

Colorectal anastomotic leakage

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Valorisation addendum

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Valorisation is often defined as the process of value creation from knowledge, by making it applicable and available for economic or societal utilisation, and by translating it in the form of new business, products, services or processes¹.

The aim of this chapter is to take a brief look upon the return of investment society has received from the knowledge gathered during this PhD trajectory. As the work in this thesis largely focuses on experimental animal studies, it is evident that not all results can directly be translated to the clinical setting. Here the translation of our academic findings regarding possibilities for future implementation and economic/societal value will be discussed.

Economical relevance

This thesis focused on the problem of anastomotic leakage, a severe complication after colorectal surgery. The burden to society of colorectal cancer surgery can significantly be reduced by implementation of the knowledge obtained from this project for several reasons. In the Netherlands approximately 10.000 oncological colorectal operations are performed each year². With an incidence in anastomotic leakage of about 15%, this implies 1500 cases. Notably, the incidence of colorectal carcinoma is expected to rise in the coming years due to national screening programs, increasing the frequency of colorectal cancer treatable by surgery and people becoming older.

We estimate that a reduction of 30-40% in anastomotic leakage incidence can be achieved by combining perioperative innovations – some of which have their basis in this thesis -, preventing complications in approximately 500 patients yearly in the Netherlands. With a mortality of 15%, roughly 75 deaths can be prevented each year. Moreover, a decrease in intensive care unit admissions can reduce national healthcare costs dramatically. Additional significant contributions to the cost build-up that can be decreased are prolonged hospitalization, extra radiographic studies during and after admission, more consultation services, more extended use of the operating room, stoma-related complications, re-intervention for ostomy closure, longer nursing care, materials (e.g. antibiotics, ostomy bags)³. It has been estimated that the actual cost per patient increased fivefold in case of serious anastomotic leakage (in patients who did not receive a diverting stoma)⁴⁻⁵.

No attempt has been made in the Netherlands to assess the total cost involved for a single case of colorectal leak. This largely due to the fact that hospitals do not have a scale of charges for individual consultations and services involved. Moreover, the costs of rehabilitation, physiotherapy, prolonged absence from work

of patients and family members (i.e. caregivers), and nursing homes must be considered.

Societal relevance

Not only would a solution to anastomotic leakage be beneficial for the economy, it also has significant advantages for patients who undergo colorectal surgery; as anastomotic leakage is associated with high disability, diminished quality of life and a potential worse oncological outcome^{6,7}. In 2008 a study was published that describes how patients receiving a stoma after colorectal surgery had poorer quality of life, lower body image, poor social activity and also had significantly higher depression and anxiety⁸. All these morbidities can be explained by the fact that these patients face problems including adapting to the new anatomy, managing the stoma and continuing normal activities in their socio-cultural environment. Also, work productivity of these patients decreases significantly due to the level of disability related to multiple abdominal operations or presence of a stoma. Finally, anastomotic leakage itself has an adverse effect on postoperative health-related quality of life when compared to patients that also received a stoma, but did not develop anastomotic leakage postoperatively⁹.

Scientific relevance

As stated in the introduction of this thesis, unraveling the healing process of bowel anastomosis and identifying local molecular and biochemical responses that disturb healing is scientifically relevant in itself. In depth studies into this topic are essential in order to develop effective strategies and agents to combat healing disturbance and to prevent leakage. Knowledge gained on disturbed bowel anastomotic healing can be tested on other intestinal anastomoses, such as pancreatic and esophageal anastomoses, that are known to frequently leak. In this thesis relative new techniques such as mass spectrometry were used in a pilot study and this study will be able to define the value of mass spectrometry in identifying biochemical processes in the gut wall. This may reveal data relevant for other pathophysiological processes, such as cancer development and inflammatory bowel disease and diverticulitis. In addition to new techniques, relatively new animal models were used to investigate leakage prevention.

Use of animal models

The studies performed during this PhD thesis focused on risk factors of anastomotic leakage on the one hand and on potential preventive interventions on the other hand. The latter was extensively studied in the European AnastomoSEAL project¹⁰. The AnastomoSEAL Consortium worked on the development of a new

product to prevent anastomotic leakage. AnastomoSEAL was produced as a biocompatible, resorbable sealant patch that was applied around the site of anastomosis; unfortunately this project did not reach its final goal, since experimental studies showed unexpected adverse events. The use of animal models during the development of new biomaterials for human use is irreplaceable and crucial since the effect of biomaterials in vivo are a complex, dynamic process that sadly cannot be investigated in vitro yet.

In this thesis we have reached consensus on animal models specifically designed for research into bowel anastomoses of the lower gastrointestinal tract (Chapter 2). One of the main conclusions was that rabbit and dog models should be abandoned in this type of research. Furthermore, more standardization can be reached by following the ARRIVE guidelines¹¹. Experienced researchers in the field are convinced that this provides more transparency and more comparability between studies. In addition, experts on intestinal anastomotic leak have held an International Summit (first in 2012, recently in 2016) where the majority of the respondents consider that current experimental animal models of anastomotic leakage are useful and should continue¹². However, they also advocate the use of human anastomotic tissues for more analytical research and promote clinical studies to define and characterize the biological variables that are associated with anastomotic healing versus leakage. The REVEAL study (started Summer 2015 in Maastricht) aims to establish and validate a diagnostic algorithm for the pre-operative prediction of AL using a combination of inflammatory, immune-related and genetic parameters¹³. With the results from the REVEAL study, the recognition of patients who are at risk for AL is expected to increase; subsequently recommendations for patients at risk can be made regarding deviating stomas and possible preventive strategies. Lastly, the REVEAL study aims to develop an algorithm for post-operative diagnosis of AL at an earlier stage, which will positively reflect on short-term survival rates.

Perspective on knowledge utilisation

During the work for this thesis, collaboration with several national and international scientists has been established. These partnerships are crucial to accelerate research, improve transparency between research centres (Rotterdam & Nijmegen) and to direct cross-fertilize, which leads to innovation. Furthermore, it can be considered irrational that in a relative small country as the Netherlands researchers are investigating the same topics, unintentionally delaying work – not to mention wasting time and money – that may lead to the solution of AL; an important health problem that is too extensive to be studied by a single researcher. Therefore, the taskforce anastomotic leakage was re-established (as part of the work group Coloproctology), with the purpose to provide more transparency in

current experimental research, national registration of patients with AL and increase collaboration regarding the conduction of clinical studies¹⁴. This is in line with one of the aims of the Dutch Organization for Scientific Research (NWO): that researchers should no longer work against each other, back to back, but instead work together, side-by-side¹⁵.

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