

Changing Role of Surgery in Cancer Treatment

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Surgery is, and always has been, the main treatment modality of solid malignant tumors. For a long period, it consisted of a number of surgical procedures dictated by basic oncological principles, most of which are still adhered to. Over the last few decades, increased understanding of the disease, new or improved diagnostic facilities, novel and perfected adjuvant treatments, improved surgical techniques and daring challenges to established dogmas have all contributed to the development of surgical oncology. The heritage from the past came under close scrutiny, and the fruits of basic and clinical science were added to an ever expanding body of knowledge.

Today practicing and investigating surgeons are involved in all aspects of cancer management including: (1) assessing risk, (2) screening, (3) diagnosis, (4) performing primary treatment, (5) assessing prognosis, (6) directing patients to adjuvant therapies, and (7) pursuing long-term follow-up of the cancer patient. These responsibilities require the surgeon to be familiar with the genetic and molecular basis of cancer etiology, the methods of screening and detection, the latest surgical technologies, the prognostic features of tumors and staging features, the efficacy of adjuvant therapies, and the appropriate guidelines for follow-up.

A historical overview

Malignancies are neoplasms characterized by infiltrative growth and the capability to metastasize. Infiltrative growth demands wide excision and, to eradicate locoregional disease, regional lymphadenectomy. Halsted and Handley formulated their hypothesis, in which en bloc dissection was considered mandatory to improve locoregional control and mortality rates from carcinoma of the breast. Accordingly, extended procedures were devised for other malignancies, like colorectal cancer. In an effort to achieve the maximum in this respect, radical and supradical operations were employed up to hemicorporectomies, along with extensive lymphadenectomies. The principle of radical resection, including lymphadenectomy, to obtain locoregional control stands firm. Yet, today's practice looks different for a number of reasons, including improved understanding of biological behavior, early diagnosis (including screening programs), risk-group identification (including cancer genetics), scientific evaluation of existing treatment protocols, improved preoperative and preoperative staging, adjuvant treatments helpful in controlling micro-residual disease and distant metastasis, improved techniques in surgery, anesthetics and intensive care, all

enforced by the introduction of multidisciplinary treatment.

Biologic behavior and the natural course of malignant disease

If locoregional control is not obtained, the disease cannot be cured. Locoregional recurrence can often be tackled, but indicates poor prognosis. One of the important notions in the last decades has been the growing awareness that locoregional recurrence is not the main cause of impaired prognosis: metastatic disease disseminated to vital organs is the cause of death in the majority of patients.¹ If heroic surgery is necessary to obtain locoregional control, the patient is not likely to benefit from it in terms of survival, as he or she is likely to die from distant disease. This has led to a tendency of more restricted radical surgery and increased emphasis on systemic treatment in locally advanced tumors, often rendering accurate lymph node staging of major importance. Paradoxically, another important notion on biologic behavior is the finding that cells spreading to distant localizations are not identical: the metastasizing cells may be organ specific. This explains why extensive lymph node metastasis or widespread liver metastasis from colorectal cancer can be isolated phenomena. In such cases, there is a rationale for intensive treatment of the anatomical location.

Early diagnosis and screening programs

The notion that distant spread constitutes the real threat to the patient's life led to efforts to diagnose malignancy before metastasis had even occurred. The advanced tumors (that also stimulated heroic surgery to obtain local control) that were frequently encountered in previous years have now become less common for more than one reason. Much effort has been made to make the public and physicians aware of those subtle symptoms and signs that may indicate the presence of early malignancy. Along with this, there seems to be more awareness that so-called early cancer is frequently curable, encouraging people to seek early medical advice. All this has resulted in an increased proportion of early-stage, curable malignancies.¹ Screening programs can only be effective if there is a relatively high incidence of the lesions sought for as well as a test with high specificity. For a number of frequently occurring malignancies, such techniques have become available in the past decades, and the screening approach has proved useful: breast cancer screening by mammography is now increasingly employed, resulting in increased proportions of T1 and Tis tumors being identified. Mor-

tality attributable to breast cancer has decreased² for the first time,³ although this is also attributable to adjuvant systemic treatment. In Japan, with its high incidence of gastric carcinoma, many of these lesions are now diagnosed in the stage of curable early gastric cancer due to gastroscopy screening.⁴ Screening for colorectal cancer in the general population may be just a matter of time.⁵ Identification of risk groups opens the opportunity to screen for lesions that are too rare to make general population screening attractive. Epidemiology has identified several landmarks that are associated with increased cancer risks, like smoking, sun exposure and familial position. This enables the screening of high-risk groups and guides our index of suspicion during diagnostic evaluation. One special form of risk-group evaluation has become available only in recent years. High familial incidence of diseases like breast cancer, colorectal cancer, and endocrine malignancies had been noted before. Due to increased genetic expertise, it subsequently became possible to identify those individuals belonging to families with such a cancer predisposition (as opposed to an accumulation of sporadic tumors within one family), and often different syndromes with associated risk ratios could be identified. In recent years, several of the responsible genes have been identified, and can be tested for in patients. Subsequently, healthy relatives of such a patient may be tested for the presence of the genetic anomaly involved. This allows an accurate individual risk estimation, enables us to identify those persons (rather than entire families) that are at risk, and those that have a risk equal to the average population. According to the severity of the risk and the patient's wishes, we may individually screen these more intensively, employing more invasive methods. This is widely done with serial colonoscopy in colorectal cancer families and other risk groups as opposed to yearly fecal benzidine reactions and sigmoidoscopy every five years, that seems a more appropriate strategy for the general population.⁵ Gene mutation-positivity may imply a very high risk ratio as well as a specific biologic behavior of the tumor. Therefore the development of cancer family genetics and gene diagnostics has also raised the issue of prophylactic surgery: removal of healthy organs with a high likelihood of carcinogenesis and screening/surveillance failure.

Diagnostic tools

Apart from such highly specialized diagnostic tools like the gene diagnostics mentioned above, the past decades have shown an impressive expansion of widely available and used diagnostic tools. Additionally, rationalization of diagnostic procedures during follow-up has turned out to be a difficult task. New radiographic tools, like ultrasonography, computerized tomography (CT), and magnetic resonance imaging (MRI) have become widely available, and often set new standards for diagnosis. Not only has sensitivity of diagnosis improved, it has also resulted in more accurate preoperative staging. Treatment is no longer planned once the tumor has reached the surgeon in theatre; as a rule, operability is now judged correctly beforehand, individual treatment carefully planned and discussed in advance. Operations that do nothing other than diagnose stage (as irresectable) and harm the patient have not disappeared, but their number has been reduced substantially. Flexible endoscopy of upper gastrointestinal tract and colon have not only improved sensitivity of diagnosis, but also enabled preoperative histological diagnosis and the treatment of many benign lesions without an operation; more recently endoultrasonography

allows accurate estimation of the depth of invasion in some tumors, making such information available pre-operatively.

The goal of initial biopsy and evaluation is to obtain sufficient tissue and information to diagnose and stage a cancer and then to begin therapy. Biopsy can be accomplished by fine-needle aspiration, large-core needle biopsy, or open surgical biopsy. In certain situations, the histologic diagnosis is established by resection of the tumor itself (e.g., gastrointestinal neoplasms). However, with more effective pre-resection diagnostic capabilities, such as endoscopy and fine-needle biopsy, definitive resection often is undertaken with a well-established pathologic diagnosis. If a suspected neoplasm is to be treated by any modality other than surgical resection (i.e., radiotherapy or chemotherapy), an essential factor is to establish an accurate histologic diagnosis and stage prior to beginning treatment. Also, sufficient biopsy material must be obtained prior to treatment to allow for assessment of tumor biological markers, special immunohistochemical staining, and genetic studies of the tumor, as these factors may influence treatment and prognosis.

The increased availability of diagnostic tools applies to the follow-up period too. There has been increasing awareness that routine follow-up diagnostic screening only makes sense if positive findings lead to therapeutic interventions that in turn improve prognosis. In many malignancies extensive follow-up diagnostic procedures have been replaced by symptom-guided approaches.⁶⁻⁷

Surgical techniques

The adequate margin redefined

As already stated, the old paradigm of wide surgical resection and lymphadenectomy of malignancy is still valid. Recent decades have seen some interesting changes in what were considered adequate margins at least in some tumors. For example, randomized studies in breast cancer comparing radical mastectomies with less radical modified procedures⁸ showed equal locoregional control and survival rates. Consequently, less radical procedures with breast conservation therapy (wide excision of the tumor, complete axillary lymph node dissection and radiotherapy to the breast) were employed. After adequate follow-up, all randomized trials showed equal regional control and survival rates for both groups.⁹ Further studies revealed risk factors for breast relapse after breast conserving treatment. The most important consistently identified independent factors: incompletely excised invasive and/or in situ carcinoma, vascular invasion, young age and insufficient radiation dose.¹⁰ The aim of breast conserving treatment is to achieve a good or excellent cosmetic result in over 70% of the patients with an annual local recurrence rate of less than 2% per year. If bad cosmesis or high risk of local recurrence is anticipated, mastectomy with or without reconstruction is still the preferred option to achieve good local control.

Standard operations refined

Old standard procedures have been refined. Surgical oncology has benefited from more general developments in surgery, ranging from the introduction of stapling devices to drastically reduced hospitalization. Improved surgical and supportive (anesthetic, intensive care) techniques have reduced operative risks (as in the Whipple procedure, where mortality has been reduced to 5%). Some examples exist, for example in rectal surgery, where rethinking the original concept (re-examining the embryo-

logical significance of planes in which dissection is carried out) has had an important impact on disease outcome and patients suffering. The controversy as to which method is best (abdominoperineal [APR] or low anterior resection) has not been resolved. Many publications have shown a clear decrease in percentage of APR in rectal cancer: from around 60% in the early 1980s to 15% or less of the total rectal cancer population now.¹¹ Sphincter preservation techniques such as coloanal anastomoses, with or without a pouch construction, have become common practice to preserve the sphincter. Heald, introducing total mesorectal excision, claims hardly to ever sacrifice the sphincter. The total mesorectal excision was introduced to ensure lateral clearance of the tumor, including the lymph nodes in the mesorectum, by careful dissection surrounding the integral visceral mesentery of the embryological hind gut. The occurrence of mesorectal involvement, well beyond the apparent inferior border of the tumor was reported by Heald and co-workers, but will be cleared with their formal total mesorectal excision (TME).¹²

Resection of visceral metastasis

In some clinical settings, resection of isolated visceral metastasis of certain tumors is associated with long-term disease-free control and possibly a cure. Surgical resection of visceral metastasis requires consideration of the following important factors: (1) type of primary tumor, (2) interval between primary diagnosis and metastasis, (3) number and location of the metastases, (4) technical feasibility of a clear margin of resection, (5) performance status of affected patients, and (6) ability to treat such patients further with additional antitumor therapies. Tumors presenting with isolated pulmonary metastasis that might be considered for surgical resection include Wilms' tumor, osteogenic sarcoma, soft tissue sarcomas and, occasionally, colorectal carcinoma. Likewise, some tumors presenting with isolated liver metastasis that might be controlled by resection include colorectal cancer and carcinoid tumors.

New procedures

Some entirely new procedures have appeared on the theatre lists of surgical oncologists, often resulting from interactions with other specialties. Without presenting a comprehensive overview, I would like to highlight some examples. Chemotherapeutic agents as well as cytokines usually have a dose limiting toxicity. However, the biological behavior of some tumors requires regional rather than systemic treatment. Examples of these are satellite metastases in malignant melanoma, large sarcomas and metastasis of colorectal carcinoma (that may well be spread throughout, but are restricted to, the liver). Systems have been devised in which the surgeon isolates the arterial and venous blood flow and connects these to machinery for extracorporeal circulation. Such a system of isolated perfusion allows local tissue concentrations of the agents which would otherwise be lethal to the patient. Isolated perfusion of limbs,^{13,14} and in a more investigational setting, liver,¹⁵ are performed nowadays. With a similar intent, optimal cytoreduction and hyperthermic chemotherapeutic treatment of the abdominal cavity for peritoneal implant metastasis has been employed and promising results reported.¹⁶

The introduction of laparoscopy in surgical oncology made a proper scientific comparison with conventional techniques impossible. The fear of metastasis arising from high intraperitoneal pressure, port site metastasis and prac-

tical problems gave rise to proper investigation in clinical trials. Convincing evidence in favor of laparoscopic resections is still awaited.

Recent years have seen the re-introduction of the concept of sentinel node biopsy, mainly in melanoma and breast cancer surgery. Lymphatic drainage from the site of the tumor usually progresses in an orderly fashion to one, or a few, lymph nodes. If these sentinel nodes do not contain metastatic tumor, according to the sentinel node concept, the remaining regional lymph nodes should be tumor free too. Correct identification and pathological examination of this sentinel node as tumor negative would obviate the need of a complete lymphadenectomy.

With complete lymphadenectomy, the pathologist has to examine a considerable number of lymph nodes. In the sentinel node procedure, one or few lymph nodes are removed in which lymph node metastasis should be detectable if present at all. This allows a careful histological work-up of these single nodes. Particularly with the widespread application of multiple section and immunohistochemical staining, micrometastasis will be identifiable in the sentinel node, resulting in more accurate staging. Moreover, standard lymphadenectomies may not harbor the sentinel node in a proportion of cases, resulting in an under-staging that does not occur with sentinel node procedures.¹⁷ Sentinel nodes can be reliably identified, using the combination of scintigraphic lymphatic mapping, radioactive probe guided surgery and confirmation of these by passage from the tumor (injection) site of patent blue to the sentinel node. Further confirmation on the results available and a careful widespread introduction of this technique should result in a marked reduction in lymphadenectomies and to associated morbidity.

The surgical management of the regional lymph node basins has been revolutionized after the development and introduction of sentinel lymphadenectomy. Advances in both surgical technique and pathologic analysis have combined to make sentinel lymphadenectomy a powerful tool. The data strongly support the notion that histological examination of the first nodes to receive primary lymphatic drainage, the SLNs, accurately reflects the overall status of the regional nodal basin. The SLNs are therefore able to identify those patients who are most likely to benefit from completion lymphadenectomy while sparing patients with negative nodes the morbidity of an additional surgical procedure.

The advent of the SLN technique has helped ushers in a new era of molecular pathologic analysis of nodal tissue. Rather than traditional routine histological examination, the SLN is now subjected to more extensive pathologic examination with step sectioning, immunohistochemistry, and RT-PCR. In the future, cDNA microarray technology will make possible a genomic approach, potentially allowing the identification of genetic markers or expression profiles that might be important for diagnosis, prognosis, and even therapy.¹⁸ Furthermore, the clinical significance of detecting a single cluster of cells by immunohistochemistry or submicroscopic disease found by PCR remains unclear. Treatment of such minimal disease may represent over-treatment for many patients, because less than one fifth of patients with a positive SLN have additional tumor cells in the non-sentinel nodes removed during the completion lymphadenectomy.

Adjuvant treatment and multidisciplinary approach

Adjuvant treatment, mainly chemotherapy and radiotherapy, have undergone impressive development in the

past decades. New agents and techniques, and proper scientific evaluation of these, have resulted in improved results, more accurately defined indications for treatment, and reduced toxicity. Surgeons, who used to have sole rights to the treatment of cancer patients in the times when locoregional excision was the only effective treatment available, now share much of the management of cancer patients with medical oncologists and radiotherapists in a multidisciplinary approach. The collaboration of today's surgeons with other specialists also involves diagnosis, pre-operative preparation, and scientific efforts to optimize treatment protocols.

The discovery and use of antitumor chemotherapeutic agents for advanced cancer led to the logical development of strategies to use chemotherapy in combination with surgical resection or irradiation (or both) to reduce the incidence of local recurrence and distant metastasis, thereby improving survival. Such combinations of adjuvant therapy have been developed and now are being used effectively in a number of cancer sites, including head and neck, breast, colorectal region, ovaries, and lung (small-cell cancers). Currently, many examples demonstrate success derived from using combined therapy by reducing morbidity with increased local control and survival. Examples include breast conservation surgery and anal sphincter preservation.

Aggressive systemic chemotherapy or modern radiotherapy requires considerable support to manage such complications as poor nutrition, neutropenia, sepsis, and opportunistic infections. Many current chemotherapeutic agents cause severe toxicity and local tissue slough if extravasated from intravenous (IV) injection. The need for frequent blood sampling and IV drug administration requires a reliable venous access. Likewise, if patients are to complete their therapy successfully, long-term nutritional support via the parenteral or enteric route can be accomplished by a long-standing venous line inserted in a central vein (e.g., the superior vena cava) and brought through the skin by way of a subcutaneous tunnel to

avoid infection. The alternative is a central venous catheter attached to a subcutaneous injectable port, which can be accessed by needle either for administration of chemotherapy or for obtaining venous blood samples. With proper placement and care, the lines and ports can be used for months or years if necessary.

New adjuvant treatments are under development. Of these, immunotherapy and gene therapy are probably the most promising. What is known as immunotherapy is in fact a group of treatments aiming at an activation or support of the immune system. Several of these are now ready for clinical application. Best known are cytokine treatment (e.g., IL-2 and IFN α) aimed at support of existing immune responses (e.g., melanoma, renal cell carcinoma), active specific immunotherapy (vaccination, as in colon cancer, melanoma, renal cell carcinoma), adoptive transfer of immune effector cells (lymphokine activated killer cells, tumor infiltrating lymphocytes, as in melanoma) and infusion of monoclonal antibodies (as in breast and colon carcinoma). Many promising results have been obtained, and with the possibility of further improvement, widespread application can be anticipated in the years to come. Undoubtedly, cancer remains the area of greatest activity for gene therapy.¹⁹ Various options exist, including the introduction of cytokine genes, genes that render target cells susceptible to drugs, restoration of normal tumor suppressor gene function, or to correct the overexpression of tumorigenic mutated genes.

CONCLUSION

The role of surgeons in modern cancer management has continued to evolve from heroic and radical operations to remove extensive tumors to an integrated approach combining a variety of cancer treatment modalities: surgery, radiotherapy, and chemotherapy. Of course, the best opportunity for cure is sought while reducing associated morbidity and mortality. Based on extended knowledge of tumor biology and other basic sciences, the heritage from the past has been developed further and technological innovations integrated, usually after thorough scientific evaluation. All these changes combined represent an impressive leap forward: loco-regional control rates have improved, treatment related morbidity and mutilation have been limited. Together with the advent of adjuvant therapies, patients' chances of survival have improved. Facing the increasing load of oncology patients associated with our aging populations, it is a challenge further to improve the standard of patient care by multidisciplinary approaches in which surgical oncology remains an integrated part (Table 1). It is important to realize that the real key to reducing mortality from cancer lies in prevention and early detection. Involved surgeons should be active participants in these and other cancer control efforts to reduce morbidity and mortality from cancer.

TABLE 1. Responsibilities of surgical oncologist.

1. To be involved in adjuvant and neo-adjuvant treatment protocol in solid tumors using chemo-, radio-, immuno- and hormonal therapy.
2. To be involved in radio-, chemo-, immuno- and hormonal therapy in advanced tumors if surgery is part of the standards for each of them (e.g. neo-adjuvant therapy in following subspecialties; general surgery, vascular surgery, advanced tumors).
3. To have knowledge of regional chemotherapy (e.g. liver metastases, peritoneal carcinomatosis, melanoma and soft tissue tumors of the extremities).
4. To take part in the organization of interdisciplinary oncological consultation with other specialties (e.g. pathology, medical oncology and radiation oncology).
5. To be responsible for adherence to treatment protocol.
6. To take a leading role regarding surgical oncology among general surgeons who are partly engaged in this disease.
7. Tumor prevention.
8. Tumor follow-up program.
9. To translate new concepts from research into clinical practice, whether or not combined with surgical procedures (collaboration with basic researchers in relevant fields, aimed at the use of biological, immunological, molecular therapies and molecular genetics).

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