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Building a collaboration to improve surgical research through EORTC/ ESSO 1409-CLIMB study: A prospective liver metastasis database with an integrated quality assurance program



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ABSTRACT

The challenges of conducting surgical oncology trials have resulted to low quantity and poor quality research [1,2]. Considering the definitive role of surgery to offer cure, immediate response to improve surgical research is needed [3]. The European Organization for Research and Treatment of Cancer (EORTC) and the European Society of Surgical Oncology (ESSO) share the vision to achieve excellent surgical research and care for cancer patients. Building on their complimentary expertise, they embarked on a pilot project to map out challenges and initiate a sustainable collaboration to advance cancer surgery research in Europe. This pilot project is EORTC-ESSO 1409 GITCG/ ESSO-01: A Prospective Colorectal Liver Metastasis Database with an Integrated Quality Assurance Program (CLIMB). This article will describe the challenges, milestones and vision of both organizations in setting up this collaboration.

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Realizing a common vision and complimentary expertise

EORTC and ESSO identified a common vision and mission: the need for better quality surgical trials in Europe that can improve

patient outcomes. The next step was to identify a field where a pilot project can be easy to develop and where the expertise of EORTC and ESSO are also well-established: treatment of metastatic colorectal cancer (mCRC). The last two decades produced research that pushed the boundaries of colorectal liver metastasis (CRLM) management. EORTC 40983 study demonstrated the benefit of peri-

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operative chemotherapy with surgery for upfront resectable CRLM through an 8% improvement in progression free survival (PFS) among patients who received the combined modality compared to surgery alone [4]. Since then, several chemotherapy regimens and targeted agents have been established as effective line of treatments. These improvements allowed surgical techniques to rapidly evolve by allowing conversion of unresectable to resectable mCRC. EORTC Intergroup study 40004 (CLOCC) study was the first randomized controlled study that prospectively investigated the efficacy of radiofrequency ablation (RFA) with chemotherapy for unresectable CRCLM without extra-hepatic metastases [5]. With a significant difference in the over-all survival of patients who underwent combined modality treatment using systemic therapy and RFA (HR = 0.58, 95% CI: 0.38–0.88, $p = 0.01$), the CLOCC study clearly demonstrated a clinical benefit in aggressively treating extensive CRLM through combined chemotherapy and RFA. The limits of resectability and the treatment options for mCRC have also expanded through advancements in imaging and molecular biology [6–8]. The molecular understanding of colorectal cancer (CRC) has especially been rapid with new classification systems based on gene expression data and tumor microenvironment characteristics being utilized side by side with the traditional TNM staging [9,10]. Most importantly, the emphasis on the multidisciplinary approach to advanced CRLM treatment has never been more relevant as it is today. These are reflected on the current European Society of Medical Oncology (ESMO) guidelines for mCRC with more extensive oligometastatic disease involving more sites or lesions, e.g. primary, liver, lung, peritoneum, nodes, bones, brain, ovary and >4 organs. A toolbox of local ablative treatments that may be considered in MDT discussions have been included in the guidelines although the value of a surgical approach remains controversial. In these patients, surgery may contribute to long-term survival but is rarely curative [11]. Local treatment like surgery and ablation are relevant in combination with systemic therapy but must be in the context of a careful MDT discussion and assessment [12].

Considering all these, it is worth investigating how different strategies such as staged hepatectomies, combined ablation and resection, extra-hepatic metastasis surgery in combination with different systemic therapy regimens are utilized in clinical practice

and the treatment outcome of patients with advanced hepatic and extra-hepatic metastases outside of clinical trials. While doing a randomized trial is the best way to prove efficacy of one treatment over the other, a prospective, high quality observational study from real-life clinical setting can be useful in understanding variabilities in multidisciplinary team (MDT) treatment strategies, short-term and long-term patient outcomes and directing the next wave of research [13]. It can be useful to benchmark surgical quality in Europe and bridge the knowledge gap between real-life and clinical trials in mCRC.

The EORTC-ESSO 1409 CLIMB study: a collaboration for surgical quality

CLIMB (NCT02218801) is a prospective cohort study assessing the surgical outcome of patients who underwent treatment for complex mCRC. Patients with borderline resectable, unresectable, recurrent, and those with extra-hepatic metastasis were prospectively included in a central database after being assessed in an MDT and before any surgical treatment. The objectives were to evaluate the surgical outcomes, the impact of the quality assurance program on the trend of complication rates during the study, to establish quality parameters for complex CRLM surgery and to describe the outcome of patients who underwent surgery and those who did not after 2 years of follow up within CLIMB. The primary endpoints were 30 and 90 day surgical morbidity and mortality rate and a proposal for quality indicators in complex liver metastasis surgery (Fig. 1).

A pre-trial credentialing that considered hospital and surgical volume, presence of a regular MDT and experience in participating in clinical research were required from sites. The MDT must have at least a liver surgeon, oncologist, and radiologist. Patient demographics, medical history, imaging, biomarker assessments and systemic treatment data were collected at baseline. Patients who underwent conversion systemic therapy were monitored until they received surgery either combined ablation and resection (CARE), one-stage or two-stage hepatectomies, synchronous surgery for either primary tumor, liver metastasis or extra-hepatic metastasis. Surgical outcomes based on the Modified Clavien-Dindo Grading, and the consensus of the International Study Group of Liver Surgery

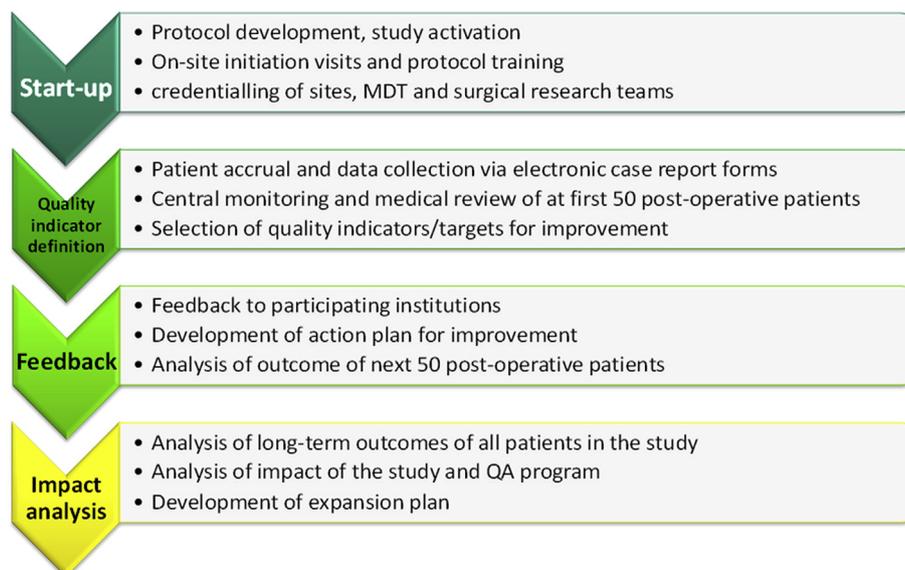


Fig. 1. Study Design of EORTC-1409/ESSO-01 CLIMB study.

(ISGLS) for the definition and grading of post-hepatectomy liver failure and biliary leakage at 30 and 90 postoperative day and long-term outcome up to two years from enrollment were documented [14,15]. Patients who were inoperable due to comorbidities or progressive disease were also followed-up to document survival status until two years from enrollment. The primary analysis will be focused on the immediate surgical outcomes of at least 100 post-operative patients and the secondary analysis will be on survival data of all patients, whether they had surgery or not.

CLIMB opened in 2015 and included nine countries and 14 highly specialized centers for liver surgery across Europe. An abstract of the primary results was presented during American Society of Clinical Oncology Congress in 2018 [16]. Full manuscript is under development and will include description of clinical and molecular profile of post-operative patients, 30 and 90 day morbidity and mortality outcomes, quality indicators related to surgical technique and imaging, variability of systemic therapy regimens among advanced CRLM patients. Each participating site will receive the datasets of their own patients to enable them to benchmark and facilitate their own scientific publications.

This study is an example how observational studies can complement randomized clinical trials in evaluating impact of treatments [17]. Although there are numerous cancer surgery registries all over Europe, CLIMB is a unique program because surgical outcomes of all patients registered in the study are documented prospectively. This aims to avoid reporting or selection bias that commonly occurs in surgical studies. Surgical registries usually require fewer resources compared with trials and have the huge potential to collect long term, prospective outcome and safety data [18]. But the challenge of harmonizing and sharing data as well as maintaining quality and integrity of information during long term follow up must be overcome across different observational studies or registries. Most importantly, CLIMB can serve to generate hypothesis for future randomized surgical studies that can improve quality of surgical treatment or validate innovative technologies. Beyond trials, observational studies and registries like CLIMB are important tools for mapping and understanding variations or practices across countries. This is essential for formulating sensible recommendations for different healthcare systems, creating policy frameworks and developing international collaboration [19].

Implementing quality assurance in surgical research

Any surgical research must be high quality scientifically and methodologically yet feasible [20]. This is first assessed through the independent peer-review process within EORTC and ESSO that requires clear objectives, study endpoints and analysis plan for all its studies. To implement quality assurance (QA) for CLIMB pretrial credentialing, standardization and central monitoring were performed [21]. Credentialing was done through a feasibility survey and site initiation visits to evaluate the research capacity of each site and to observe MDT board discussions. High-volume centers treating at least 100 unresectable or borderline resectable liver metastasis cases a year, with a capability to perform complex surgical procedures and carry out research activities were selected. Standardization was carried out following the EORTC principles of developing one protocol and a central database. For the CLIMB study, the Clavien-Dindo Classification of Surgical Complications was used to document 30 and 90 day complications. At the same time, the consensus of the International Study Group of Liver Surgery (ISGLS) on the definition and grading of post-hepatectomy liver failure and biliary leakage were used to document complications specific to liver surgery. Central monitoring was performed by a surgical research fellow and data managers who conducted independent medical reviews. Protocol compliance, assessment of

resectability, complications and survival status of all registered patients were reviewed.

Essential to the study were the regular and specialized MDT in the eligibility criteria and prospective patient registration to guarantee accurate documentation of surgical complications from all eligible patients, decreasing the risk for retrospective selection of only good cases to report. Variations on the use of systemic therapy, imaging and biomarker assessments for unresectable CRLM were documented. Active engagement with sites was established by a surgical research fellow who conducted training and medical monitoring.

Conducting this international study required the expertise of an academic research organization like EORTC and the dedication of surgical teams involved in the study from the GITCG and ESSO network. The importance of having an experienced and well-structured research infrastructure such to carry out a process of QA and to overcome the hurdles of running a clinical trial cannot be over-emphasized [22,23]. The active participation of surgical investigators during all the stages of protocol development, patient recruitment and QA implementation confirmed the engagement of this network in prospective surgical research. CLIMB also provided opportunities for several young surgeons to be actively involved in the development and coordination of this large-scale study [24]. Such activities stimulate them to be committed to the path of clinical research early in their surgical careers [25,26].

Developing integrated quality assurance: DREAM and SURCARE

CLIMB study was developed in the context of the EORTC-ESSO collaboration. The aim was to set a framework for conducting surgical research and to engage a bigger network of surgeons in prospective research. They hoped to create an impact not only on better methodology of surgical research but most importantly on patient outcomes. Surgical research must no longer be a “comic opera” [27]. EORTC and ESSO have recognized the need to look at pragmatic ways to overcome methodological and feasibility of surgical trials [1,2] to bring surgical innovation and development up to the standards of evidence-based medicine where surgical research makes an essential contribution [3]. This initiative must be sustained to support more cancer-specific quality improvement programs both in the conduct of clinical trials and ultimately in delivery of surgical care.

EORTC and ESSO in collaboration now with the Japan Clinical Oncology Group (JCOG) are taking on the challenge to build a surgical research infrastructure that will actively develop prospective and systematic approaches to achieve high standards of QA in surgical clinical research for Europe and beyond [28]. This is called SURCARE: A Platform for High Quality Standards for Prospective Surgical Research. It aims to establish a framework for surgical quality assurance for clinical trials based on credentialing, standardization and central monitoring (Fig. 2). It will develop more prospective surgical oncology research studies, facilitate training of young surgeons in clinical research methodology, open opportunities for multi-disciplinary and international collaborations (Fig. 3). SURCARE has the potential to create a global impact as it begins to involve new partners from Asia and United States [29].

A new project under SURCARE is EORTC 1527 GITCG-IG: Diffusion-weighted magnetic resonance imaging to assess liver metastasis and improve surgical planning (DREAM). This study (NCT02781935) aims to evaluate the accuracy of using DW-MRI to assess response of lesions after conversion chemotherapy and predict the viability of disappearing liver metastasis. New imaging, pathological and molecular predictive and prognostic biomarkers will be explored among patients with disappearing liver metastasis.

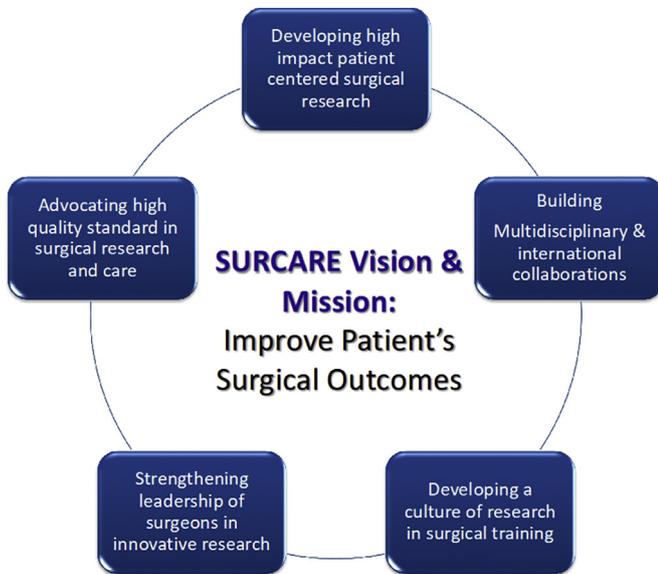


Fig. 2. Vision and Mission of the SURCARE infrastructure for surgical quality assurance in prospective surgical oncology trials.

DREAM translational research will be developed in collaboration with La Ligue Le Contre Cancer (France) and JCOG. This study is open and already accruing patients in Europe, Japan, and United States (Fig. 4).

Conclusion

It is the firm belief of EORTC and ESSO that when surgeons are committed to implement measures of QA in clinical research, this

can translate to an over-all improvement in surgical care and patient outcomes in clinical practice. Institutions can enhance their capability to deliver high quality research and more importantly, better treatment strategies for patients. Quality improvement requires team effort, especially in complex fields of surgery and clinical research. For such initiatives, we need the leadership of surgeons in today's cancer research field [30].

There is a huge potential for surgical oncology to thrive in clinical research. Surgery remains to be the most cost effective option to cure most cancers. Improving the quantity and quality of research in this field can improve patient outcomes, decrease hospital costs and improve quality of life [31]. This is a global challenge that is highly relevant in the ever-changing landscape of cancer research. An evidence-based, integrated, multidisciplinary and pragmatic approach for surgical oncology research is needed. EORTC and ESSO have responded to this challenge by collaborating for EORTC-ESSO 1409: CLIMB study and initiating SURCARE.

Conflicts of interest

None declared.

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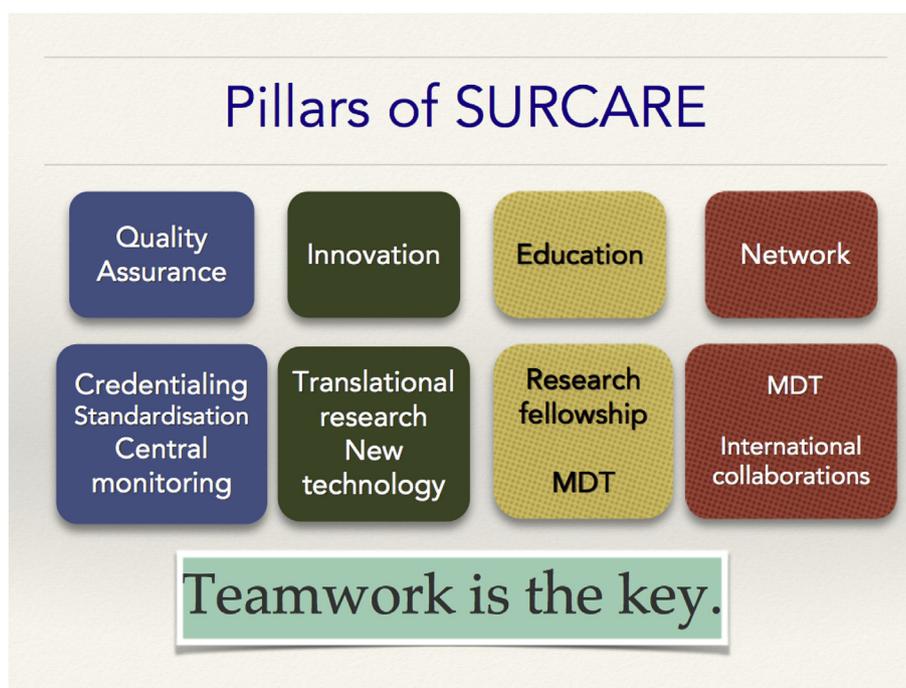


Fig. 3. SURCARE aims to develop a framework that will consistently implement quality assurance in surgical trials, develop innovative studies, integrate the culture of research in surgical training and strengthen multidisciplinary and international collaborations.

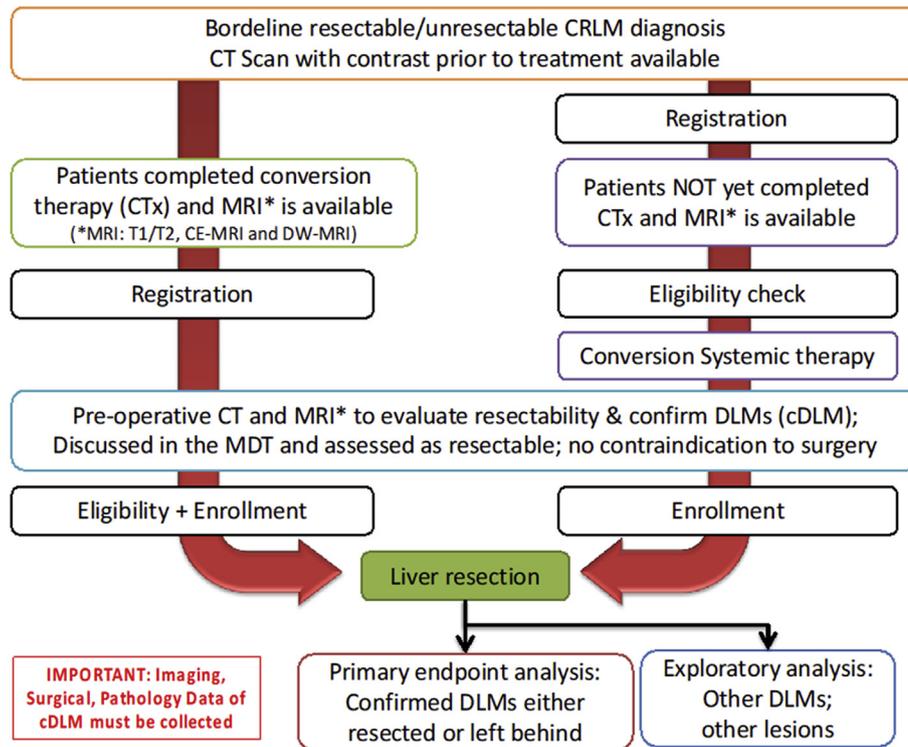


Fig. 4. Study design of EORTC 1527 GITCG-IG/ESSO 02/COG 1609INT: Diffusion-weighted magnetic resonance imaging to assess liver metastasis and improve surgical planning (DREAM).

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ejso.2019.05.028>.

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