The management of colorectal liver metastases: Expanding the role of hepatic resection in the age of multimodal therapy

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Abstract
Colorectal cancer (CRC) caused nearly 204,000 deaths in Europe in 2004. Despite recent advances in the treatment of advanced disease, which include the incorporation of two new cytotoxic agents irinotecan and oxaliplatin into first-line regimens, the concept of planned sequential therapy involving three active agents during the course of a patient’s treatment and the integrated use of targeted monoclonal antibodies, the 5-year survival rates for patients with advanced CRC remain unacceptably low. For patients with colorectal liver metastases, liver resection offers the only potential for cure. This review, based on the outcomes of a meeting of European experts (surgeons and medical oncologists), considers the current treatment strategies available to patients with CRC liver metastases, the criteria for the selection of those patients most likely to benefit and suggests where future progress may occur.

Keywords: Colorectal cancer; Hepatic metastases; Surgery; Neoadjuvant therapy; Survival; Disease-free survival

1. Introduction

More than 200,000 deaths from colorectal cancer (CRC) are reported in Europe annually [1] with little variation over the last 20 years in incidence of hepatic metastatic disease as first presentation [2,3]. Despite the introduction of newer
The philosophy (and definition) of hepatic resectability in colorectal liver metastatic disease has changed in the last few years where more extended resections are offered in selected cases somewhat regardless of the number of metastases [8,9], their locoregional invasiveness or even the presence of demonstrable extrahepatic disease [10,11]. This approach has been predicated on several important factors. Firstly, there has been considerable improvement in chemotherapeutic agents and scheduling with a greater utilization of neoadjuvant strategies to downstage previously defined inoperable cases to those of potential resectability [12,13]. This neoadjuvant strategy has been recently extended to include selected cases of first presentations of advanced metastatic disease with the primary colorectal tumour in-situ [14,15]. Secondly, this aggressive approach has been coupled with improvements in preoperative staging [16] which better delineates potentially resectable cases and which have shown enhanced survival when utilized preoperatively [17,18]. This has developed in association with technical advances in hepatic parenchymal transection and vascular isolation methodology as well as improvements in perioperative care [19,20], each of which has resulted in very low rates of perioperative mortality even after extended resection [21]. This level of safety has been maintained in formal hepatectomy independent of patient age [22,23].

Thirdly, given this low perioperative mortality and morbidity even when the estimated volume of tumour-free remnant liver is initially deemed too low for survival (i.e. <20% of parenchymal volume), there has been improved outcome and liver function with the selective use of preoperative portal vein embolization – PVE [24,25] supporting the use of two-stage hepatectomy by enhancing the natural regenerative capacity of the liver [26,27]. The alternative approach of adjunctive locally destructive therapies although widely used, is as yet unvalidated. To date, cryotherapy and radiofrequency ablation (RFA) are the most popular technologies designed to support resectional surgery [7]. Here, it is recognized that inadequate treatment results in a high locoregional recurrence rate using RFA alone or in combination with non-anatomical hepatic wedge resection [28–30].

This issue is complex, however, because there are currently no consistently defined criteria of complete response to neoadjuvant therapy [31,32] along with substantial evidence for histological persistence of malignant disease in the liver in the face of objective radiological evidence of complete response [33,34]. The understanding of this point may explain some data showing improvements in progression-free rather than disease-free survival where less than one-half of patients treated with neoadjuvant therapy are rendered disease-free at 3 years [35]. Early data would suggest no clear evidence for an increased overall morbidity or mortality with hepatic resection following neoadjuvant chemotherapy [36] or chemoimmunotherapy [37], although this is somewhat dependent upon the technique of hepatic parenchymal transection with higher morbidity when surgery is more prolonged and where there is an estimated greater blood loss in the post-chemotherapy liver [21,38,39]. The accurate selection of patients suitable for curative hepatectomy may be scored by performance criteria with the impression that larger metastatic nodules and the presence of extrahepatic spread (particularly when the latter is non-resectable), provide independent negative prognostic variables for post-hepatectomy cancer-specific survival [40].

This article reviews recent developments in the management of hepatic colorectal metastatic disease where surgery is still the ‘gold standard’ for cure [41] defining the ‘new’ role for hepatic resection in the presence of more extensive disease and the impact of multimodality chemoimmunotherapy in metastatic response.

1.1. Modern hepatectomy performance in colorectal liver metastases

The only curative option in patients with hepatic metastases from CRC is margin-free resection where the 5-year overall survival rates in selected cases range from 37 to 58% in recent series [42–45]. The traditional view that only 10–15% of all patients with hepatic metastases are eligible for resection has given way in recent years to an extended concept of the large number of patients potentially suitable for such surgery given the reasonable quality of life and perioperative morbidity of hepatectomy in such cases when compared with best supportive care and chemotherapy [5,46–48]. This concept has in part come about from the development of prognostic indicators and scoring systems for both early perioperative outcome and survival designed to select patients for hepatectomy and trial stratification. In these settings, Nordlinger et al. showed that resection margin positivity, extrahepatic disease, node positivity in the original CRC primary, large and multiple hepatic deposits, high pre-hepatectomy CEA levels and a short disease-free interval between primary resection and the development of hepatic metastases functioned independently as negative outcome variables [49]. This approach has been confirmed by Fong et al. in a retrospective analysis of over 1000 cases [50] and recently validated by Mann et al. [51] as part of their clinical risk score – CRS. These CRS protocols have not yet been shown to be advantageous, however, over more simplified staging systems [52]. Such an approach failed to define specific subgroups based on these criteria, except for confirming that hepatectomy is specifically contraindicated with progression of disease during neoadjuvant therapy [31]. The use of intraoperative ultrasound (IOUS) has extended hepatic resec-
tions in this context for the detection of small non-visible and palpable metastatic deposits [53,54].

This extended approach towards curative hepatectomy results in a different attitude to the utilization of preoperative investigations. It has become more directed towards the discovery of significant extrahepatic disease where magnetic resonance (MR) imaging may have limitations in the detection of peritoneal and pulmonary disease. The emphasis is likely to shift in favour of initial FDG-PET and PET/CT scanning in the assessment algorithm despite limited knowledge regarding its economic impact [16,55], poor tissue definition, limited availability and an unproven benefit in metastasis management [56,57]. It is likely that this modality will be used selectively in the first instance to define extrahepatic resectability, in-situ liver recurrence, the delineation of widespread extra-abdominal disease and in some cases of locally advanced disease at presentation with metastatic disease and an unresected primary. To date, the cost–benefits of its use particularly when the post-hepatectomy course is complicated in aggressive surgery and in selected cases of resectable extrahepatic disease with contiguous organ extension (with or without locoregionally recurrent CRC) is unclear [10,11,58].

Guidelines for safe hepatectomy are now defined on the concept of adequate remnant liver. The American Hepato-Pancreato-Biliary Association Consensus Conference of 2006 concluded that hepatectomy should be considered where two adjacent liver segments can be retained with vascular inflow and outflow and adequate biliary drainage [59]. This future liver remnant (FLR) is defined as 20% in the normal liver [60] and around 40% in the diseased liver [61], with little available evidence that histologically close (i.e. <1 mm) but free resection margins compromise prolonged survival [62–64]. Liver resection can be accompanied by considerable blood loss and the requirement for inflow occlusion, where ischemia/reperfusion cycles [65,66] and haemorrhage represent the causes of major morbidity and mortality following surgery [67]. Various methods and modalities have been used during the last two decades to reduce blood loss during liver resection [68–73], each of which may or may not be coupled with inflow occlusion or vascular isolation, potentially further impairing perioperative hepatic functional reserve [74–76]. These recommendations extend to hepatectomy in metastatic disease in elderly patients [22,77] and to sustained survival advantage in those undergoing repeat hepatic resection for colorectal metastatic disease [78,79].

Although extended resections are planned on the basis of an estimated preoperative volume of the FLR, there is considerable variability in constitutive lobar and segmental volumetry [80–82]. Values of FLR outside this recommended range are considered an indication for some candidates for pre-hepatectomy PVE [24–26,83] either primarily performed or as part of a two-stage hepatectomy [26]. These approaches may be supplemented by locally destructive RFA therapy, as yet unproven as a modality capable of extending the expanded definition of resectability [28–30,84].

1.2. Neoadjuvant chemotherapy: current controversies

The data concerning the use of first-line neoadjuvant therapy in metastatic disease being followed by curative rescue surgery is increasing with initial survival results in this group being almost comparable to that of patients undergoing resection at the time of presentation [12,85,86]. Although there are no randomized studies comparing liver resection with systemic chemotherapy, these retrospective series have compared liver resection patients with those who did not undergo hepatectomy, showing survival advantage in the operated group.

Surgical resection is undoubtedly the best alternative given its low mortality and curative effect in selected cases with the neoadjuvant strategy likely to have considerable impact on the 85–90% of patients with hepatic metastases which are currently deemed irresectable. In the latter case, oxaliplatin-based regimens of chemotherapy have sufficiently downstaged cases to a resectability rate approaching 40% overall [87,88]. Substantial improvements have occurred in systemic chemotherapies for hepatic metastatic disease over the last decade with a shift from an overall response rate (RR) of 20–30% and an average life expectancy of approximately 12 months on fluorouracil/leucovorin (5-FU/LV) regimens to 2-year survival rates which are around 39% overall with the first-line introduction into the treatment algorithm of irinotecan and oxaliplatin. Both of these agents have shown an improvement in RR and overall survival when compared with 5-FU/LV standard therapy [89–91].

There has been some initial concern regarding this approach with some reporting worse overall cancer-specific survival [92] and a moderately high rate of recurrence with comparatively worse disease-free survival [93,94]. Capussotti et al. showed a worse disease-free survival and particularly early recurrence in patients after neoadjuvant therapy when compared with a group which underwent primary hepatic resection [86]. Conclusions from a non-randomized comparison are potentially biased, since the decision to undertake preoperative systemic therapy or primary surgery is typically based on the extent of the resection. Patients who undergo expanded resection are selected for preoperative treatments, rather than postoperative adjuvant systemic therapies [9]. They may tend to have more metastases which are more frequently bilobar [95].

Recurrence following the neoadjuvant approach tends to be early and associated with a higher incidence of extrahepatic disease suggestive of an improvement in progression-free rather than disease-free survival. The only evidence-based factors governing acceptable disease-free survival in these patients is tumour shrinkage during therapy where the only independent predictor of improved disease-free survival is the resection of recurrent disease [96]. This view is coupled with the recognition that there is frequently histological evidence of disease persistence despite of radiologic responsiveness, with Benoist et al. showing that even in the presence of complete radiologic responsiveness, macroscopic disease
is evident in 25% of cases and microscopic disease in 80% of patients pretreated with neoadjuvant therapy [33]. Moreover, nearly three-quarters of patients where there is no macroscopic evidence of disease with the liver segment is left in-situ, develop local intrahepatic recurrence. This finding effectively redefines the philosophical approach to the palliative/curative intent of treatment of advanced cases [97,98] as well as the agreed criteria of complete response with conventional radiology where post-chemotherapy hepatic steatosis results in an underestimation of recurrence within the remnant liver [99–101].

The technical details of the chemotherapy regimen and its mode of delivery (systemic vs intrahepatic) still remain unclear and should be based on a clear cut definition of resectability/unresectability [2]. Such an approach will standardize the concept of preoperative planning for R0 resections, making data more comparable. In this respect, a prospective, single-centre trial by Pozzo et al. of neoadjuvant irinotecan/5-FU/FA therapy in selected cases with clearly defined criteria of non-resectability recently reported an RR of 48% with an overall resectability rate (RER) of 33% [102]. These results were reproduced by Alberts et al. in a prospective, multicentre trial assessing the efficacy of FOLFOX-4 in patients with liver-only CRC metastases deemed not to be optimally resectable using pre-defined criteria [103]. Among them, 17 patients (40%) went on to have surgery, 14 of whom (33%) underwent R0 resections. This latter group, although the 3-year cancer-specific survival rate was 71%, experienced a significative recurrence rate (71%) despite the initial adequacy of the hepatic resection. In this Mayo Clinic trial non-resectability was considered in case of involvement of the hepatic vein confluence, or of the portal vein confluence or infrahepatic cava or of main portal vein branch and the contralateral hepatic vein as well as in case of disease which required more than a trisegmentectomy. Similar resectability criteria have been independently reported elsewhere [104] although there is an evolving policy towards hepatectomy after some form of neoadjuvant response where we would still consider metastases resectable irrespective of overall tumour size or number when at least one major portal radical and hepatic vein was preserved with >40% of liver parenchyma in the tumour-free liver remnant.

Agreement on resectability criteria have been suggested by the OncoSurge group of 16 experts drawn from Radiology, Oncology and Liver Surgery who have defined resection as absolutely contraindicated when there was non-resectable extrahepatic disease, >70% liver involvement with tumour, liver failure and/or surgical unfitness [96]. This group has largely abandoned some of the classic contraindications to hepatectomy as outlined by Eckberg et al. [105] of >4 metastases, extrahepatic disease or a resection margin <1 cm as well as those refined by Bismuth who included large tumours, multinodular and ill-located tumours and extrahepatic non-resectable disease [93]. Factors not altering resectability criteria included patient age, primary stage, timing of metastasis detection, prior blood transfusion, liver resection type, pre-treatment CEA level or prior hepatectomy [106].

Recent analysis of available published trials and retrospective studies that have reported evaluable RR and RER figures pertaining to initially non-resectable liver metastases has demonstrated a strong correlation between the RR and RER with isolated liver metastases [107]. This analysis by Folprecht et al. showed a linear relationship between RR to neoadjuvant therapy and resectability (Fig. 1) particularly when patients were preselected for their unresectability at entry into datasets. This assessment could be criticized as it was based on a very selected group of studies [102–104,107–110] where resection was considered as the primary endpoint only in three cases [102,104,110]. The correlation between tumour response and resection in non-selected patients was based on data from a much larger number of studies assessing over 2900 patients where the relation between RR and RER although less strong was still highly significant (p < 0.001). The interpretation of the data should be careful for both patient populations as it is also influenced by access to liver surgery, differences in the definitions of resectability between the different studies and the absence of clear reporting of the quality of resections (i.e. numbers of R0 vs. R1 hepatectomies) performed.

Even greater controversy exists over whether patients with resectable liver metastases should also receive neoadjuvant therapy where some have shown a low incidence of histologically involved resection margins when such an approach is used [111] whereas others have shown rates of histological involvement ranging from 9 to 19% overall.

Fig. 1. The rate of liver resection (RER) following chemotherapy plotted against the response rate (RR). Squares represent patients in prospective studies and retrospective analyses with non-resectable metastases confined to the liver: r = 0.96, P = 0.002. Studies with non-selected patients with colorectal cancer are shown as triangles (reprinted with permission by Folprecht et al. [107]).
Intra-arterial chemotherapy has particularly been associated with a time and dose-dependent increase in hepatic peliosis and sinusoidal congestion as well as with specific histological changes including sclerosing cholangitis, centrilobular fibrosis and cholestasis [114,115] where some have found an increase in intraoperative bleeding and septic and respiratory complications along with extreme hepatic friability after neoadjuvant therapy [116]. This is particularly noted when there is a short interval between cessation of therapy and surgery [21]. Post-chemotherapy steatosis is more common in obese males [117] with severe sinusoidal obliteration especially when oxaliplatin-based regimens are utilized [118]. There is currently such limited information concerning the specific hepatic effects of the different therapies that it is unclear whether liver resection should be delayed in order to preserve more hepatic parenchyma, or there should be a more liberal policy towards preoperative PVE as an adjunct to liver function when there is a borderline acceptable FLR or whether the type of chemotherapy utilized should influence the technique of parenchymal transaction in order to reduce perioperative liver dysfunction [119].

Recently Bevacizumab and other monoclonal antiangiogenesis therapies have been utilized in first-line combination regimens in advanced colorectal cancer as well as for irinotecan/oxaliplatin refractory cases [120,121]. The former approach has been questioned as additive first-line bevacizumab show low chances cost-effectiveness for basic gain of quality-adjusted life years in this disease at the present time [122]. In this context second-line conventional chemotherapy has shown a very poor RR overall, where the use of FOLFOX administered to irinotecan-refractory cases results in a RR <10% and a median survival of 9.8 months on average [123]. The newer biologic therapies including the anti-EGF receptor antibody Cetuximab as a second-line treatment in combination with irinotecan provides a RR exceeding 23% in irinotecan-refractory cases showing that their addition alters the biology of progressive disease [124]. This data should be viewed in combination with the finding that Bevacizumab may be safely incorporated in conventional first-line therapy [125] as can Cetuximab in combination with curative hepatectomy [126] although the results of trials incorporating these biologic therapies in a neoadjuvant approach are currently unavailable [127]. There is limited amount of data on the hepatotoxicity and perioperative morbidity following Bevacizumab therapy either alone or in combination regimens [4,37,128] although in localized cancer when introduced within 60 days after surgery there is no increase in wound-related complications as a result of angiogenesis inhibition [129]. The theoretical disadvantages of anti-VEGF therapy include a potentially deleterious effect on hepatic regeneration, [130,131] a diminution of endothelial cell repair mechanisms and an increase in bleeding/thromboembolic events [132–134].

Another controversy in these patients concerns the need for post-hepatectomy chemotherapy. Since it has been noted that there is progression in three-quarters of areas deemed to have completely responded to chemotherapy but never operated upon this would imply that postoperative chemotherapy is required as a routine. Initial data using postoperative 5-FU/LV reported in the ENG study [135] (EORTC/NCIC-CTG GIVIO trial) showed little survival advantage for postoperative chemotherapy although this and other initial trials have been relatively poorly randomized with a variable number of metastases in the treated groups [136,137].

This approach is currently being addressed in the EORTC 40983 trial comparing pre- and postoperative FOLFOX-4 chemotherapy with surgery plus observation only in patients with resectable colorectal liver metastases [138]. In this trial surgery has been performed within the planned timelines in those cases randomized to receive preoperative chemotherapy with R0 resections being carried out so far in 96.7% and 88.5% of operated patients in the chemotherapy and surgery alone arms, respectively.

2. Conclusions – future directions

The consensus for hepatic resection as an operative strategy in an age of neoadjuvant therapy for hepatic metastatic disease from CRC has created a dramatic expansion of the indications for hepatectomy with curative intent [139]. There is still great controversy in this approach as there is minimal data randomization with considerable evidence that macroscopic disease resolution is often associated with a high in-situ recurrence rate. The advantages of immediate neoadjuvant chemotherapy would suggest that there is a reduction in hepatic micrometastatic disease leading to better outcomes following major hepatectomy. Alternatively, the ability to better gauge treatment responsiveness and to define poor prognosis cases with progression during therapy as well the possibility to reduce the overall tumour size/burden which could be liver sparing have been claimed. Obviously, the disadvantages of this approach would include liver toxicity, the possibility of disease progression during chemotherapy (suggesting that there is in many cases a narrow window for potentially curative hepatectomy), and an overall inability to achieve a complete histological response.

Neoadjuvant therapy in such cases does not appear to lead to increased the development of non-resectable metastases during follow-up [140,141] encouraging the delineation of those patients potentially advantaged by a formal hepatic resection as opposed to a tailored segmentectomy whilst awaiting chemotherapeutic response [142]. Debate concerning the need for anatomical resection, however, still continues. Our group has suggested that the issue of repeated resectability in those selected cases where in-situ recurrence occurs (regardless of whether the initial hepatic resection was...
anatomical or not), is a more important issue [143]. Moreover, in those cases where larger metastases completely respond to neoadjuvant therapy in one area of the liver, resection of the contralateral lobe may become an operative option. This ‘non-synchronous’ view towards surgery is corroborated by recent evidence showing that the prognosis is adversely affected in those patients undergoing synchronous resection of liver metastatic disease with their primary tumour when the primary is extensive (T4), when it is infiltrating adjacent structures, when there is extensive peritoneal lymphadenopathy or venous infiltration and when there are multiple hepatic metastases at initial presentation regardless of the timing of adequate hepatectomy [144,145]. This issue, however, remains controversial, even for the presence of some evidences showing the oncological value in synchronous resections in some series except in the emergency setting [146]. In the absence of relevant randomized data, some have argued for synchronous resection with a right colonic primary and where regardless of the number of hepatic metastases, resection can be readily performed with minor hepatectomies [147].

The argument against synchronous resection has been promoted by recent data where patients randomized into synchronous groups tend to be younger and have more metastases which are more bilobarly distributed [95]. In this respect, although there are many multi-institutional reports of the safety of major synchronous hepatic resection at the time of the presentation of the primary CRC, many of these cases have been selected where major synchronous hepatectomy appears to be associated with a greater morbidity when compared with simultaneous non-anatomical wedge-style resections [148]. It is likely that the biology of the presentation rather than the facility for simultaneous resection will favour a neoadjuvant approach and where features of the primary CRC itself will determine prognostic outcome. In this respect the future may hold the promise of initial neoadjuvant therapy with the primary in-situ followed by synchronous resection [149,150]; an approach which may also be selectively applied to those patients with synchronous or metachronous resectable pulmonary secondaries [151].

At present, although the management of such cases is tailored for each patient and may be informed by consensus opinion [96,106], there is no objective data yet available to assess surgical decision making. Future trials must address the timing of rescue surgery so that an operable window is not effectively lost as well as the role of neoadjuvant therapy in such resectable disease. There does not now appear to be a limit governing the number of hepatic metastases which render a case irresectable [152] and this philosophical approach where many (>10) metastases are resected alters the importance of surgical resection margins so that closer margins can still be associated with curative outcomes [42,62]. The definitive role of ablative therapies (in particular RFA) also remains unclear and may be reserved for multiple recurrent cases or as an adjunct to hepatectomy in more extensive bilobar disease [153,154] although it is recognized that there is a higher morbidity of RFA when utilized in conjunction with hepatic resection [155]. The overall management paradigm towards hepatic metastatic disease from CRC must be informed by a shift in focus towards an assessment of progression-free survival as a surrogate endpoint of tumour response indicating the efficacy of first-line therapy regardless of measures used after disease recurrence [156–158]. This will alter the preoperative staging algorithm particularly aimed at the demonstration of non-resectable extrahepatic disease as well as the place of laparoscopic evaluation of cases prior to hepatectomy. Such an approach will also modify the availability and use of sophisticated techniques such as PVE to enhance the FLR, the use of two-stage hepatectomy and the ancillary utilization of locally ablative therapies designed to prolong overall but not disease-free survival. The philosophical separation in hepatectomy for metastatic CRC with palliative and curative therapy intent, in the absence of better neoadjuvant chemo- and immunotherapies, should remain indistinct as curatively intentioned therapy shifts the survival curve to the right (Fig. 2) and may alter the curve shape without affecting overall survival time. This would suggest that conventional endpoints of analysis and comparison in the treatment of hepatic colorectal metastases with new cancer treatments may be less meaningful in the modern more aggressive approach to this disease [159].

References


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**Biographies**

**Antonio Chiappa** was born in Milan, Italy. He received his M.D. Degree in Medicine, from the University of Milan. He trained in General Surgery Microsurgery and Transplantation Surgery in Milan, and in several other institution including Pittsburgh University, USA, Nagoya University, Japan, Athens Medical Center, Greece and Tokyo University, Japan. He is assistant professor of Surgery at the University of Milan and Senior Deputy Director of the Department of General and Laparoscopic Surgery at the European Institute of Oncology. He is leading clinical research projects in the field of surgical oncology including: immuno-reactivity in cancer and seriously septic patients, role of cancer markers in the diagnostics and follow-up of liver, pancreas colon-rectum neoplasies, hepatic tolerance to ischemia, echo-guided surgery; radio-immuno-guided surgery; multi-mode treatments for hepatic metastases caused by colon-rectum cancer and circulating tumour cells. He is member of several international societies and Fellow of the American College of Surgeon and of the Royal College of Surgeon. He is author and co-author of about 300 scientific publications printed on the most
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Aaron Goldhirsch was born in Germany, he received his M.D. from the Milan State University in 1972. He trained in internal medicine and medical oncology in Switzerland and in the United States. He is director, of the department of Medicine at IEO, Professor for Medical Oncology, University of Bern, Switzerland, Professor of Oncology at the University of Milan, Italy, and Visiting Professor at Harvard School of Medicine in Boston, USA. He is chairman of the Scientific Committee of the International Breast Cancer Study Group (IBCSG) and head of Division of Medical Oncology at Oncology Institute of Southern Switzerland (IOSI) in Lugano, Switzerland. He is involved in clinical research for new adjuvant treatments for breast cancer, definition of biological features that predict responsiveness or resistance to anti-cancer treatments, quality-of-life-oriented approaches, definition of optimal systemic treatments for very young women, and development of personalized treatments for elderly patients with breast cancer. He has received several international prizes: Robert Wenner Prize of the Swiss Cancer League, San Salvatore Prize, International «La Madonnina» Prize for Research of the City of Milan, Prize Farmitalia of the German Oncology Group, and the Swiss Lavezzari Prize. The University of Gothenburg, Sweden, awarded him an Honorary Doctor in 1993. Author of 450 peer-reviewed articles and chapters in reference books and editor or co-editor of 10 books.