or macroscopic (R2) tumor margins (16% of trial patients). Patients treated with sequential NT ChRT presented higher lymph node downstaging (64% *vs* 53%), albeit without statistically significant differences. In this study, it is also important to point out two things. First, all the patients were resectable and had low-bulky disease, and second, the trimodal therapy was not radical NT with concurrent ChRT, but rather NT Ch plus sequential RT and surgery. Sequential ChRT is far from being as effective as concurrent ChRT. To our knowledge no study has compared the differences in PHR of sequential *vs* concurrent ChRT, but there is a meta-analysis on the efficacy of these treatments[14].

A true trimodality phase II trial was published by the RTOG 02-29[15]. This trial evaluated downstaging rates in 57 patients with stage III NSCLC (pathologically proven N2 or N3) who received weekly carboplatin and paclitaxel with concurrent RT (50.4 Gy to mediastinal nodes and pT and 10.8 Gy boost to gross disease). The mediastinum was pathologically reassessed after completion of ChRT. Forty-three

Table 6 Univariate analysis investigating the impact of neoadjuvant therapy radiochemotherapy on the response

	OR	95%CI	*P* value
Radiological response			
Disease progression	Reference		
Stable disease	4	0.39-40.42	0.240
Partial response	12.5	1.21-128.61	0.035
Complete response	NA[1]		
Pathological tumor response			
0%-10%	Reference		
11%-30%	0.474	0.05-3.92	0.489
31%-50%	0.14	0.17-1.13	0.065
51%-70%	0.03	0.004-0.30	0.002
> 70%	0.01	0.001-0.16	0.001
Pathological nodal response			
0%-10%	Reference		
11%-30%	0.474	0.057-3.92	0.489
31%-50%	0.14	0.17-0.13	0.065
51%-70%	0.03	0.004-0.30	0.002
> 70%	0.01	0.001-0.16	0.001
Downstaging			
No	Reference		
Yes	8	2.34-27.32	0.001

[1]Not applicable: only one patient in the chemoradiotherapy group and none in the Chemotherapy group. CI: Confidence interval.

patients (75%) were evaluable for the primary endpoint. Twenty-seven patients achieved the primary endpoint of downstaging (63%). Thirty-seven patients underwent resection. The 2-year OS rate was 75% for those who achieved downstaging, 52% for those with residual nodal disease, and 23% for those who were not evaluable for the primary endpoint ($P = 0.0002$).

Radical ChRT attempts to eliminate the possibility of administering a subtherapeutic dose of RT (45 Gy) and/or RT interruptions in patients who, for whatever reason, cannot undergo surgery. The rationale for combining NT Ch with full-dose RT was supported by a retrospective analysis of RT series in NSCLC in which a dose in the range of 58–77 Gy might be necessary to control 50% of gross tumors[16].

During the years of the RCTs comparing NT with Ch and ChRT in stage III NSCLC, other RCTs such as that of the EORTC 0894[17], INT 0139[8] and the ESPATUE trial [18], carried out another line of research on whether surgery adds any real benefits in OS compared to radical concurrent ChRT.

The EORTC 08941 RCT randomized patients to definitive RT *vs* surgery (with PORT in patients with R1 resection) in NSCLC with pathologically proven N2 responding to the initial Ch doublet. It should be noted that 39% of the 579 patients progressed or did not respond to NT Ch and only 61% of all patients were randomized to RT or surgery. There were no statistically significant differences in PFS or OS between the two groups.

In the INT 0139 trial, 396 patients with resectable stage IIIA N2 NSCLC were randomized to concurrent radical RT (61 Gy) with 2 cycles of cisplatin and VP16 *vs* concurrent RT (45 Gy) with the same Ch regimen and surgery. The median OS was not significantly improved with the addition of surgery. However, in an exploratory analysis, the median OS was significantly higher for patients undergoing lobectomy compared with definitive ChRT (33.6 *vs* 21.7 mo; $P = 0.002$). Other factors related to an improvement in OS were pathologic N0 status (34.4 *vs* 26.4 mo; $P \leq 0.0001$) and pathological complete response (PCR) (T0N0: 39.8 mo). Criticisms regarding the INT

0139 trial were the incomplete accrual rate, an under-powered subset analysis suggesting an advantage of trimodal therapy, and a very high mortality rate among patients who underwent pneumonectomy[19]. It should also be noted that the EORTC and the Intergroup trials were designed at a time when routine PET/CT scan had not yet been incorporated into usual clinical practice, and nodal staging using EBUS or EUS was not available in most hospitals.

The ESPATUE trial compared definitive treatment with ChRT *vs* trimodal therapy. Patients with stage IIIA (N2) and IIIB NSCLC underwent 3 cycles of NT Ch with cisplatin and paclitaxel. Patients who did not progress were treated with hyperfractionated RT (45 Gy in 30 fractions twice daily) plus Ch. The patients were reevaluated for operability during the last week of RT, and those eligible for surgery were randomized to completing RT or surgery. The study closed prematurely, with 246 patients being enrolled and 161 patients randomized. Seventy of 81 of the surgical patients underwent surgery, of which 66 underwent R0 resection. A total of 5 (7%) patients presented grade 5 toxicity after surgery. After a median follow-up of 78 mo, there were no differences in PFS or OS.

A cumulative meta-analysis of RCT comparing definitive ChRT *vs* NT therapy followed by surgery[20] in stage III NSCLC found no significant differences in OS in these patients after NT Ch and surgery. It is also noteworthy that the trials with concurrent NT ChRT and radical ChRT showed a better OS than the other trials with NT Ch alone before surgery.

Another line of research has been to combine ChRT with antibodies against epidermal growth factor receptors (EGFR) in stage III NSCLC. The NRG oncology RTOG 0839 study[21] was designed to test the hypothesis that adding an EGFR antibody to the standard ChRT could potentially improve the outcome in this group of patients. The endpoint was downstaging, but an unexpectedly high mortality rate was observed in the panitumumab group.

In addition, a phase II RCT with erlotinib *vs* gemcitabine plus cisplatin as NT was performed in patients with stage IIIA-N2 NSCLC with EGFR mutations in exon 19 or 21[22]. A total of 72 patients were randomized. No PCR was found in any of the arms. Three of 31 patients in the erlotinib arm and none of 23 Ch patients achieved maximal pathologic response (MPR).

A recent line of investigation of NT in stage III (N2) NSCLC has been the combination of concomitant Ch with immunotherapy. NADIM, a single-arm, phase II multicenter trial in resectable stage IIIA NSCLC, included 46 patients who received 3 cycles of NT Ch plus nivolumab followed by surgical resection, and then continued nivolumab for one year. At 24 mo, PFS was 77.1% (95%CI: 59.9-87.7). No patient presented disease progression during NT, and 34 (83%; 95%CI: 68-93) of 41 operated patients had MPR, 26 of whom (63%; 95%CI: 62-91) showed PCR. Thirty-seven (90%) of the 41 patients operated presented nodal downstaging (from N2 to N1-N0)[23].

For nearly three decades, PHR after NT has been correlated with survival[24]. According to Pisters *et al*[24] PCR predicts a higher OS, which is considered an important endpoint for Ch. However, the mean frequency of PCR after NT Ch is 4% to 7% (the PCR rate appears to be higher in squamous cell carcinomas). Due to the low proportion of PCR after NT Ch, another surrogate parameter of OS in relation to PHR was considered for NT Ch by Hellman *et al*[25] who proposed MPR, defined as a value < 10 % of viable cells in resected tumors, as a surrogate endpoint for OS. This proposal was based on a previous analysis by Pataer *et al*[3] in 192 resected stage I-IV NSCLC patients treated with NT Ch. The percentage of viable tumor cells after NT Ch was considered a categorical variable and analyzed in relation to the risk of death. A significant improvement in OS was demonstrated in those with 0-10% viable tumor cells compared to other groups (11%-30%, 31%-50%, 51%-70%, and 71%-100%).

This correlation between MPR and OS has not been validated in NT ChRT[5], although a positive association between lymph node downstaging and improved OS has been shown in pathological IIIA N2 NSCLC after NT ChRT and NT Ch[25]. Even if the degree of PHR is a predictor of OS, only a few studies have described a detailed pathological assessment (percentage of viable cells) at the pT and metastatic node level. The PHR to NT can significantly vary between the tumor and metastatic lymph nodes. The extent of lymphadenectomy may vary between centers and may depend on the methodological approach of the surgeons and pathologists at each hospital. Furthermore, the minimum number of lymph nodes or lymph node levels that must be resected has not been defined. This last fact is directly related to the experience of thoracic surgeons in tumor resection and / or in the extension of radical complementary lymphadenectomy with a minimum of nodal stations evaluated.

There is little consensus on the precise definition of what is considered as "resectable" T4 or N2-N3 disease, and there is no universally accepted definition of "potentially resectable N2" disease. Surgical treatment largely depends on the experience of the hospital and the expertise of the thoracic surgeons involved. T4 disease involves a locally aggressive tumor with invasion of nearby mediastinal structures, such as the carina, great vessels, and / or vertebrae. In these cases, it can be very difficult to achieve complete resection (R0) as defined by the IASLC[26].

The importance of the so-called "time window" recommended for performing surgery after NT ChRT has been reported. A retrospective study of 1623 patients with stage IIIA NSCLC treated with concurrent NT ChRT found a statistically significant decrease in OS when surgery was performed more than 6 wk after completion of RT [27]. OS was compared in patients operated at 0-3 wk, 3-6 wk, 6-9 wk and 9-12 wk after completing RT. The multivariate analysis demonstrated no significant difference in those who underwent surgery within 6 wk of NT ChRT. However, significant reductions in OS were observed in patients operated at more than 6 wk and ≤ 9 wk after NT [hazard ratio (HR) = 1.33, 95%CI: 1.01-1.76, P = 0.043].

The optimal treatment strategy in resectable stage III (N2) NSCLC is debated, and different guidelines from the United Kingdom, Europe and the United States have made recommendations. The common recommendation is to administer multimodal treatment to prevent distant disease with systemic therapy and achieve local control by surgery, RT, or both. Furthermore, multimodal treatments require experienced multidisciplinary teams to minimize the secondary risks of the treatments and maximize their benefits[28].

The most recent guidelines are the National Institute for Health and Care Excellence guidelines[29]. On pages 33-34 of these guidelines, detailed recommendations for operable stage IIIA-N2 NSCLC are described: "... the available evidence showed that ChRT and surgery are more effective than ChRT alone in people well enough for surgery and when the disease is operable...There was an 89% chance that ChRT and surgery improved the mean OS time compared to ChRT...".

The authors of this recent English guideline do not recognize as methodologically true or scientific some meta-analyses and/or systematic reviews of different articles of supposed NT comparisons reporting the absence of benefits in OS with the addition of RT to Ch as NT in stage III (N2) NSCLC[30-34].

Our phase II study is the first study in the scientific literature on NT in patients with stage III NSCLC, in which a true comparison is made between NT ChRT *vs* NT Ch prior to surgery performed by specialists with lengthy experience and a centralized group of thoracic surgeons and pathologists. This latter fact avoids biases due to different surgical skills and reduces the probability of morbidity and mortality in stage III patients after NT[35]. The evidence supports the association between the experience of thoracic surgeons and lower mortality and improvement in long-term OS after lung resection[36]. In addition, histological evaluation by the same two pathologists with experience in lung cancer reduces interobserver variability, achieving greater homogeneity in the results. To our knowledge, this is the first study in the literature in which the same two pathologists made an exhaustive description of the percentage of viable cells in the tumor and in all lymph nodes resected after NT, actually comparing the response to Ch *vs* ChRT. Two other factors of our study must be highlighted. A detailed description of the lymph node stations (mediastinal and hilar) affected prior to NT was made as well as the lymph node levels resected by lymphadenectomy. To our knowledge, this has never been reported in any other NT study, and both could be considered as a factor of surgical quality and may have a positive prognostic role in the evolution of the disease. This pathological description of the resected nodes is being studied in order to better differentiate surgically treated patients into different stages[37].

The main limitation of our study is that it is not an RCT. However, there were no significant differences in the characteristics of the patients, such as gender, performance status, tumor location or histology (Table 1). Nevertheless, the median age was slightly higher in the NT Ch group compared to the NT ChRT group (67 *vs* 60 years), and we also observed a higher proportion of apical / Pancoast tumors (7 *vs* 1) and stages IIIB (16 *vs* 7) in the NT ChRT group compared to the NT Ch patients. There was a significant difference in the Ch schemes used (Table 2) in NT ChRT compared to NT Ch, with 55.6% of ChRT patients being treated with cisplatin-VP16 compared to 0% in the NT Ch group. There is no evidence in the literature that one cisplatin doublet-based regimen is better than another. There is perhaps more experience with concurrent cisplatin-VP16 treatment with RT, and therefore the data could support this scheme in favor to others[19].

Furthermore, in relation to the evaluation of the RR, it should be noted that 4 NT Ch patients (14.8%) progressed locally to NT compared to none in the NT ChRT group. Of these patients who progressed, 2 did not undergo surgery and the other 2 were considered by the Lung Committee for salvage surgery. Both underwent R1 resection, and were therefore considered for PORT, and 1 developed multiple metastases during PORT planning. This evolution with local progression of the tumor during Ch is consistent with the results (between 20% and 30%) of the previously commented studies of induction Ch (EORTC, ESPATUE and the study of Thomas *et al*[5]). In relation to PHR, more than 38% of the NT Ch patients did not respond to Ch, with persistence of 70% or more of viable cells in the tumor and/or the nodes. In contrast, local progression and unresponsiveness after concurrent NT ChRT was 0% and 2.8%, respectively, being very similar to NT with Ch and immunotherapy in the NADIM trial. Indeed, the limited response to NT Ch in approximately 50% of the patients has not been adequately addressed in any previous study to assess whether this could be detrimental to long-term outcomes, and studies are needed to determine the impact of this treatment on PFS and OS.

Regarding the type of surgery, we observed more complex interventions in the NT ChRT group, according to the more advanced stages (*e.g.*, T4) in 27.5% compared to 7.4% in the NT Ch group. The first group included patients with locally advanced NSCLC, which was not easily amenable to primary resection, and in whom treatment with definitive ChRT could have been a valid option. These patients could be stratified into high-volume nodal disease (bulky, multilevel N2 or N3) or locally invasive pT (T4 N0-1 or superior sulcus tumor). According to the literature, in these patients only the experience of the thoracic surgeon provides greater local control and perhaps greater PFS and OS compared to definitive ChRT[19]. In our opinion, locally advanced tumors were the main cause of greater post-surgical morbidity and complications in the NT ChRT (3) compared to NT Ch (0), with two brocho-pleural fistulas and one cerebrospinal fluid fistula. The last case was a Pancoast tumor treated with lobectomy and vertebrectomy. The remaining NT ChRT patients and all the NT Ch patients could be considered as low volume N2 disease (IIIA) in which total resection could be achieved.

The median time between the end of RT and surgery was 6 wk (3-19). This is slightly longer than the recommended time of 3 w to 4 wk for resection after NT ChRT [27]. The median time between the last cycle of Ch and surgery was 8 wk (3-21). The recommended time between NT Ch and the intervention is unknown, which may explain why our treatment interval was so long. Cases with a longer interval (*e.g.*, 19 wk and 21 wk) were patients requiring salvage surgery.

There was also a significant difference in favor of the NT ChRT group in the PHR in the tumor and lymph nodes (Table 5). It should be noted that the NT Ch patients obtained 4.8% PCR at the tumor level, which is in line with what was observed by Pataer *et al*[3].

In the analysis of lymph node downstaging, we found significant differences between the patients receiving NT ChRT and those with NT Ch. In the ChRT group, 2 patients had positive nodes outside the initially diagnosed nodes. This is probably due to the volume of radiation treatment in these patients being limited to gross disease, and thus, these "out-of-field" nodes did not receive RT, and no local effect should be expected at this level. The involvement of these nodes was limited to intracapsular microscopic disease, which was diagnosed in the detailed pathological study after radical lymphadenectomy.

When comparing the PHR of our results of the NT ChRT group with that of the NADIM trial (the study with the best results published to date in this type of patients), the results are slightly better in the NADIM[23] study, with MPR in the tumor of 83% and 90% downstaging compared to an MPR of 54.5% in the tumor and 80% downstaging in our NT ChRT group, and 9.5 % and 33.3% in the NT Ch group, respectively. A longer follow-up will show whether these differences in PHR between NT ChRT and NT Ch have any impact on the PFS and OS of our patients.

When most of our patients were treated, the interim results of the LungART trial on the role of PORT had not yet been published[38]. Our NT Ch patients with persistent pN2 after surgery received PORT (54 Gy) following the LungART recommendations.

After the results published by the NADIM[23] trial, it is unlikely that an RCT will be conducted comparing NT Ch *vs* NT ChRT with robust results. In our opinion, the current line of research that should be followed in patients with stage III NSCLC is the combination of NT with immunotherapy and Ch or RT, concomitantly or in consolidation, as in the PACIFIC study[39].

We therefore believe that despite not being a RCT or prospective study, the results of our study may be useful to guide NT in patients with resectable stage III (N2) NSCLC, according to the experience in multimodal treatment and the surgical skills of each center in this type of patient.

CONCLUSION

Neoadjuvant treatment with ChRT provides significant benefits in both radiological and PHR in patients with resectable stage III NSCLC. However, a longer follow-up is necessary to assess the impact on clinical outcomes.

ARTICLE HIGHLIGHTS

Research background

There is no standardized clinical consensus for the evaluation of the surgical specimen in patients with non-small cell lung cancer (NSCLC) who have received neoadjuvant treatment with chemotherapy, radiotherapy, or a combination of both.

Research motivation

Following the recently published recommendations by the International Association for the Study of Lung Cancer (IASLC) for the pathological evaluation of tumors and lymph nodes, we analyzed the radiological and pathological response of patients treated with neoadjuvant chemotherapy or chemoradiotherapy.

Research objectives

Our intention was to contribute to the IASLC recommendations with clinical results that reflect the differences in the response to neoadjuvant therapy with chemoradiotherapy *vs* chemotherapy.

Research methods

We performed a retrospective analysis of patients with resectable stage III NSCLC treated with chemotherapy or chemoradiotherapy as neoadjuvant treatment followed by surgery. All histological samples were examined to assess pathological response by the percentage of viable cells in the tumor and the resected lymph nodes.

Research results

We observed better results in the chemoradiotherapy group for both radiological and pathological response, with a lower risk of persistence of cancer cells in the tumor and resected lymph nodes, and with a greater probability of achieving downstaging.

Research conclusions

In this study we observed a greater response to neoadjuvant treatment when adding radiotherapy to chemotherapy. We believe that this could contribute to improving the management of this group of patients.

Research perspectives

Longer follow-up of these patients is necessary to establish a relationship between pathological response and clinical outcomes.

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ORIGINAL ARTICLE

Observational Study

Modulated electro-hyperthermia in stage III and IV pancreatic cancer: Results of an observational study on 158 patients

Giammaria Fiorentini, Donatella Sarti, Girolamo Ranieri, Cosmo Damiano Gadaleta, Caterina Fiorentini, Carlo Milandri, Andrea Mambrini, Stefano Guadagni

ORCID number: Giammaria Fiorentini 0000-0002-5615-889X; Donatella Sarti 0000-0002-8031-7846; Girolamo Ranieri 0000-0002-7952-694X; Cosmo Damiano Gadaleta 0000-0003-2398-691X; Caterina Fiorentini 0000-0002-9346-1409; Carlo Milandri 0000-0001-6932-8977; Andrea Mambrini 0000-0001-9736-4991; Stefano Guadagni 0000-0001-8525-084X.

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Giammaria Fiorentini, Department of Onco-Hematology, Azienda Ospedaliera "Ospedali Riuniti Marche Nord", Pesaro 61122, Italy

Donatella Sarti, Oncology Department, Ospedale S. Maria Della Misericordia, ASUR1, Urbino 61029, Italy

Girolamo Ranieri, Cosmo Damiano Gadaleta, Interventional and Integrated Medical Oncology, National Cancer Research Centre, IRCCS Istituto Tumori "Giovanni Paolo II", Bari 70124, Italy

Caterina Fiorentini, Department of Medical Biothecnologies, Division of Cardiology, University Hospital of Siena, Siena 53100, Italy

Carlo Milandri, Medical Oncology Unit, San Donato Hospital, Arezzo 52100, Italy

Andrea Mambrini, Department of Oncology - ASL Toscana Nord Ovest, Massa Carrara Hospital, Massa 54100, Italy

Stefano Guadagni, Applied Clinical Sciences and Biotechnology, Section of General Surgery, University of L'Aquila, L'Aquila 67100, Italy

Corresponding author: Giammaria Fiorentini, MD, Adjunct Professor, Chief Doctor, Director, Department of Onco-Hematology, Azienda Ospedaliera "Ospedali Riuniti Marche Nord", Via Lombroso, Pesaro 61122, Italy. g.fiorentini2020@gmail.com

Abstract

BACKGROUND

An increasing number of studies report the beneficial effects of regional hyperthermia in association with chemotherapy (CHT) and radiotherapy for the treatment of pancreatic cancer; in particular, the use of modulated electro-hyperthermia (mEHT) results in increased survival and tumor response.

AIM

To compare outcomes of CHT alone or in association with mEHT for the treatment of stage III and IV pancreatic cancer.

METHODS

This was an observational retrospective study; data were collected for patients

technical appendix, statistical code, and dataset are available.

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with stage III-IV pancreatic cancer that were treated with CHT alone or in combination with mEHT from 2003 to 2019. A total of 158 patients were included in the study out 270 patients screened in four Italian hospitals; 58 (37%) of these received CHT + mEHT and 100 (63%) CHT. CHT was mainly gemcitabine-based regimens in both groups.

RESULTS

Overall (19.5 mo *vs* 11.02 mo, $P < 0.001$) and progression-free (12 mo *vs* 3 mo, $P < 0.001$) survival were better for the CHT + mEHT group compared to the CHT group. The association of mEHT resulted also in an improvement of tumor response with disease control rate 95% *vs* 58% ($P < 0.001$) at 3 mo. Toxicity was comparable in the two study groups, and mEHT related adverse events were limited in 8 patients presenting G1-2 skin burns.

CONCLUSION

The addition of mEHT to systemic CHT improved overall and progression-free survival and local tumor control with comparable toxicity.

Key Words: Modulated electro-hyperthermia; Locally advanced pancreatic cancer; Tumor response; Survival

Core Tip: Modulated electro-hyperthermia is a relatively new regional hyperthermia method. It targets tumor cell membranes and extracellular matrix to increase their temperature. New studies have appeared in tumor palliation reporting incremental benefits of chemotherapy and radiotherapy and few additional side effects. In patients with stage III and IV pancreatic cancer, modulated electro-hyperthermia in association with chemotherapy results in significant improvements of overall and progression-free survival and tumor response with comparable toxicity.

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INTRODUCTION

Pancreatic cancer has one of the worst prognoses in oncology, with a 5-year overall survival (OS) of 9%, and is the seventh most common cause of cancer deaths in the world in 2018[1]. Adenocarcinoma is the main morphology of this tumor (90%), and its incidence and mortality are increased during the last 2 decades[1]. Surgery followed by adjuvant therapy is the only curative treatment of pancreatic tumors; however, only 10%-20% of them are resectable at diagnosis, whereas 30%–40% are locally advanced and 50%-60% are metastatic.

Non-metastatic, locally advanced pancreatic cancer (LAPC) can be treated with neoadjuvant chemotherapy or chemoradiotherapy to allow surgical resection. Gemcitabine in association with nab-paclitaxel and FOLFIRINOX (leucovorin, fluorouracil, irinotecan, oxaliplatin) for fit patients are two current standard first-line options in LAPC, but they have high toxicity and often low efficacy[2-4]. Pancreatic cancer is quite resistant to radiotherapy (RT) and chemotherapy (CHT) because of its hypoxic microenvironment that diminishes sensitivity to these therapies. In order to increase tumor response, the use of regional hyperthermia is often associated to CHT and RT[5]. Regional hyperthermia (RHT) efficacy in cancer remission is well known, indeed, it enhances drug delivery and diffusion inside the tumor cells, improves blood flow, reduces hypoxia, and inhibits DNA repair, resulting in apoptosis[6].

RHT is achieved by increasing the cancer cells' temperature to 39.5-43 °C with an external device. A new method of RHT has been recently developed: The modulated

electro-hyperthermia (mEHT) that is performed with a 13.56 MHz capacitive coupled device. It targets malignant cell membranes and extracellular matrix, allowing to overcome the issue of reaching deep tumors and achieving homogenous heating[7,8]. The mEHT has comparable benefits to other RHT methods and improves survival and local tumor control for several tumors, including pancreatic cancer[9-11].

MATERIALS AND METHODS

Patient selection

This was a large retrospective observational multicentric study aimed to compare outcomes of chemotherapy alone or in association with mEHT for the treatment of locally advance pancreatic cancer, in terms of survival and tumor response. Data were collected retrospectively, and patients were selected according to the following inclusion criteria: > 18 years, stage III and IV pancreatic cancer, treatment with CHT alone or in combination with mEHT, and informed consent signed. Patients were excluded from the study if they had a pacemaker, bilirubin, or transaminase level > 3 times the normal value upper range level or bleeding.

From January 2003 to December 2019, 270 patients with stage III and IV pancreatic cancer were screened in four Italian hospitals; 158 of these patients met the inclusion criteria and were included in the study, 58 (37%) of these received CHT + mEHT and 100 (63%) CHT alone. CHT was mainly gemcitabine-based regimens in both groups.

mEHT protocol and device

Modulated electro-hyperthermia was performed using the EHY-2000plus device (CE0123, Oncotherm, Torisdorf, Germany), applying a radiofrequency current of 13.56 MHz as carrier frequency that was modulated by time-fractal fluctuation. The energy was transferred by capacitive coupling, with precise impedance matching[12].

The hyperthermia protocol included three mEHT treatments/week for 2 mo, starting at a 60 W power for 40 min. Following treatments were performed by increasing the power up to 150 W and the time up to 90 min in 2 wk. mEHT was administered after CHT or within 48 h, in order to couple the high drug blood concentration with the modulated electro hyperthermia and optimize their synergy.

The majority (95%) of gemcitabine-based treatments were administered on the same day of electro-hyperthermia treatment. In a minority of patients (5%), it was administered the following day or within the following 72 h because of precarious clinical conditions and geographic accessibility. Even if gemcitabine had a half-life of 42-94 min and was eliminated within 5-11 h after infusion, the pharmacokinetic elimination half-life for dFdU varies between 2 and 24 h, and it is still present systemically in concentrations greater than 1 μmol/L up to 1 wk after infusion[13].

Outcome measures

The primary outcome was to monitor OS and progression free survival (PFS). OS was considered from diagnosis to death or last follow up date; PFS was considered from treatment start to date of progression.

Secondary outcome was local tumor control and toxicity. Response Evaluation Criteria in Solid Tumors version 1.4 was used for tumor assessment from magnetic resonance imaging or computed tomography scans. Complete response (CR) was considered when all target lesions disappeared. Partial response (PR) was considered when the sum of diameters of all target lesions was reduced of at least 30%. Progressive disease (PD) was considered when the sum of diameters of all target lesions was increased of at least a 20%, or one or more new lesions appeared. Stable disease (SD) was considered when the sum of diameters of all target lesions reduced < 30%, increased < 20%, or did not change.

Toxicity was assessed with Common Terminology Criteria for Adverse Events version 5.0.

Statistical analysis

Age and survival were reported as median and ranges; frequencies were reported as percentages. Kaplan-Meier non parametric estimates was used for OS and PFS analysis, reporting survival probability on the y axis and time in months on the x axis. Chi square test, Student's *t* test, and log-rank test were used for statistical significance, and $P \leq 0.05$ was used to indicate statistically significant differences.

RESULTS

Sample characteristics

The study included 158 consecutive patients, 58 (37%) of these received CHT + mEHT and 100 (63%) CHT alone. The two sub groups had similar characteristics concerning gender distribution, presence and site of metastases, and previous surgery (Table 1). Some differences were found between CHT + mEHT and CHT groups in median age (64 *vs* 69 years, $P = 0.013$), previous RT (2% *vs* 12%, $P = 0.023$), number of previous CHT lines (2 Lines: 19% *vs* 35%, $P = 0.037$), and type of chemotherapy. Gemox was the most used chemotherapy in CHT + mEHT group ($P = 0.004$), whereas FOLFOX and FOLFIRINOX were used only in CHT group ($P < 0.05$).

Survival

Median OS was greater for CHT + mEHT group than CHT group (19.5 mo *vs* 11.02 mo, $P < 0.001$); also PFS was improved (12 mo *vs* 3 mo, $P < 0.001$) for the CHT + mEHT group (Figure 1A and B).

Tumor response

The association of mEHT resulted also in an improvement of tumor response at the 3 mo time point, with a disease control rate (DCR) 95% *vs* 58% ($P < 0.001$) in CHT + mEHT group and CHT group, respectively (Table 2). CHT + mEHT group, in particular, had a greater PR (52% *vs* 14%, $P < 0.001$) and lower PD (5% *vs* 58%, $P < 0.001$) than CHT group.

Adverse effects and safety

Each patient received an average of 13 (range = 4-28) sessions of mEHT. Out of a total of 754 mEHT delivered sessions, the safety assessment of mEHT showed a limited number of adverse events 23/754 (4%). mEHT toxicity consisted of skin pain in 15 (3%) patients and burns in 8 (1%).

All these side effects were G1-G2 intensity and resolved with local medications and discontinuation of treatment for 1 wk. All patients were evaluated before and after mEHT with electrocardiogram and cardiac ultrasound. No one had cardiac toxicity.

DISCUSSION

Hyperthermia has been used as cancer therapy for decades, especially for its benefits in enhancing chemotherapy and radiotherapy efficacy[6,14-22]. mEHT has been more recently introduced among hyperthermia methods, targeting malignant cell membranes and the extracellular matrix and overcoming the issue of homogenous tissue heating[7,8]. The efficacy of mEHT was shown for several types of tumors, including pancreatic cancer, increasing tumor response and survival[5,9,15-21].

The current study showed that mEHT improved OS (19.5 mo *vs* 11.02 mo, $P < 0.001$) and PFS (12 mo *vs* 3 mo, $P < 0.001$), resulting also in an increased tumor response with DCR 95% *vs* 58% ($P < 0.001$) than CHT alone. Toxicity was comparable in the two study groups and hyperthermia-related adverse events were mainly G1-2.

The beneficial effect of hyperthermia on survival of locally advanced pancreatic cancer was reported if combined with chemotherapy by Tschoep-Lechner, reporting in 23 patients an OS 12.9 mo (95%CI: 9.9-15.9) and a DCR in 16 patients with available CT scans of 50%[20].

Similar results are observed when associated to chemo-radiotherapy (CRT). Three studies, in particular, showed OS of 8.8-15 mo *vs* 4.9-11 mo ($P < 0.05$) in the association group than CRT alone group and PFS = 18.6 mo *vs* 9.6 mo ($P = 0.01$)[17-19]. The association of CHT to RHT also result in encouraging survival: Median OS of 12.9-17.7 mo, 1-year OS = 41% and 2-year OS = 15%[15-17]. Similar survivals are reported by other four studies on mEHT for the treatment of locally advanced pancreatic carcinoma, OS of 8.9-19 mo and PFS of 3.9-12.9 mo[9-11]. The results of the present study were in agreement with the above data, showing OS of 19.5 mo and PFS of 12 mo for CHT + mEHT group. In OS analysis, the survival curve was crossed; this may be due to the fact that stage III-IV pancreatic cancer has always had a poor outcome and, inevitably, when comparing the curves of two treatments, they cross because all patients had died.

Improvements were reported also in tumor response for locally advanced pancreatic carcinoma a consequence of the association of CHT to mEHT with a DCR of

Table 1 Sample characteristics

	CHT + mEHT, *n* (%)	CHT, *n* (%)	*P* value
Median age (range)	64 (38-82)	69 (34-92)	**0.013**
M	39 (67)	57 (57)	0.204
F	19 (33)	43 (43)	
Non-Metastatic	16 (28)	37 (37)	0.223
Metastatic	42 (72)	63 (63)	
Site of Metastases			
Liver	40 (61)	51 (70)	0.164
Peritoneum	16 (24)	6 (8)	
Lymph nodes	9 (14)	6 (8)	
Lung	1 (2)	8 (11)	
Previous surgery	14 (24)	24 (24)	0.981
Previous RT	1 (2)	12 (12)	**0.023**
Previous CHT	52 (90)	52 (52)	**< 0.001**
Number of previous CHT lines			
1	31 (60)	25 (48)	0.334
2	10 (19)	18 (35)	**0.037**
> 3	11 (21)	9 (17)	0.619
Type of CHT			
Gemox	28 (54)	12 (23)	**0.004**
Gemcitabine	12 (23)	7 (13)	0.205
Gemcitabine abraxane	16 (31)	15 (29)	0.830
FOLFIRINOX	0 (0)	5 (10)	**0.022**
FOLFOX	0 (0)	4 (8)	**0.041**
Other	2 (4)	9 (17)	

Significative values were reported in bold. mEHT: Modulated electro-hyperthermia; CHT: Chemotherapy; RT: Radiotherapy.

Table 2 Tumor response at 3 mo

	CHT + mEHT, *n* (%)	CHT, *n* (%)	*P* value
DCR	53 (95)	40 (58)	**< 0.001**
PR	29 (52)	13 (14)	**< 0.001**
SD	24 (43)	27 (28)	0.064
PD	3 (5)	56 (58)	**< 0.001**

Significative values were reported in bold. mEHT: Modulated electro-hyperthermia; CHT: Chemotherapy; DCR: Disease control rate; PR: Partial response; SD: Stable disease; PD: Progressive disease.

95% that were in agreement with previous data: DCR of 71%-96%[8-11] and resulted higher than that reported by CHT associated with local hyperthermia, showing a DCR of 50%-61%[17-19]. The level of hyperthermia related toxicity was 5% as reported by other studies, showing G2 pain and a skin rash and 5% grade III–IV toxicity[15,18]. These data suggest that RHT increases CRT and CHT benefit both in terms of median OS and in DCR in pancreatic cancer with a low toxicity.

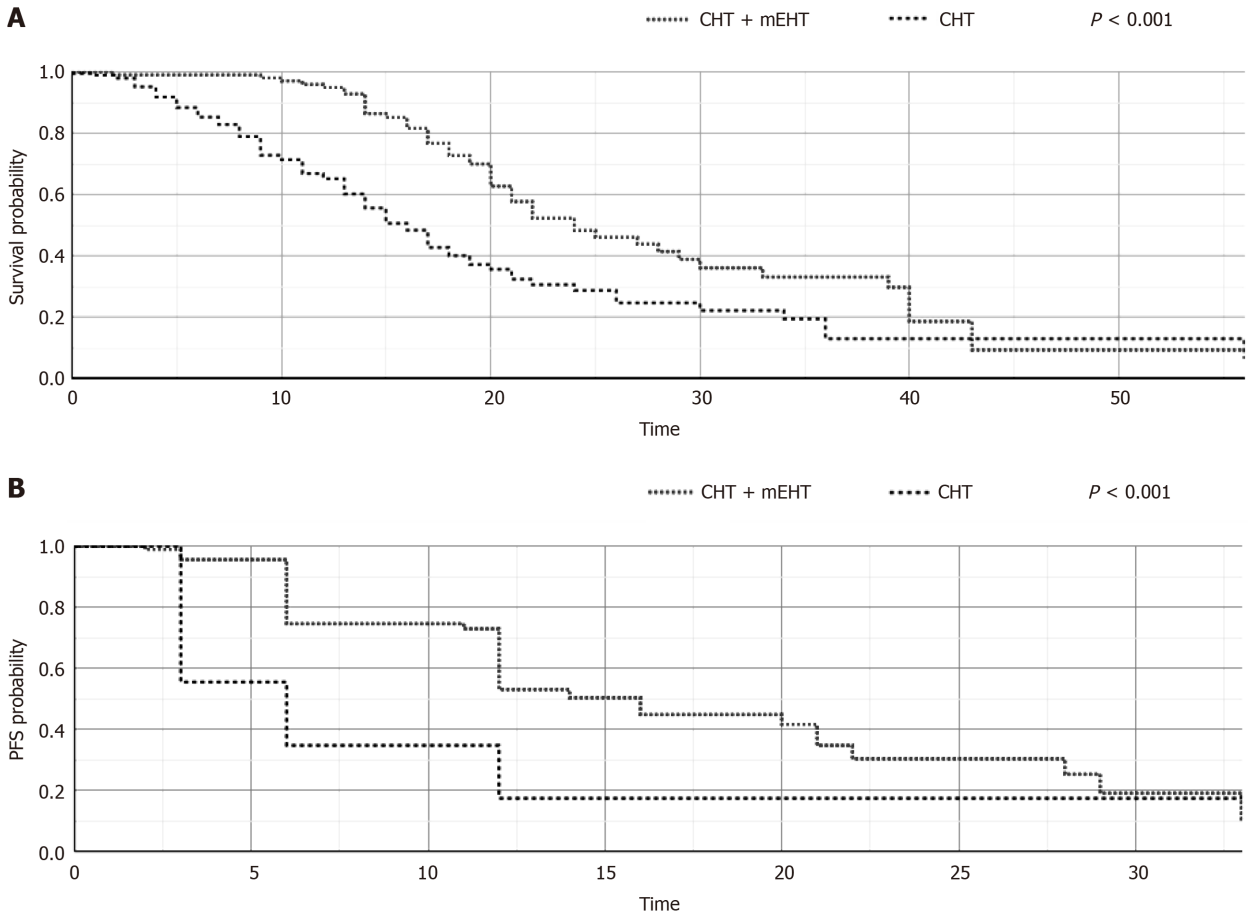

Figure 1 Overall survival (A) and progression free survival (B) analysis of the two study groups. mEHT: Modulated electro-hyperthermia; CHT: Chemotherapy; PFS: Progression-free survival.

The main limitations of this study were due to the observational nature of this study that resulted in some imbalances distribution between the two subgroups as concerning number of patients and median age, since CHT group had a greater number of subjects (100 *vs* 58) that were of median older age (69 years *vs* 64 years) than CHT + mEHT group. Age should not be considered an issue, since the improvement of survival and tumor response was observed also in older patients (> 65 years) with stage III and IV pancreatic cancer[9]. Further prospective, randomized trials on a larger number of patients are required to develop these initial data.

CONCLUSION

The addition of mEHT to systemic CHT improved OS and PFS and local tumor control with comparable toxicity.

ARTICLE HIGHLIGHTS

Research background

Hyperthermia has been used as cancer therapy for decades, especially for its benefits in enhancing chemotherapy and radiotherapy efficacy. Modulated electro-hyperthermia (mEHT) is a relatively new method of hyperthermia that targets malignant cell membranes and the extracellular matrix, overcoming the issue of homogenous tissue heating.

Research motivation

The efficacy of mEHT is known for several types of tumors, including pancreatic cancer. Pancreatic cancer has a poor prognosis, and the combination of mEHT with

chemo- and/or radiotherapy might be important to increase tumor response and improve survival.

Research objectives

The aim of this study was to compare outcomes of chemotherapy (CHT) alone or in association with mEHT for the treatment of locally advanced pancreatic cancer.

Research methods

Data were collected retrospectively from a cohort of 158 consecutive patients with stage III-IV pancreatic cancer that were treated with CHT alone (63%) or in combination with mEHT (37%) from 2003 to 2019. These data included patients' characteristics, type of chemotherapy, previous surgery or radiotherapy, tumor response, survival, progression free survival, and adverse events.

Research results

The evaluation of survival showed that CHT + mEHT group had a longer overall (19.5 mo *vs* 11.02 mo, $P < 0.001$) and progression free (12 mo *vs* 3 mo, $P < 0.001$) survival. The association of mEHT improved also tumor response with disease control rate 95% *vs* 58% ($P < 0.001$). Toxicity was comparable in the two study groups and hyperthermia-related adverse events were mainly G1-2.

Research conclusions

The results obtained in this study provided new evidence that mEHT improved survival and tumor response, delaying the progression insurgence. The introduction of mEHT, moreover, did not influence chemotherapy tolerability, and hyperthermia-related adverse events were limited.

Research perspectives

This observational study provides further evidence that mEHT association to chemotherapy can enhance its benefit in pancreatic cancer patients. Further studies are required to confirm these results in a large cohort study and to evaluate treatment safety and efficacy.

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CASE REPORT

Anaplastic myxopapillary ependymoma: A case report and review of literature

Hiroshi Kanno, Yukiko Kanetsuna, Masamichi Shinonaga

ORCID number: Hiroshi Kanno 0000-0002-4335-3899; Yukiko Kanetsuna 0000-0002-8518-0252; Masamichi Shinonaga 0000-0003-0335-1431.

Author contributions: Kanetsuna Y performed the histological evaluation; Kanno H drafted the manuscript, the table and figures; Shinonaga M evaluated the clinical data and reviewed the manuscript.

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Hiroshi Kanno, Masamichi Shinonaga, Department of Neurosurgery, International University of Health and Welfare Atami Hospital, Atami 413-0012, Shizuoka, Japan

Yukiko Kanetsuna, Department of Pathology, International University of Health and Welfare Atami Hospital, Atami 413-0012, Shizuoka, Japan

Corresponding author: Hiroshi Kanno, MD, PhD, Professor, Surgical Oncologist, Department of Neurosurgery, International University of Health and Welfare Atami Hospital, 13-1 East Coast, Atami 413-0012, Shizuoka, Japan. hiroshikannomd@nifty.com

Abstract

BACKGROUND

Myxopapillary ependymoma (MPE) is a pathological grade I tumor that arises in the filum terminale. MPE with anaplastic features is extremely rare, and only 5 cases have shown malignancy at the time of recurrence.

CASE SUMMARY

The patient (a 46-year-old woman) had undergone a MPE operation 30 years ago. After subtotal resection of the tumor located in L4-S1, it had a solid component that extended to the adjacent subcutaneous region. Histologically, the tumor consisted of a typical MPE with anaplastic features. The anaplastic areas of the tumor showed hypercellularity, a rapid mitotic rate, vascular proliferation, and connective tissue proliferation. Pleomorphic cells and atypical mitotic figures were occasionally observed. The MIB-1 index in this area was 12.3%. The immunohistochemical study showed immunoreactivity for vimentin, glial fibrillary acidic protein and S100. The morphological pattern and immunohistochemical profile were consistent with anaplastic MPE. The patient tolerated surgery well without new neurological deficits. She underwent local irradiation for the residual tumor and rehabilitation.

CONCLUSION

Although extremely rare, anaplastic MPE occurs in both pediatric and adult patients, similar to other ependymomas. At a minimum, close monitoring is recommended, given concerns about aggressive biological potential. In the future, further study is needed to determine the WHO classification criteria and genetic indicators of tumor progression. The possibility of malignant transformation of MPE should be taken into account, and patients with MPE should be treated with care and follow-up.

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Core Tip: Myxopapillary ependymoma (MPE) is a pathological grade I tumor that develops in the filum terminale. MPEs with anaplastic features are extremely rare; only 5 cases have shown malignancy when they relapsed. Here we report a case of MPE with anaplastic features in local late recurrence in a 46-year-old woman and review anaplastic MPE in the published literature. MPEs have the potential for malignant transformation after a long period of time despite being a pathological grade I tumor. Therefore, the possibility of malignant transformation of the MPE should be considered, and patients with MPE should be treated carefully and monitored over a long period of time.

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INTRODUCTION

Myxopapillary ependymomas (MPEs, grade I) account for 9%-13% of ependymal tumors and about 83% of ependymomas are found in the area of the filum terminale [1]. MPEs are typically encapsulated, slow-growing benign neuroepithelial tumors that occur primarily in regions of the medullary conus and filum terminale, and removal without breaking the capsule is curative[2,3]. The average age at presentation is approximately 36 years, with a significant male prediction[1]. They differ morphologically and biologically from other ependymomas and often require immunohistochemical analysis to distinguish them from phenotypically similar tumors[4]. Despite an overall favorable prognosis and classification as a grade I tumor, MPEs have been associated with distant metastases, subarachnoid disseminations and local late recurrences[5-8].

In the 2016 WHO classification of central nervous system tumors, ependymal tumors are classified into the following five subtypes: MPE and subependymoma, and MPE (grade I), classic ependymoma (grade II), RELA fusion protein positive ependymoma (grade II / III) and anaplastic ependymoma (grade III)[1]. MPEs account for 9%-13% of ependymal tumors and around 83% of ependymomas are found in the area of the filum terminale[2]. MPEs are usually benign, slow growing neuroepithelial tumors that occur predominantly as intradural neoplasms in the region of the medullary conus, cauda equine, and filum terminale, although rare occurrences have been reported in the neck, thoracic spinal cord, lateral ventricles, and cerebral parenchyma[3-6,9]. MPEs are usually encapsulated and removal without damaging the capsule is curative[2,3]. Distant metastases from MEPs in the brain parenchyma and other organs have also been reported[10-20]. They differ morphologically and biologically from other ependymomas and immunohistochemical study is often required for differential diagnosis from chordomas or chondrosarcomas that morphologically resemble ependymomas[6]. The mean age at manifestation is around 36 years, with a male predominance[1]. Anaplastic features in glial tumors including ependymomas include frequent mitotic figures, hypercellularity, necrosis, vascular proliferation, and pleomorphologic cytoplasm and nuclei[21]. However, classification and grading of ependymomas with anaplastic features are historically controversial. Hence, their diagnosis is difficult and subjective. MPEs with anaplastic features are usually locally invasive. They frequently tend to disseminate to other areas of the brain and spinal cord *via* cerebrospinal fluid (CSF), and more frequently recur with a shorter survival[1,21]. Grade II gliomas often transform into more malignant types[22]. However, grade I gliomas rarely transform into more malignant types[23], and MPEs have only shown malignant transformation in 4 cases[24]. MPEs with anaplastic features are extremely rare in the literature (20 cases)[25-29] and recurrent MPEs have

only shown malignant transformation in 5 cases[29]. We report the case of a 46-year-old woman with MPE with anaplastic features and local ultra-late recurrence. Clinical and histopathological findings are described and the malignant transformation of the MPE is discussed.

CASE PRESENTATION

Chief complaints

Lumbar to sacral pain and weak legs for 6 mo.

History of present illness

The patient (a 46-year-old woman) had lumbar to sacral pain and leg weakness for 6 mo and attended the Atami Hospital of the International University of Health and Welfare.

History of past illness

The patient underwent a subtotal resection for a myxopapillary filum ependymoma 30 years ago by the same surgeon.

Personal and family history

No other relevant personal or family history.

Physical examination

The neurological examination showed bilateral muscle weakness of the gastrocnemius, anterior tibia and urethral sphincter as well as sensory disturbances in areas of L4, L5 and S1.

Laboratory examinations

Laboratory examinations showed normal levels of all parameters tested.

Imaging examinations

Magnetic resonance imaging (MRI) (Figure 1) and computed tomography (CT) imaging (Figure 2) studies showed a mass that occupied most of the spinal canal from L2 to S1 and extended into the adjacent subcutaneous region.

FINAL DIAGNOSIS

Examination of the tumor with hematoxylin and eosin staining showed neoplastic cells with round nuclei and clear cytoplasm in the background of the fibrillar stroma. These neoplastic cells formed two transition structures: A typical MPE area and a high quality area with anaplastic features. The low-grade area of the tumor had the following appearance: Typical MPE area with a somewhat poor and pointed arrangement with Alcian blue-positive myxoid matrix. The MIB-1 index in this area was 5.1%. On the other hand, the high-grade anaplastic areas of the tumor showed hypercellularity, a rapid mitotic rate, vascular proliferation, and connective tissue proliferation. Pleomorphic cells and atypical mitotic figures were occasionally seen. The MIB-1 index was 12.3%. The immunohistochemical study showed immunoreactivity for vimentin, glial fibrillary acidic protein (GFAP) and S100, but no immunoreactivity for epithelial membrane antigen and chromogranin A (Figure 3). The morphological pattern and immunohistochemical profile were consistent with an MPE with anaplastic features[29]. The combination of areas of typical MPE-appearing tumor interspersed with areas of ependymoma with anaplastic features was consistent with the diagnosis of MPE with anaplastic features. The final diagnosis was MPE with anaplastic features (Figure 4).

TREATMENT

Prior to surgical treatment, written informed consent was obtained from the patient. After placing the patient in the prone position, a midline incision was made at 15 cm from L2 to S2. After exposing the rostral end of the previous laminectomy at L2, the

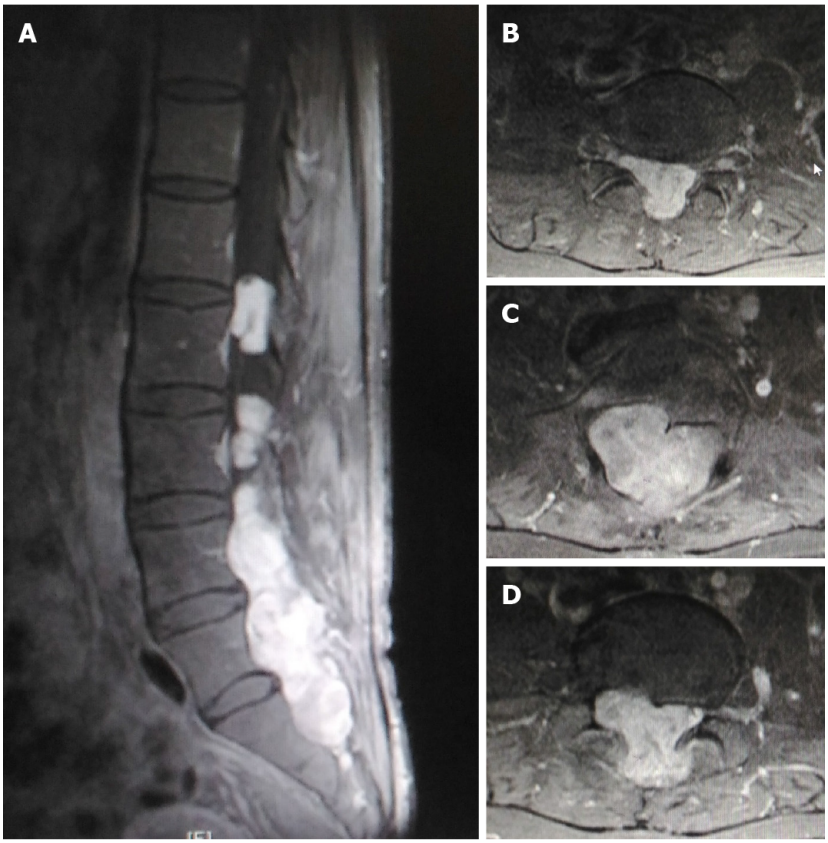

Figure 1 Gadolinium-enhanced T1 weighted magnetic resonance imaging at ultra-late recurrence of a myxopapillary ependymoma. A: Sagittal magnetic resonance imaging (MRI) demonstrated an enhanced mass localized at L3-S1 in the intraspinal canal. A part of the mass extended into the spine axis and dorsal extraspinal tissues; B-D: Axial MRI demonstrated a slightly enhanced mass from intracanal to extraspinal regions.

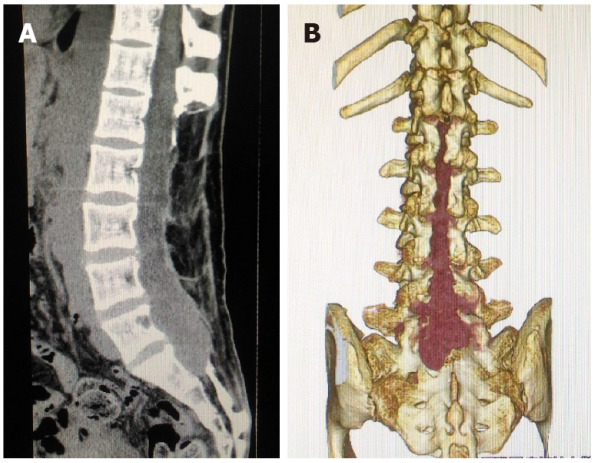

Figure 2 Computed tomography at ultra-late recurrence of a myxopapillary ependymoma. A: A plain sagittal image demonstrated the previous laminectomy area (L1-S1); B: Three-dimensional image demonstrated a recurrent tumor (dark red) in the previous laminectomy area (L1-S1).

previous laminectomy area up to S2 was exposed. In addition, the lamina sacralis was partially drilled. The dura mater was adhered to the granulated soft tissue and opened, but no CSF was found. The encapsulated tumor was observed (Figure 3). The tumor was dark red mixed with gray and appeared to be highly fibrous and hemorrhagic. The filum terminale was compressed by the tumor at the L2 level. Part of the filum penetrated the tumor and was scarified by fibrous restriction due to the difficult dissection. The tumor was debulked with a Cavitron ultrasonic surgical aspirator (Integra Life Science, Dublin, Ireland) and a subtotal resection was performed. Postoperatively, the patient was well without any new neurological deficits.

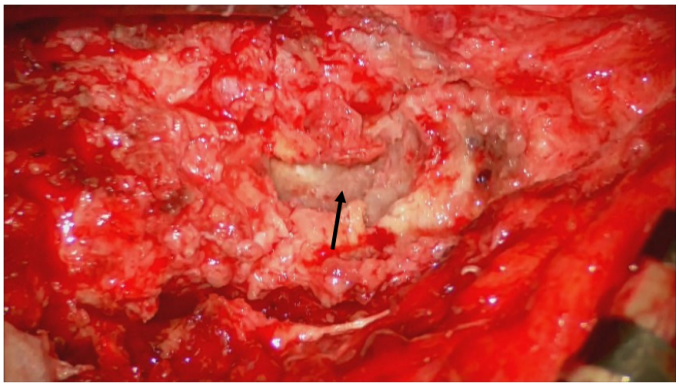

Figure 3 Intraoperative photograph showing an encapsulated tumor (arrow) surrounded by granulated tissues. Right side: Caudal; Left side: Rostral.

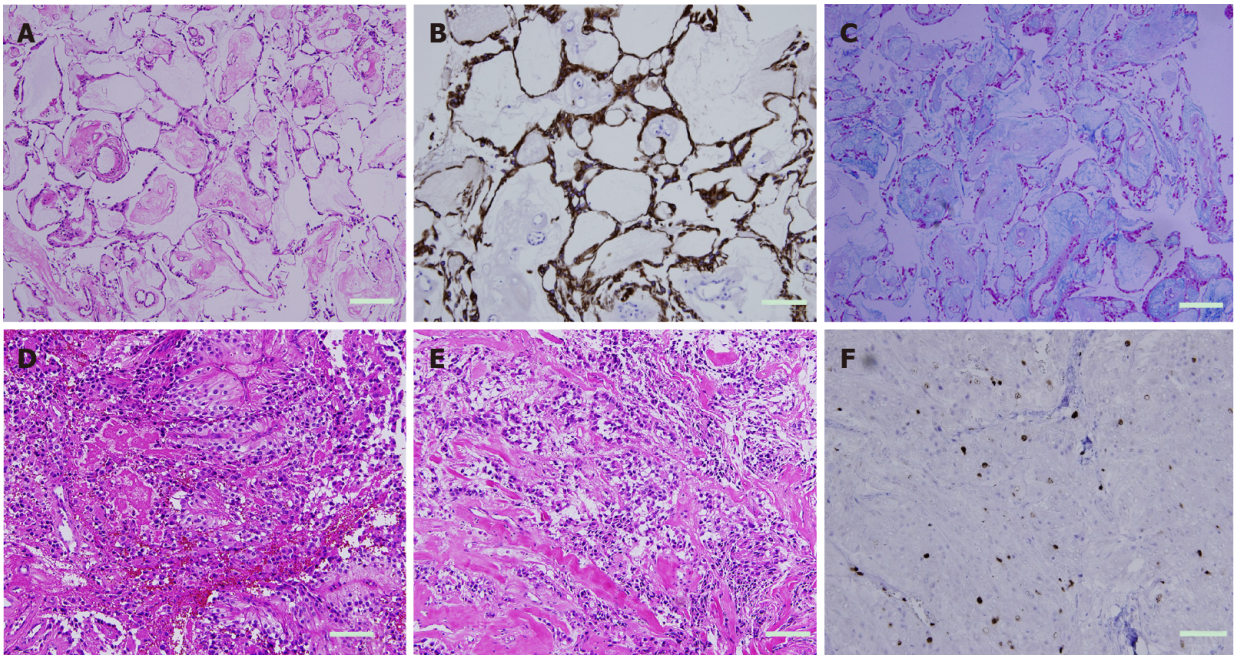

Figure 4 Microscopic appearance of the tumor. Magnification: 200 ×; scale bar: 50 μm. A: Microphotography with hematoxylin and eosin (HE) stain showed the appearance of a typical myxopapillary ependymoma including much mucoid; B: Immunohistochemical microphotography with anti-glial fibrillary acidic protein (GFAP) antibody showed distinct expression of GFAP; C: Microphotography with Alcian blue stain showed much Alcian blue positive mucoid; D and E: Microphotography with HE stain showed anaplastic features such as hypercellularity, rapid mitotic rate, vascular proliferation, and connective tissue proliferation; F: Immunohistochemical microphotography showed a high MIB-1 labeling index (12.3%) in the area with anaplastic features.

OUTCOME AND FOLLOW-UP

Postoperatively, the patient showed no new neurological deficits; and bladder and bowel functions were intact. She presented unchanged motor strength in the lower extremities. She had local radiation of the residual tumor and rehabilitation. She was examined again and showed no deterioration.

DISCUSSION

Pathological and genetic anaplastic MPE

According to a recent report[24], anaplasia of MPE was defined on the basis of histopathological findings that are similar to the criteria currently used to define anaplasia in classical ependymomas, that is, they have at least two of the following features: Mitosis per 10 high power field (HPF), MIB-1 labeling index > 10%, microvascular proliferation and spontaneous necrosis. In the present case, the MIB-1

index of 12.3% corresponds to previous reports. In addition, endothelial proliferation was found in the present case. These pathological findings are compatible with anaplastic MPE. The immunohistochemical description of MPE has been reported, which, in agreement with the present case, consists of a positivity for GFAP and vimentin[16,30,31]. In the present case, interestingly, the histopathological features showed anaplastic features mixed with those of three different components of low-grade ependymoma including MPE. This finding could suggest that an original MPE cell has the potential to become different types of ependymomas that are molecularly different[32]. Recent genetic analyses have shown that MPE is characterized by genome-wide polyploidy, often between several chromosomes[33]. MPE shows specific losses of chr16 and chr12 and increases of chr4, chr9 and chr18, while the classical grade II ependymoma shows a specific loss of chr16 and an increase of chr12 [34]. MPE differs molecularly, transcriptionally and histologically from classical 2nd degree ependymoma. Gene expression profiling also showed that MPEs have a Warburg phenotype[33] and increased gene expression of HOXB13 compared to non-MPEs[34]. The specific familial, epigenetic, or environmental cause that predisposes to malignant transformation of MPE has not been identified. In contrast to grade II gliomas, which have a high progression to high-grade gliomas, grade I gliomas such as pilocytic astrocytoma, ganglioglioma, and MPE rarely undergo malignant transformation with a maximum incidence of 10%[22,23]. Malignant transformation occurred spontaneously or after radiation therapy in these tumors. The specific familial, epigenetic, or environmental cause that predisposes to malignant transformation of the MPE has not been identified.

Clinical features of anaplastic MPE

Similar to previous reports, the present case showed a large mass occupying the spinal canal. In spite of an overall favorable prognosis and classification as a grade I tumor, MPEs have been associated with distant metastases, subarachnoid disseminations, and local late recurrences in almost half of all patients, regardless of adequate resection[3,4,6,7,35-40]. In 20 reported cases of anaplastic MPE, including this case, the age of the patients ranged from 0.9 to 57 years, with a mean of 24.7 years. The majority of patients with anaplastic MPE were under 20 years old, while in a study of 183 patients with classic MPE the mean age at diagnosis was 35.5 ± 15.8 years. CSF dissemination and involvement of adjacent tissue were observed in 50% and 50% of anaplastic MPEs, while distant metastases to the spinal cord and brain were observed in 9.3% and 6% of anaplastic MPEs, respectively[6]. Other studies on classical MPEs have reported higher rates of CSF dissemination of 35% to 57%[7,41], particularly in pediatric cases of MPE and including pediatric dissemination at first presentation in 14%-58% of pediatric cases[8,41]. In the present case, aggressive clinical features such as soft tissue invasion were identified, while distant metastases were not observed. Therefore, many of these patients, particularly those with aggressive clinical features, can undergo radiation therapy. Frequent surveillance scans of patients with MPE are recommended for early detection of recurrent disease with anaplastic features. The 5-year survival rate of patients with non-MPE anaplastic ependymoma has been reported to be less than 20%. The classification of ependymal tumors is currently difficult and according to the current WHO guidelines of questionable clinical benefit[9].

The histopathological criteria for anaplastic ependymoma are as follows: Mitoses (> 4/10 per HPF), hypercellularity, endothelial proliferation, and necrosis[42]. In addition, it has been suggested that anaplastic ependymoma could be defined by the presence of two of these parameters[42]. Large retrospective series of MPE have been conducted, including a large multi-institutional series with 183 patients[6] who had a 10-year overall survival (OS) of 92.4% and a 5- and 10-year progression-free survival (PFS) of 69.5% and 61.2%, respectively. Local MPE relapse occurred in 84% of patients and leptomeningeal spread was observed in 9.3% of patients.

A strong correlation was found between surgical capsule injury and recurrence[43]. A 10-year OS of over 90% was recently confirmed in an epidemiology, surveillance, and outcome analysis of 773 MPE patients[44]. Presacral MPE showed a worse prognosis than MPE in the filum terminale/cauda equina.

Management of anaplastic MPE

According to the 2017 EANO guideline for ependymal tumors, with the exception of gross-total removal (GTR), no factors have been defined that influence the prognosis of spinal cord ependymomas other than MPE[45]. Advances in microsurgical techniques have enabled *en bloc* GTR, which is the standard treatment for spinal cord ependymoma. GTR mostly resulted in good functional outcomes, and a good functional result was related to small tumor size and little neurological deficit at

surgery. Therefore, surgery at an early stage should be considered[46,47]. If GTR cannot be performed due to infiltration of the spinal cord or nerve roots, postoperative local radiation therapy is often used. Multivariate analysis showed that the tumor grade and the extent of resection were independent prognostic factors for OS and PFS, and that radiation therapy extended PFS in patients undergoing subtotal removal (STR). Studies suggest that doses > 50 Gy lead to either better or equivalent results[48,51]. With respect to conventional chemotherapy, it is reported that continuous oral etoposide for recurrent intramedullary ependymomas is well tolerated[53]. Bevacizumab may be of clinical benefit in some patients[52]. Large retrospective series of MPE suggested that the extent of resection was an important independent factor in forecasting local control, while younger age (< 36 years) was a negative prognostic factor. On the other hand, the irregular shape surrounding nerve roots and the formation of a myxoid matrix are related to the risk of postoperative neurological disability[43]. In the treatment of MPE, it has been shown that postoperative radiation therapy with high doses (≥ 50 Gy), compared to patients treated with only one procedure, leads to better local control and longer PFS without significant late toxicity [51,52]. In a small series of adult patients with spinal MPE, it was shown that patients treated with GTR followed by adjuvant radiation therapy had better local control than patients treated with GTR alone[3]. Although patients often have a disseminated tumor and/or develop recurrent or progressive disease after treatment[54], OS is estimated to be 97% and 95% after 5 and 10 years, respectively[55]. A recent series from the Johns Hopkins Hospital[56] showed a significant reduction in local failure in patients receiving radiation therapy after STR or GTR. A smaller series[57] also confirmed good local control with surgery and radiation therapy compared to GTR alone. In summary, according to the 2017 EANO guideline for ependymal tumors[45], the following key recommendations for the treatment of WHO grade I and anaplastic (WHO grades II and III) MPEs are proposed: Total resection is the goal of MPE-surgery (II B). MRI after surgery should be performed to assess the extent of the resection (N/A). Since all patients with newly diagnosed ependymoma are at risk of CSF dissemination, disease staging, including craniospinal MRI and CSF cytology, is recommended after surgery (N/A). A watch-and-wait strategy is recommended for WHO grade II ependymomas after total resection (IIIC). In the case of anaplastic (WHO grade II and III) MPE, postoperative radiation therapy with doses of 45-54 Gy is recommended, irrespective of the extent of the resection (IIIC). Following the incomplete resection of an MPE of WHO grade I, postoperative local radiation therapy with a dose of 50 Gy is recommended (IIB). In the event of relapse, reoperation, re-radiation, and chemotherapy should be considered (IIIC). As the risk of later relapse exists, patients should be followed up with an enhanced MRI over a long period (N/A).

Review of anaplastic MPE

Anaplastic MPE is an extremely rare event and 19 cases have been reported in the literature[24-29]. In 20 reported cases of anaplastic MPE, including this case, the patients ranged in age from 0.9 years to 57 years, with a mean of 24.7 years. The majority of patients with anaplastic MPE were under 20 years old, while in a study of 183 patients with classic MPE the mean age at diagnosis was 35.5 ± 15.8 years. Of the previously reported MPEs with anaplastic features, anaplasia was present in only 5 cases with only one recurrence. In addition, the present case is the most recent relapse in the literature. Similar to previous reports, the present case showed a large mass occupying the spinal canal, and aggressive clinical features such as soft tissue invasion were identified, while distant metastases and CSF dissemination were not observed (Table 1). Despite being histological grade 1 tumors, typical MPEs are often associated with distant metastases, CSF disseminations and local late recurrences. Therefore, patients with a typical MPE can be irradiated after surgery, and it is recommended that patients with MPE be monitored regularly to detect distant metastases or local recurrences[1,2]. In the present case, the patient was not irradiated after the previous operation 30 years ago due to the lack of histological anaplasia. If the patient had been irradiated after the previous operation, recurrence could have been avoided. A 5-year survival rate of less than 20% has been reported for anaplastic ependymoma without MPE. The histopathological parameters of anaplastic ependymoma include > 4 mitoses per 10 HPF, endothelial proliferation, hypercellularity, and necrosis, and the presence of two of these parameters define the diagnosis of anaplastic ependymoma[42]. However, the classification of ependymomas with pathologically anaplastic features remains controversial. Hence, diagnosing these tumors is difficult and subjective at times. Anaplastic ependymomas often recur and survival time is reduced[2]. In addition, the tumors often spread to other regions of the central nervous system

Table 1 Summary of the clinicopathologic features of myxopapillary ependymomas with anaplasia

Ref.	Age (yr) at MPE with anaplasia (age at typical MPE)	Sex	Location of MPE with anaplasia	Adjacent tissues involved	CSF diss	MIB-1 Index	MVP	Treatment	
								Initial	Recurrence
Awaya *et al*[25], 2003	15	M	Th12-L2	No	No	10%	Yes	GTR	No
Beschorner *et al* [26], 2007	3	M	Subcutaneous sacrococcyx	Yes	No	40%	Yes	GTR	No
Vega-Orozco *et al* [27], 2011	38 (22)	M	Inguinal node metastasis	Yes	Yes	NA	Yes	STR, RT	RT
Chakraborti *et al* [28], 2012	0.9	F	Subcutaneous sacrococcyx	Yes	No	70%	Yes	GTR, CT	No
Huynh *et al*[29], 2018	24	F	L2-3	Yes	Yes	8%-38%	Yes	GTR	GTR
Lee *et al*[24], 2019	6	F	L4-S1	No	No	20%	Yes	GTR, RT	No
Lee *et al*[24], 2019	7	F	T12-L3	No	No	11%	Yes	STR, RT	No
Lee *et al*[24], 2019	10	M	L1-2	Yes	No	34%	Yes	GTR, RT	No
Lee *et al*[24], 2019	10	M	S1-2	No	No	15%	Yes	GTR, RT	No
Lee *et al*[24], 2019	11	M	L4-S3	No	No	14%	Yes	GTR	No
Lee *et al*[24], 2019	12	M	Lumbo-sacral	Yes	Yes	10%	Yes	GTR	GTR, RT
Lee *et al*[24], 2019	13	M	L1-2	No	Yes	8%	Yes	STR, RT	No
Lee *et al*[24], 2019	20 (16)	F	L3-S1	No	Yes	10%	No	GTR	RT
Lee *et al*[24], 2019	32 (31)	M	S1	No	Yes	10%	Yes	STR, CT, RT	RT
Lee *et al*[24], 2019	40	F	4th ventricle	No	No	20%	Yes	STR, RT	No
Lee *et al*[24], 2019	45 (31)	F	Extraspinal pelvic	Yes	Yes	40%	Yes	STR, RT	GTR, CT
Lee *et al*[24], 2019	50	M	L5-S3	Yes	Yes	10%	Yes	GTR, RT	No
Lee *et al*[24], 2019	55	F	L1-2	No	Yes	20%	Yes	GTR, RT	No
Lee *et al*[24], 2019	57 (45)	M	T8-L5	Yes	Yes	26%	Yes	STR, RT	GTR, RT
Kanno *et al*, 2021	46 (16)	F	L4-S1	Yes	No	12%	Yes	STR	STR, RT

CSF diss: Cerebrospinal fluid dissemination; MVP: Microvascular proliferation; F: Female; M: Male; GTR: Gross total resection; STR: Subtotal resection; Chem: Chemotherapy; RT: Radiation therapy; CT: Chemotherapy; NA: Not available.

through CSF and are usually locally invasive. Recently, it was suggested that the diagnostic criteria for anaplastic MPE should be based on histopathological findings that include at least two of the following parameters: > 5 mitoses per 10 HPF, > 10% MIB-1 labeling index, spontaneous necrosis, and, microvascular proliferation. In the present case, the MIB-1 index of 12.3% is compatible with previous reports. In addition, endothelial proliferation was found in the present case. These pathological findings were consistent with anaplastic MPE[32]. Malignant transformation of MPE can occur in both pediatric and adult patients and is associated with either relapse, local invasion, CSF spread, or metastatic disease. These anaplastic clinical features indicate a more aggressive biological potential than classic MPE. Therefore, regular close observation is recommended. Further studies are needed to refine the proposed assessment criteria for anaplastic MPE and to identify the genetic biomarkers of tumorigenesis and malignant transformation of MPE[33].

CONCLUSION

MPE has the potential for malignant transformation after a long period of time despite

being a pathological grade I tumor. Therefore, the possibility of malignant transformation of MPE should be considered, and patients with MPE should be carefully managed and followed up over a long period of time.

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CASE REPORT

Foreign body granulomas mimic peritoneal dissemination caused by incarcerated femoral hernia perforation: A case report

Shinpei Ogino, Tatsuya Matsumoto, Yosuke Kamada, Noriaki Koizumi, Hiroshi Fujiki, Kenji Nakamura, Takeshi Yamano, Chouhei Sakakura

ORCID number: Shinpei Ogino 0000-0001-9867-7623; Tatsuya Matsumoto 0000-0002-1191-1729; Yosuke Kamada 0000-0002-9592-6900; Noriaki Koizumi 0000-0003-4455-5588; Hiroshi Fujiki 0000-0001-7072-4387; Kenji Nakamura 0000-0002-5301-7557; Takeshi Yamano 0000-0003-3195-4870; Chouhei Sakakura 0000-0003-4404-6740.

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Shinpei Ogino, Tatsuya Matsumoto, Yosuke Kamada, Noriaki Koizumi, Hiroshi Fujiki, Kenji Nakamura, Chouhei Sakakura, Department of Surgery, Akashi City Hospital, Akashi 673-8501, Hyogo, Japan

Takeshi Yamano, Department of Pathology, Akashi City Hospital, Akashi 673-8501, Hyogo, Japan

Corresponding author: Shinpei Ogino, MD, PhD, Doctor, Surgeon, Department of Surgery, Akashi City Hospital, 1-33 Takasho-machi, Akashi 673-8501, Hyogo, Japan.
s-ogino@koto.kpu-m.ac.jp

Abstract

BACKGROUND

Foreign body granuloma (FBG) is a well-known type of granulomatous formation, and intraabdominal FBG (IFBG) is primarily caused by surgical residues. Multifocal IFBGs caused by gastrointestinal perforation is an extremely rare and interesting clinicopathological condition that resembles peritoneal dissemination. Here, we present a case of IFBGs mimicking peritoneal dissemination caused by bowel perforation and describe the value of intraoperative pathological examinations for rapid IFBG diagnosis.

CASE SUMMARY

An 86-year-old woman with an incarcerated femoral hernia was admitted to the hospital and underwent operation. During the operation, the incarcerated ileum was perforated during repair due to hemorrhage necrosis, and a small volume of enteric fluid leaked from the perforation. The incarcerated ileum was resected, and the femoral hernia was repaired without mesh. Four months later, a second operation was performed for an umbilical incisional hernia. During the second operation, multiple small, white nodules were observed throughout the abdominal cavity, resembling peritoneal dissemination. The results of peritoneal washing cytology in Douglas' pouch and the examination of frozen nodule sections were compatible with IFBG diagnosis, and incisional hernia repair was performed.

CONCLUSION

IFBGs can mimic malignancy. Intraoperative pathological examinations and operation history are valuable for the rapid diagnosis to avoid excessive

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treatments.

Key Words: Foreign body granuloma; Peritoneal dissemination; Peritoneal seeding; Perforation; Operation; Case report

Core Tip: Multifocal intraabdominal foreign body granulomas (IFBGs) caused by gastrointestinal perforation are clinically rare and mimic peritoneal dissemination. An 86-year-old woman underwent an operation to treat an incarcerated femoral hernia; however, the incarcerated ileum was perforated due to hemorrhage necrosis, resulting in incarcerated ileum resection. After 4 mo, a second laparoscopic operation was conducted for an umbilical incisional hernia; however, small, white nodules were identified throughout the entire abdominal cavity, mimicking peritoneal dissemination. Using intraoperative cytology and frozen sections, the nodules were diagnosed as IFBGs. IFBGs sometimes mimic peritoneal dissemination, and intraoperative pathological examinations are effective for rapid diagnosis.

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INTRODUCTION

A foreign body granuloma (FBG) is a tissue reaction caused by retained foreign bodies, and intraabdominal FBGs (IFBGs) are typically caused by materials used in a previous operation, such as surgical sutures, gauze, and sponges[1-3]. However, in rare cases, bowel perforation, bile or gallstone spillage, and foreign bodies unrelated to operations, such as fish bones, can result in IFBGs[4-6]. Furthermore, IFBGs sometimes occur multifocally and can closely resemble peritoneal dissemination, leading to misdiagnosis[5,7]. Here, we present a case of IFBGs mimicking peritoneal dissemination 4 mo after an operation to treat an incarcerated and perforated femoral hernia.

CASE PRESENTATION

Chief complaints

An 86-year-old woman presented to our hospital with anorexia and vomiting for 3 d.

History of present illness

Her medical history was unremarkable.

History of past illness

Past appendectomy.

Personal and family history

No special in personal and family history.

Physical examination

Severe pain with redness and a palpable bulge was observed in the right inguinal area.

Laboratory examinations

The laboratory workup showed a white blood cell count of 17.1 × 10^9/L and C-reactive protein levels at 6.13 mg/dL.

Imaging examinations

Abdominal computed tomography (CT) showed a right incarcerated femoral hernia with small bowel obstruction.

FINAL DIAGNOSIS

FBG (see TREATMENT section).

TREATMENT

The laparoscopic repair of an incarcerated femoral hernia was attempted; however, the incarcerated ileum was perforated during the repair because it had become necrotic. The necrotic ileum was resected, and the right femoral hernia was repaired using the McVay procedure (Figure 1). Although postoperative intensive care for septic shock and disseminated intravascular coagulation was necessary, the patient was discharged one month after the operation. The patient revisited our hospital 3 mo later due to an umbilical incisional hernia, and laparoscopic incisional hernia repair was performed. During the operation, the hernia orifice, 11 cm in diameter, was identified at the umbilical wound, and multiple small white nodules expanded throughout the entire abdominal cavity (Figure 2). We suspected the peritoneal dissemination of some tumors. Because no observable tumor could be located in the abdominal cavity, peritoneal wash cytology of Douglas's pouch was performed, and frozen sections of the nodules were examined. The cytology was negative for malignancy (Figure 3), and the frozen sections showed a multinucleated giant cell containing a foreign body, surrounded by inflammatory cells, fibrosis, and granulomatous formations (Figure 4), which was compatible with an FBG reaction. Therefore, laparoscopic intraperitoneal onlay mesh repair with hernia orifice closure (IPOM-plus) was performed.

OUTCOME AND FOLLOW-UP

The postoperative clinical course was uneventful, and no malignant findings were observed on chest-to-abdominal enhanced CT or gastrointestinal and colon endoscopy. No malignancy was detected, and no recurrence of hernia was observed during 7 mo of follow-up.

DISCUSSION

FBG is a chronic immune reaction induced by the presence of a foreign body. IFBG is typically caused by retained surgical residues, bowel perforation, bile spillage, gallstones, or fish bones[1,2,4-6,8]. Suture granulomas are the most common type associated with surgical residuals, although gauze and sponges have also been reported[1-3]. IFBGs occasionally resemble tumorous nodules and sometimes occur multifocally, which can mimic peritoneal dissemination[2,8]. IFBG is also well-known to be caused by glove powder used in operations. IFBGs associated with lycopodium, talcum, and starch powders from surgical gloves have previously been reported, and these IFBGs can be quite difficult to differentiate from cancerous nodules[7,9,10]. Akita *et al*[5] reported that food starch released from gastrointestinal perforations could cause multiple IFBGs, mimicking peritoneal dissemination; they reported a case in which tenderness and guarding over the entire abdomen was observed due to a gastric cancer perforation, which was treated surgically. Two months later, many small, white granulomas mimicking peritoneal dissemination were observed, particularly in the upper abdominal cavity, which were diagnosed as IFBGs based on frozen sections during the second operation. In the pathological findings, saburra was observed at the center of the granuloma.

In the present case, multiple small, white nodules that expanded throughout the entire abdominal cavity were observed during the second operation, which were extremely difficult to differentiate from peritoneal dissemination. A multinucleated giant cell containing a foreign body similar to saburra and surrounded by inflammatory cells and granuloma formation was observed pathologically; thus, these

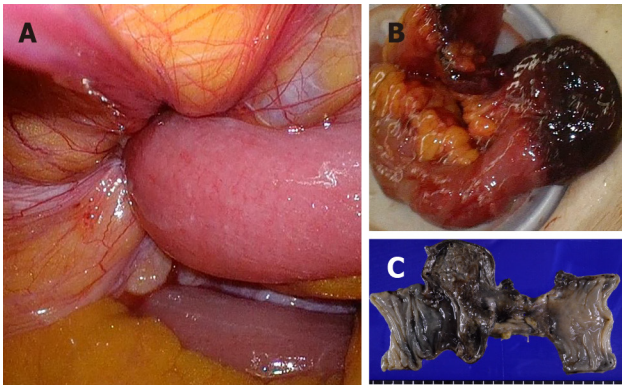

Figure 1 The necrotic ileum was resected, and the right femoral hernia was repaired using the McVay procedure. A: The ileum was incarcerated into the right femoral hernia; B: The incarcerated ileum became necrotic; C: The resected ileum showed hemorrhage necrosis over a 10 cm length.

nodules were diagnosed as IFBGs and were thought to be caused by food starch, similar to the previously reported case[5], particularly as no evidence of malignancy was identified either during or after the operations.

FBG is one type of non-infectious granulomatous reaction, characterized by the presence of a foreign body surrounded by granuloma formations in foreign body giant cells. FBGs have also been associated with granuloma formation due to an excessive immune response to foreign bodies, potentially related to allergic reactions and microbiological factors[11]. Intriguingly, in the present case, the IFBG expanded to the entire abdominal cavity at the time of the second operation, although the amount of enteric fluid that leaked from the perforation was limited to a small range and was localized within the lower abdominal cavity during the first operation. Because the lower abdominal cavity was rinsed after the resection of the incarcerated ileum during the first operation, the remaining food particles released from the small enteric fluid leak should have been minimized and at low concentrations, which suggested that each IFBG was either caused by an extremely minute food starch quantity or represented an allergic response, resulting in the accumulation of microbiological factors. Furthermore, the characteristic histological findings of FBG were very supportive of an IFBG diagnosis, especially during the operation. The misdiagnosis of IFBGs as malignancies can potentially lead to ineffective or unnecessary treatments. A previous case reported IFBGs mimicking peritoneal dissemination 3 mo after laparoscopic cholecystectomy, resulting in the wedge resection of the liver and transverse colon and omentectomy, and IFBGs were later diagnosed pathologically as likely due to bile or gallstone spillage[6]. As reported by Akita *et al*[5], intraoperative cytology and frozen sections are valuable for the rapid diagnosis of IFBGs. In the current case, these quick pathological examinations performed during the operation provided an important and powerful method for differentiating IFBGs from peritoneal dissemination.

The physiologic activation of histiocytes generally occurs within 24-48 h[12]; however, the time required for granulomatous formation resembling nodules remains unclear. In the current case, 4 mo was sufficient for the observed granulomatous formation. The percentage of granulomas observed during operations decreases gradually, from 37% if the previous operation was performed within 6 mo to 18% when the previous operation occurred more than 2 years prior[1]. Granulomas that resemble peritoneal dissemination can form within 2 mo, according to Akita *et al*[5], and this occurred within 4 mo in the current patient. Therefore, the interval between first and second operations also supports the diagnosis of IFBG.

CONCLUSION

In conclusion, multiple IFBGs caused by bowel perforations are associated with a very rare clinicopathological condition and can mimic peritoneal dissemination. A history of past operations and the interval between the current and past operations can be helpful for distinguishing between IFBGs and peritoneal dissemination, and intraoperative cytology and frozen sections are extremely valuable methods for the rapid diagnosis of IFBG, which can prevent misdiagnosis and avoid the use of ineffective or excessive treatments.

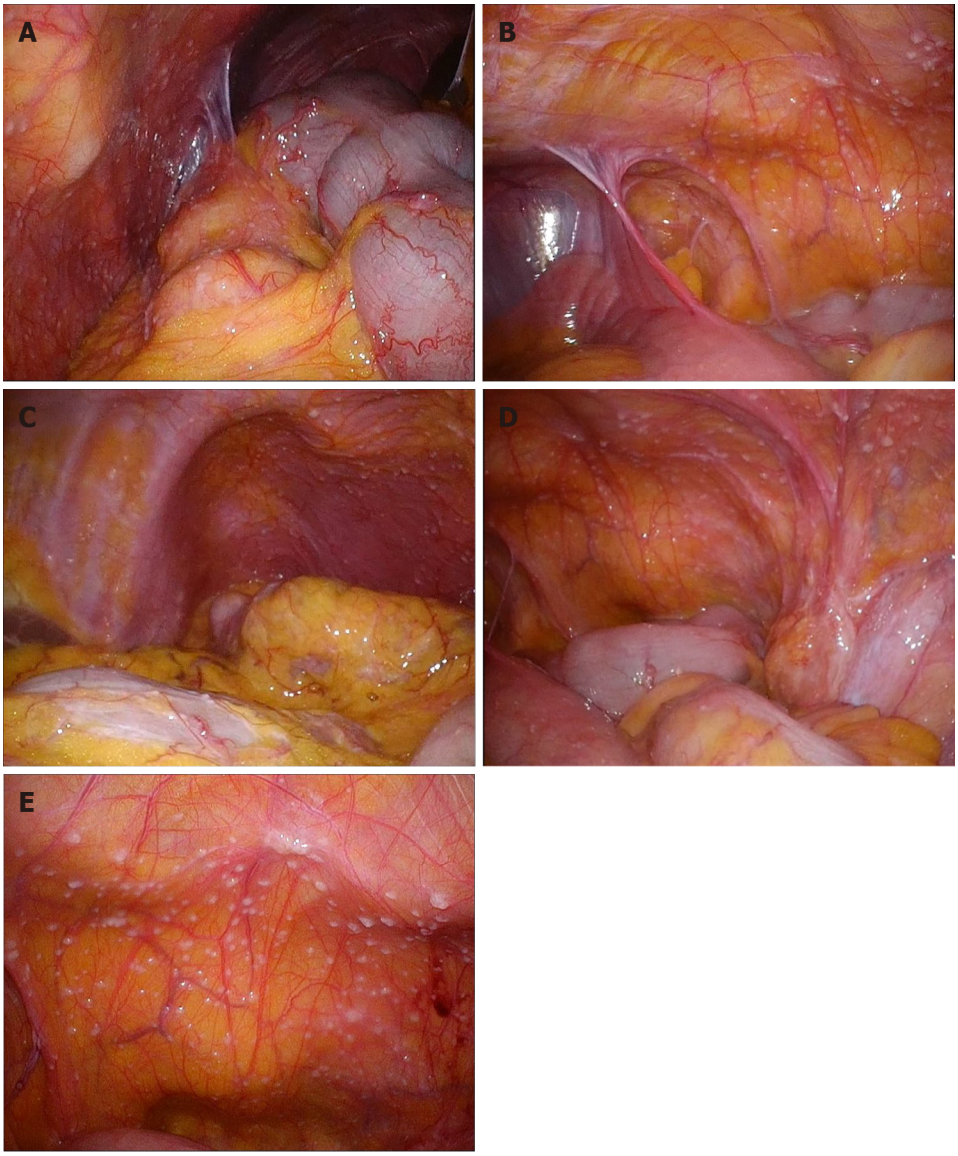

Figure 2 Multiple small white nodules mimicking peritoneal dissemination were observed throughout the entire abdominal cavity during the second operation. A: Right upper abdominal cavity; B: Right lower abdominal cavity; C: Left upper abdominal cavity; D: Left lower abdominal cavity; E: Back side of the bladder.

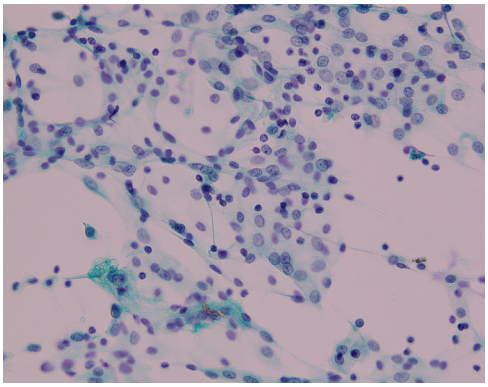

Figure 3 Papanicolaou stain of the peritoneal washing cytology of Douglas' pouch showed only inflammatory cells (× 40).

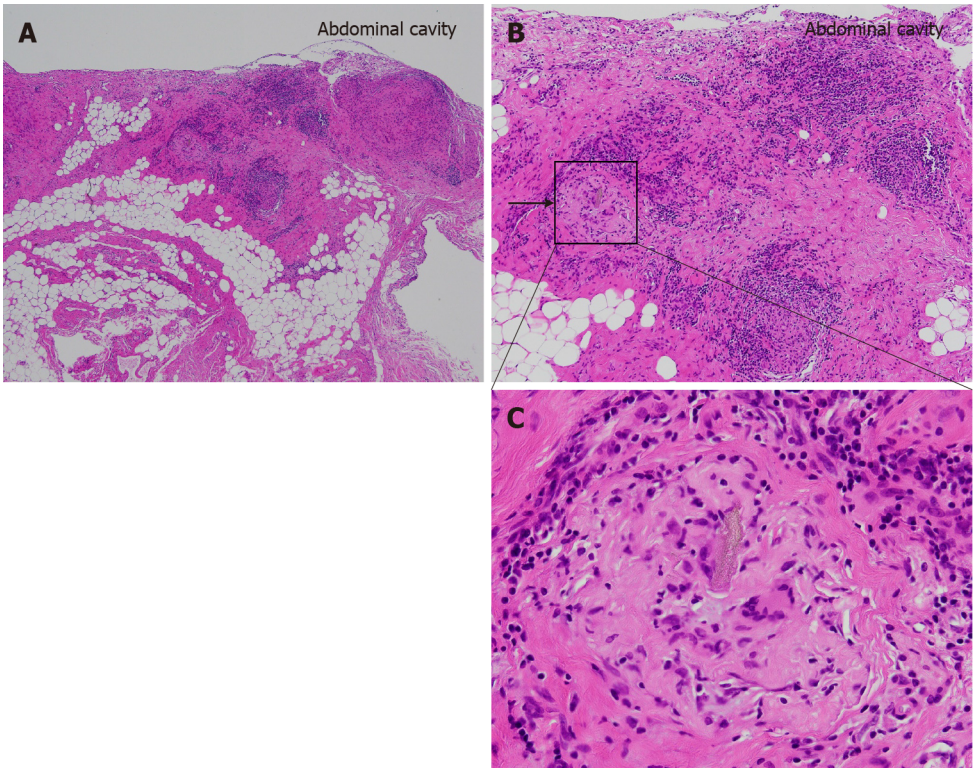

Figure 4 Pathological findings of the small white nodule. Hematoxylin and eosin stain of the nodule. A multinucleated giant cell with a foreign body (arrow) surrounded by monocytes, lymphocytes, and granuloma formations. A: × 40; B: × 100; C: × 200.

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