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Mini Review

There will be a "Surgeromic" in our Future? Where the Research on Colorectal Cancer is Leading Surgery

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Abstract

Technological innovation and knowledge have always conditioned surgery. What will be the role of surgery in the future is under discussion. Genotyping might leads the path towards personalized medical therapies. In this mini review we have compared the assumptions contained in them in order to assess whether the new diagnostic and therapeutic possibility will be able to affect surgical options in the near future.

Methods: We analyzed articles extracted from Medscape and Pubmed using some key words related to Colon cancer. Genotyping, molecular and personalized medicine and we have compared the assumptions contained in them.

Discussion and Conclusion: Research about has not yet demonstrates its potentiality but, in the future it is conceivable that molecular medicine may lead the full personalized treatment plan where the need for surgery will depend upon the relationship between the individual genotype and a constellation of factors, able to influence the effectiveness of surgery. Then, we introduce the concept of "surgeromic", a neologism binding surgery to its individual determinants and assume some research areas to be implemented in order to overcome some obstacles to the full development of this new era.

Keywords: *Surgeromic; Colorectal Cancer; Genotyping*

Introduction

At the end of the Second World War, both the European and Americans Schools of Surgery were marked on the assumption that the Oncological Surgery, had to be based on the greater removal of diseased tissue as possible since it represented the main therapeutic tool against the majority of solid tumors. Research in Surgery was accordingly geared towards the evolution of techniques and procedures, and has focused for a long time almost exclusively on the continuous improvement of these. Over the years, the role of Surgery has changed mainly along two lines: a) research and development of new techniques and procedures – supported by the new technologies and materials - able to reduce as much as possible the demolitive surgical phase, side effects, or the consequent physical mutilation, and held in more and more attention the characteristics of the individuals, their expectations and overall well-being, so ensuring the best possible therapeutic efficacy (Table 1); b) conceptual transition of Surgery from a central role in oncological therapy to be part of an integrated therapeutic plan where the synergies between clinical and laboratory activities are the conceptual basis of a new personalized therapy. In this context, Surgery has lost some of its central role - over the World we are already witnessing a steady reduction in surgical admissions and to an improvement of minimally invasive techniques- and is candidate for to assume a new role within a treatment strategy no longer concentrated on the effectiveness of tissue removal but on the use of a greater number of technological opportunities and therapeutic options [1]. Indeed, in the last decade, the technological evolution has given a major boost to the research about nanotechnology [2], molecular medicine [3] and genetics that greatly contributed to a further development of the diagnosis and treatment of cancer, opening

the way for intervention increasingly targeted to the characteristics of the patient (Table 2). The next revolution in surgery just relates to the use of nanotechnology [4-6], molecular medicine, genomics [7], and possibility to use molecules that bind selectively to tumor cells at the same time conveying the therapeutic agents (Theranostics) [8]. Thus, as argued by Tremblay., *et al.* research on the role of genomics leads the path towards personalized medical therapies [9], and in the near future it is conceivable that it may lead the full personalized treatment plan [10] including Surgery. If therefore innovation has always produced a substantial improvement in the therapeutic efficacy of surgical procedures and a repositioning of their role, combining them with technical progress and a significant decrease in negative side effects, what can be expect from the relationship between innovation and Surgery in the coming years in terms of further benefit to the patient, technical improvement and about its conceptual role? Just to be able to understand this role we should ask ourselves how the research in surgery, source of its development, will develop in the coming years: has it to continue addressing itself mainly to the technical issues then continuing to recur with a central role in cancer treatment or whether is the research in other fields to redefine the clinical role of surgery, and, consequently, its future lines of research? The hypothesis that is developed here regards these aspects: the role of surgery, in the light of technological developments and new knowledge of molecular medicine and the possible lines of research useful to set this clinical role. In this perspective, the need for surgery will depend upon the complex of relationships which will be elapsing between the individual genotype and a constellation of factors, able to influence the timing, the indication, the amplitude, the technical procedures and the effectiveness of surgery: Beggs., *et al*. [11] discussed the prognostic and predictive role of several biomarkers in colorectal cancer and the possibility to undergo surgery only after considering the possibility of molecular –targeted therapy. They concluded that the selection of the right therapy for the right patient at the right time will have to take account of technological leaps in molecular biology, and were the first to associate the words "surgery" and "omics".

From	Innovation	Field of application	Effect on surgery
1960-70	Technology equipment and Materials	Interventional Endoscopy	Reduction in open surgery indications, Biliary Tract, Urinary Tract, Prostate
1970-80	Technology equipment and Materials	Staplers	Reduction in invasiveness Abdominal and Thoracic Surgery
	Particle Physics	Nuclear Medicine, Radioisotopes	Reduction in invasiveness Brest Surgery
	Pharmaceutical Chemistry	Anti-ulcer Drugs	Reduction indications in Gastro-duodenal Surgery
1980-90	Technology Equipment and Materials	Laparoscopic Surgery	Reduction in invasiveness in General Surgery
1990-00	Technology Equipment and Materials Electronics	Robotics Prosthetics Materials	Reduction in invasiveness and Infectious complications
2000-10	Technology equipment and Materials	Nanotechnologies Molecular Medicine Genetics and "Omics"	Reductions in indications and invasiveness in General Surgery Nanosurgery
Future	All Previous and More in Genetics	Personalized Genomics Medicine and Surgery Decision Making Process	"Surgeomic"? The use of surgery will depend on the individual genetic characteristics and the complex of therapeutic possibilities

Table 1: *Relationship between innovation and effect on surgery in the second half of last century.*

Periods expressed in Decades in which started the clinical practice induced by related innovation and consequential effect on Surgery. Innovations of each decade added to the previous realize an overall reduction in number of surgical procedures intended as indications to open surgery, degree of invasiveness measurable as reduction in length of hospital stay, after surgery complications and side effects or socially disabling mutilations.

Author	Innovation	Correlation to	Clinical Outcome
Hong., *et al*. [13]	Genotyping	Diagnosis, Therapy and prognosis	Personalized medicine
Ginsburg., *et al*. [14]	Genomic Medicine	Identify individual risk Guide clinical management	Health care decision making
Simons., *et al*. [18]	Genotyping	Risk of CRC	Possible modification of therapy response
Billeter., *et al*. [16]	MicroRNA	More aggressive tumor biology Invasiveness Formation of Metastasis Local recurrence	Possible suppression of tumor progression
Li., *et al*. [17]	MicroRNA 215	Relapse of operated CRC	Potential predictive marker of relapse after radical surgery for CRC
Chae., *et al*. [52]	MicroRNA 367	Prognosis of CRC	Potential marker for prognosis after surgery for curative CRC
Blanco., *et al*. [4]	Nanotechnology	Chemotherapy	Improved anti-tumor efficacy
Weldon., *et al*. [5]	Nanomedicine	Surgical procedures	Potential to affect the field
Allhoff F [6]	Nanomedicine	Surgical treatment Philosophical aspect	Conditioning surgical procedures and techniques

Table 2: *Relationship between innovation, correlation to cancer diagnosis, treatment or prognosis and clinical outcome in the last decade.*

Perspectives about the role of surgery in the treatment plan have to be considered in the context of the personal characteristics of the patient opening the way for a real future personalized treatment

Methodology

A search was conducted on Pubmed and Medscape using the key words "Molecular medicine" and "Colorectal Cancer": respectively 4747 and 5176 articles were found. Adding the key word "decision making "they were respectively 569 and 1430; adding the key word "biomarker", 60 and 1355 and finally adding "genotyping" 50 and 198. Considering the articles present in both the research engines and excluding articles published as reviews or news in not scientific journal, remain 75 articles. A second search regarded articles about "nanomedicine" and "colorectal cancer": 201 articles resulted on Pubmed and adding "genomic" and "personalized Therapy" resulted 18 articles. The same search on Medscape gave 251 articles. By removing from these news, and reviews on non-biomedical journals remain 27 articles and /or internet sites. From a total of 120 we finally considered useful for our review 51 issues including 49 articles and 2 websites.

Discussion

The "omics"

The suffix "omics" has no precise or unique meaning: in biology adding the suffix makes the meaning of the word dynamic, since it indicates not only the characteristics of the discipline but also the techniques, the set of functions, the relationships between them and with other internal and external environments and the changes that, as a result of these interactions, can be generated. Especially in the last ten years, a large amount of information derived from studies of Nutrigenomics [12], (the study of how specific genetic polymorphisms interact with the bioactive food components in conditioning the level of cancer risk related to the dietary habits), Transcriptomics, (the study of the RNA transcripts produced by the genome at any time and the changes under different circumstances due to different patterns of gene expression), Metabolomics, (the study of the metabolites and how they are affected by specific cellular processes), Proteomics (the study of protein structure and function expressed by a genome), has been added to those relating to the Pharmacogenomics (the study of genetic variations that influence individual response to drugs) and has opened new horizons in research and therapy of cancer. The

field of colorectal cancer diagnosis and treatment is, from this point of view, highly topical. Today we currently talk about individual risk, personalized medicine and/or therapy [13] and individual response to pharmacological treatment, precisely in dependence on some of those characteristics defined by the "omics" that, as argued by Ginsburg and Willard [14], concern - "information from individual genomes, which is a fast-moving area of technological development, is spawning a social and information revolution among consumers that will undoubtedly affect health care decision making" -meaning that the whole treatment plan may have different outcomes depending on the personal characterization given by omics, abandoning the old concept of "one size fits all" in order to land a real personalized treatment plans [15].

In other words it means that the treatment plan may depend on personal ability to respond to chemotherapy, to develop metastasis, be able to use predictive or prognostic markers of outcome of surgery [16-18].

Which research in Surgery in our future?

The treatment plan for a cancer patient is currently the result of an interdisciplinary vision that takes place in a single path defined by the combined action of several therapeutic modalities and that is basically made up Chemotherapy, Radiotherapy and Surgery but already today the research about the use of nanoplatforms [19,20], the possibilities arising from the knowledge in molecular medicine, pharmacogenomics and genotyping shows us a new way to determine both the possibility and efficacy of treatments, lying the foundation of a personalized treatment. In this context, the knowledge of the genetic characteristics of a patient related to its diseases risk and to its chance to have benefit from chemotherapy or other targeted therapies allows us to draw up his own plan of both prevention and treatment. Indeed the research conducted so far, evidence of a difference in risk of cancer depending on the presence of some SNPs: in particular, in the context of neoplastic disease of the Colon and Rectum in the last decade there have been important and significant developments that have led to the identification of several SNPs - 16 genes and 35 SNPs as listed by Slattery., *et al*. [21] (Table 1) – and / or Signaling Pathways whose activity is closely linked to the onset, development, progression and metastasis of cancer [22,23], as they are understanding some of the features of therapeutic effectiveness depending on the presence or absence of particular SNPs, or specific combined oncogenic pathways: to date, we can talk about of SNPs able to affect increase or decrease of the risk of getting cancer or the efficacy of specific pharmacological treatments [24-26]. Most recently Zhand., *et al.* listed 47 SNPs [27] (Table 1), but at present day they are not fully considered medically actionable [28]. Tremblay., *et al*. refer that, currently, 10% of marketed medications propose or recommend genetic testing for optimal treatment [9]; Bartley., *et al*. [29] although considering that few biomarkers have given clinical evidence of reliability, underline their potential to improve outcomes for patients. Katsios., *et al*. [30] argue specifically about the possibility that genomic medicine will change the practice in surgical oncology and believe that this is the real challenge for the future of Surgery.

Thus, genotyping becomes preliminary to setting personalized plan of prevention and treatment of neoplastic disease, the prediction of metastasis or the effectiveness of surgery alone compared to the combination of surgery and chemo or radio-chemotherapy. Sinicrope [31] argued about the relationship among patients with MSI-H cancer, time of recurrence and survival with surgery alone compared to MSI-L patients, introducing the concept that genotyping is preliminary to the choice of therapy. Surgery, is posed, therefore, in a new position since the use of it will change in the timing, indications, amplitude of the demolition and prognostic expectations depending on the individual patient's compliance to all those factors, in turn, determined by its individual gene structure. Finally, performing surgery as the first or second instance may be decided on the basis of the individual capability to respond to drugs toxicity, to their metabolizing or intracellular transport, e.g. or as proposed by Dancey on the basis of new knowledge on molecular and genetic features of colorectal cancer [32].

In a recent study [33] Dalerba., *et al*. argued that in stage II CDX2 –negative disease colon cancer patients, currently treated with surgery alone, adjuvant chemotherapy might be a treatment option, then placing the surgical option in a subordinate position with regard to the presence of this biomarker. Biomedical research of surgical interest is currently strongly focused on topics related to the possibility to translate in clinical practice the prognostic, predictive and therapeutic potentiality of markers and biomarkers [34,35] rather than about

surgical techniques, especially in CRC. Johnston [36] refers about 15% of sporadic CRC are characterized by deficient DNA mismatch – repair related to mutations of MLH1, MSH2, MSH6, PMS" genes and invite to study in deep the role of MSR and other genes features in predicting response of chemotherapy and associated therapies.

So, will we have a future without surgery? Probably with less surgery surely with a different kind and role of surgery [37]. Currently this is only a perspective since despite the enthusiasm that current research produce, the results have not yet concretized with their transfer into clinical practice and we are not yet able to have diagnostic and therapeutic pathways applicable to individual patients directly resulting from such research [38].

Despite the recommendations for caution in the predictive test validation [39] and the need facing to conflicting results of having new large sample size well-structured trials [40] we must to continue the research in that direction, because "it is the right things to do for our patients" as asserted by Kalady [41] It is therefore feasible, that Surgery, will become a not-of-first-instance-therapeutic-tool, conditioned by nanotechnology, biomolecular and pharmacogenomics procedures [42,43]: we can then define this dynamic interaction introducing the term "surgeromic", a hybrid neologism which lexically binds surgery to its individual determinant and that defines that specific set of individual characteristics and environmental conditions, lifestyles, habits, in which the use of surgical therapy is mediated by the characteristics of individual responsiveness of the patient to the various therapies which in turn can determine both the timing and the type of surgery in the context of a more comprehensive treatment plan.

Whether this is the future, which kind of research in Surgery has needed to continue playing a key role in the personalized oncological treatment? Among the current major barriers to be overcome to transport on the clinical level the current outlook are represented by the cost still too high to standardize this new type of diagnostic [44], by the intratumoral heterogeneity which requires different treatment lines for different cell subpopulations in the same tumor [45] and that consequently also the most interesting biomarkers have not been studied in the complex context of the individual cancer subtypes [46] and by the methods of evaluation of accuracy of gene expression signatures to address the therapeutic path for Colorectal cancer patients [47] (Table 3). Besides these there are many topics and many levels on which to develop further research for testing the hypothesis considering that not a unique research but a whole body of research should aim to fully demonstrate the utility of genotyping as a basis for personalized medicine [9].

Barrier	State of art	Perspectives	Possible outcome	Clinical application
Cost	Still too high. Need for continuous updates and technological improvements following knowledge about molecular characteristics of cancers	New projects involving the large-scale introduction of diagnostic and genotyping analysis Betters cost-effectiveness ratio	Cost reduction	Increased use of genetic profile in making decision Improvement of personalized therapy
Intratumor heterogeneity	Presence of subpopulation of cancer cell needing different therapeutic agents or tools	Better knowledge of molecular characteristics of single tumor and ability to identify mutations and their role in developing cancer	Correspondence between tumor and molecular markers	Better accuracy in prediction of tumor and patient response to targeted therapy
Diagnostic Accuracy	Currently not sufficient for clinical routine application or to change the course of treatment	Greater use of international projects and controlled clinical trails	New stratification of patients with reference to the therapy	Identification of a set of therapeutic personalized options including procedures and directions to surgery

Table 3: *Main barriers to the development of diagnostic and therapeutic paths addressed to personalized surgery.*

So, in the next decade, considering also the five major lessons proposed by Collins [7] the research should develop issues which can further define: a) genotyping associated to susceptibility to cancer; b) the personal characteristics of useful use of chemotherapy; c) the personal characteristics of prognosis following surgery, and specifically:

1) **Scientific Researches Themes**: a) New associations between diseases and genes; b) interaction between polygenes and environmental factors; c) the combinations of SNPs that, in turn, condition signaling pathways and transcription; d) genomic tools able to precise prediction and treatment of therapy; e) the role of diagnostic and prognostic evaluation of cancer patients of microRNAs; f) biomarkers and their role in assessing oncological treatment and follow up; g) new therapeutic and diagnostic methods arising from technological innovation; h) new surgical techniques coming from use of new technologies.
2) **Organization Patterns**: To establish prophylactic paths for patients who show positive diagnosis for cancer susceptibility and /or a personalized therapeutic one that is affordable even to Public or Mixed Health System. To do that it is necessary to create projects involving the large-scale introduction of diagnostic and genotyping analysis whether they are established or new [48] in order to increase efficiency, lowering costs and encourage the construction of models of personalized medicine and surgery as that reported by Brunicardi., *et al.* whose ultimate goal is summarized by the sentence: "the genomic profile guides choice of therapy" [49].
3) **Laws and the Health Care System**: On example of Genomics and Personalized Medicine Act of 2007 [50] have to be proposed and approved laws and decrees defining objectives, guidelines and funding, supporting new health strategies that recognize the value of personalized genomic medicine and redefine the areas in which Health in the coming years will develop.
4) **Educational programs**: The educational curricula in the Schools of Medicine should aim to increase the knowledge of both genomic and its interrelationships with diseases and awareness for the next generation of healthcare workers, surgeons included, that genetic information can be used to induce people to adopt behaviors and actions useful for the prevention and treatment of diseases [51].

Executive Summary	
Genotyping	These fields have to be investigated further: a) susceptibility to cancer (SNPs association for colorectal cancer e.g.); b) the personal characteristics of useful use of chemotherapy; c) identification and composition of groups at risk of cancer.
Molecular Medicine	To verify the presence of predictive biomarkers. Expand clinical research on the role of Micro RNA and Signaling pathways in order to identify predictive biomarkers of disease and their actual predictive reliability
Nanomedicine	To treat and monitor the effectiveness of therapy. Deeper search of new nano platforms for diagnosis and intracellular multi therapy. Search imaging techniques are able to identify more precisely the diseased cells and their targets for the treatment.
Surgeromics	Use of surgery depending on the results of a new diagnostic and therapeutic pathway dictated both by the individual genotyping and the current availability of technologies. This will lead to further benefits for the patient and resource savings for health systems
Personalized treatment	Orient the medicine towards the creation of personalized pathways of treatment. To do that it is necessary to create projects involving the large-scale introduction of diagnostic and genotyping analysis, in order to increase efficiency, lowering costs and encourage the construction of models of personalized medicine
Laws and Health Care Systems	Single national Health Systems have to be proposing and approving laws and decrees defining objectives, guidelines and funding, supporting new health strategies that recognize the value of personalized genomic medicine and redefine the areas in which Health in the coming years will develop.
Education	The educational curricula in the Schools of Medicine should aim to increase the knowledge of both genomic and its interrelationships with diseases and awareness for the next generation of healthcare workers, surgeons included, as this will lead to new benefits for patients and lower overall costs for governments

Conclusion

Surgery is a changing world and its role in oncology as well. Much remains to be understood and defined, to transfer the daily clinical practice perspectives on which it is developing research in the field of colorectal cancer. At present research on biomarkers and their role in predicting the outcome of the diagnostic or therapy has not yet given us the option to transfer the obtained results into clinical practice, although encouraging. But the future is traced and moves towards a greater understanding of the individual genotype and its clinical applications and a new era is at the door. "Surgeromics" is a neologism, with which mean a field concerned with the use of surgery depending on the results of a new diagnostic and therapeutic pathway dictated both by the individual genotyping and the current availability of technologies, knowledge and diagnostics and that could represent the word where to converge the sum of the results of new research lines: "genotipyng" will be the basis to identify susceptible individuals and personal responsiveness to therapy; "molecular medicine" the methodology through which to verify the presence of predictive biomarkers; "nanomedicine" and imaging applied to it the way for treat and monitor the effectiveness of treatment. The results of the research conducted so far on the issue of "omics" indicate that cancer therapy is moving even more towards personalized formulas and even surgery, is moving to a new collocation in the context of a more general treatment plan, so taking part in a major new therapeutic revolution, in another step forward the clinical use of new technologies and becoming a new tool of a new customized mode to address cancer prevention and therapy. In this context research in Surgery has to lead to a its new role in the evolving word of cancer treatment, abandoning the presumption of still being the center of I this. Surgery remains an important therapeutic tool and the new research needs to be addressed to maximize the use of its benefits in the context of a personalized therapy that ever more will take advantage from knowledge coming from the molecular biology in administering the entire treatment plan of the cancer patient.

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Conflict of Interest

I have no conflict of interest.

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