Biological basis and indications for cytoreductive surgery

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DEFINITION

Surgery, as part of the multimodal treatment of cancer, may be performed at various times during the course of the disease. In most cases, surgery is the first step, whether it is for diagnostic or staging purposes or as the initial therapeutic measure. As a *radical* curative measure, the surgeon performs complete resection of the tumour or of the organ in which the tumour is found, together with the regional lymph nodes in the area of lymphatic drainage towards which the tumour cells could theoretically have emigrated.

Therefore, according to this criterion, the concept of *cytoreductive surgery*, considered from a strictly theoretical point of view, should be applied to non-radical surgical resections of tumours which develop at some time during treatment of the cancer, but for the purpose of reducing the tumour burden and removing at least 90%-95% of the tumour. It involves surgical rescue in the case of tumours that are susceptible to other types of treatment.

Consequently, according to this criterion, *previously programmed surgical resection* as part of a combined therapy, as occurs in some locally advanced carcinomas such as those of the breast and rectum, can not be included in the definition of cytoreduction. In these cases, physical or medical treatment precedes surgery, either because the tumour is not operable or because the patients form part of a clinical trial or study, one of the objectives of which is to perform surgery that is least mutilating and allows better conservation of function.

Surgery of the metastases of tumours which have no possibility of responding to medical treatment, such as sarcomas of soft tissues are not included in this concept.

Surgery that is *palliative* in nature and performed to resolve urgent life threatening complications, such as obstructions or perforations of the digestive system or serious haemorrhages, is not included either, even though it involves eliminating a greater or lesser amount of the tumour. Operations carried out to achieve *improved local hygiene* are also palliative: for example, the removal of external cancers, metastastic or not, that cause a poor quality of life because they are ulcerated, bleeding or malodorous. Likewise, resections of primary or metastastic tumours that produce hormones or vasoactive peptides such as carcinoids or vipomas like glucagonomas, insulinomas, etc., causing associated symptoms are palliative. According to this conceptual overlapping, extirpation of a brain metastasis is also palliative surgery, since the prognosis is poor if it is not removed.

Surgery of *local recurrences* is considered independently, since it may be considered radical rescue, for example in relapses in cancer of the breast or even of the rectum; palliative, as in the case of digestive anastomatic recurrences with extra-abdominal metastases, to re-establish the continuity of the digestive tract, and it may also be cytoreductive in cases of local relapses following abdominoperineal amputations with few hepatic metastases.

COMMENTS ON THE CONCEPT OF SURGICAL RADICALITY

In conceptual terms, the impossibility of total surgical resection of a tumour means that it is incurable, since it leaves a part of the tumour which is difficult to control with other types of therapy. Therefore, complete surgical resection would be equivalent to complete cure. However, follow-up of patients with an apparently local disease over a period of years does not support this hypothesis. Therefore, when an intervention is defined as radical according to traditional surgical criteria, the following points should always be taken into account:

1) The information obtained in recent years regarding the patterns of tumour growth has invalidated Halsted's theory of neoplastic dissemination based on a mainly scheme of lymph nodes stations. The alternative hypothesis considers cancer to be a systemic disease from the beginning in which the body as the host is aware from the very first moment of the existence of the tumour as the guest. Even though there is initially a negative study of tumour spread in a pa-

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tient with an apparently localized tumour and in the absence of regional gland infiltration, the mean survival of patients after five years is 75%. In other words, no local treatment, no matter how radical it is considered to be, will cure all the patients. It is likely that certain biological characteristics of the tumour itself, together with the normal immunocompetence of the individual patient, may play an important part in achieving some of the excellent results obtained in patients treated with surgery only.

Therefore the concept of surgical radicality should be qualified in that it implies that the surgeon has performed a complete macroscopic resection of the tumour and that, basically although paradoxically following Halsted's scheme, it also includes extirpation of the regional lymph nodes. Even the concept of sentinel node has this connotation: the exhaustive, selective study of the first station of the lymphatic drainage of the tumour.

2) The vascular blood and lymphatic systems are closely related, and so the cells may reach the blood system via lymphatic-venous communications. The regional lymph nodes do not form an effective barrier against spread of the tumour and the tumour cells cross them and appear in the efferent lymph from the gland.

3) Tumours have a Gompertz's-like exponential growth curve, with a pre-clinical phase that lasts between 3 and 10 years. According to biological studies, growth is greater when the tumour is smaller, and it takes only a short time for it to double in size. For this reason, tumours are very susceptible to drugs that interfere with cell development. The growth curve falls as the size increases, so the number of cells in the process of dividing is progressively smaller, which means less susceptibility to certain cytotoxic drugs. This is especially significant in most solid tumours over 2 cm in diameter, as opposed to what is seen in the case of leukaemia and lymphomas.

4) During development and when the tumour consists of at least 10 9 cells, mechanisms of angiogenesis stimulate its development and the possibility of its wide vascular dissemination. For this reason, the obligatory pass through the regional lymph nodes does not always occur. Many tumour cells pass into the blood but they are not clonogenic and do not survive. Others, however, are clonogenic and remain stationed in different parts of the organism which are difficult to locate or have a relative degree of hypoxia. Therefore, if they are not destroyed by medical treatment, they may be activated to start mitosis at any time, giving rise to micrometastases with a potential similar to that of the primary tumour. These cell deposits are responsible for the development of metastases at a given moment, which may or may not coincide with surgery, and indeed threaten survival since they are the main obstacle to the patient being cured.

5) However, although there are still many uncertainties concerning how micrometastases progress, it seems that their rate of growth is greater than that of the original tumour and in some cases they tend to increase in size when the primary tumour is removed.

6) Chemotherapy has a first order kinetics effect and so destroys a constant fraction of cells rather than a specific number. Its effectiveness is in inverse proportion to the tumour burden and its efficacy depends on the number of cells that are actively dividing. In solid tumours the number of cells in the G0 phase is directly proportional to the size of the tumour, and the cellular diversity of the tumour is also a factor affecting drug resistance. The objective is to use drugs when there is a small number of more actively dividing cells and the tumour focus has optimum conditions of local blood perfusion.

CYTOREDUCTIVE SURGERY

With these generally accepted concepts on which to base the guidelines for oncological treatment, cytoreductive surgery may be defined as surgery that intentionally performs uncomplete resection of the tumour and relies on the possibilities of other, mainly medical, types of treatment. It should be performed only in tumours in which chemotherapy is likely to be effective since they have been shown to be susceptible to such therapy. It is a type of surgery which is used together with other treatments that in other circumstances, following surgery defined as radical, would be complementary or adjuvant. Given that the small size or mass of a tumour is a favourable factor for elimination of its remains, due to its susceptibility to drugs, it is reasonable to establish a surgical strategy with this object in mind.

However, according to the basic criteria for development and dissemination of tumours, it would not be an exaggeration to consider all cancer surgery as cytoreductive. Likewise, other treatments could be defined as medial or radiotherapeutic reduction since, as part of the multimodal sequence of oncological treatment, they all attempt to eliminate the tumour burden as much as possible. Surgery is used to deal with macroscopic tumours, which are less susceptible to chemotherapy, radiotherapy, and the other treatments that attempt to eliminate the micrometastases that may well prove fatal.

In this type of intervention, it is only to be expected that there may be greater *postsurgical morbidity*, since surgery is performed in most cases on patients who have previously undergone oncolytic treatment, *already* been operated on and whose body weight and immunological state has deteriorated. Therefore, local complications such as fistulas or dehiscence of sutures and general complications such as embolisms or infections are more common.

Thus, cytoreduction may be considered optimum when it eliminates all the macroscopic disease, leaving only nodules of less than 1 cm, and results in the possibility of increasing survival by 20% after 3 years; whereas it is less than optimum when the remaining tumour is greater than this.

Based on the chemo-susceptibility, only *epithelial carcinomas of the ovaries* are candidates for this type of surgery nowadays. In these cases, following histological confirmation, even on the first laparotomy, *primary cytoreduction* should be performed with the greatest debulking possible. After a varying period of chemotherapy, usually 3 cycles, when the debulking is incomplete, *interval surgery* is performed for cytoreduction. Indications for surgery are stages III-IV, considering each case individually when there is pleural disease or metastases of more than 1 g in places in which surgical resection is impossible. Criteria for inclusion also take into account the number of peritoneal metastases.

The efficacy of treatments nowadays means that surgery to remove the residual mass of *lymphomas, especially in the case of Hodgkin's disease and germ cell tumours*, is rarely performed, as opposed to what happened formerly. In any event, this type of intervention is performed in order to determine the nature of the tumour, which, in addition to being an indication of whether or not to proceed with treatment, indicates the prognosis. However, nowadays most cases are treated by interventional radiology.

With the introduction of new instrumental techniques (mechanical sutures, auto-sutures, laparoscopic surgery, ultrasound, etc.), surgery for *metastasectomies* has improved survival in patients with tumours susceptible to chemotherapy, due to the introduction of new cytolytic drugs and monoclonal antibodies. This type of surgery, but for different reasons, is being used in cytoreduction because it eliminates a large amount of the measurable tumour burden. This occurs in particular in hepatic metastases in which, although only 10%-20% of patients are candidates for surgical resection, when removal is potentially curative, survival after five years varies between 20% and 40%, with a postoperative mortality of less than 5%. In the case of pulmonary metastases, less than 2% of the patients are candidates for surgery and when resection is complete, survival can also reach 35% with a morbidity of 10%-20%. The indications for surgery in both cases are the existence of unilobular disease, less than four tumours and a diameter of less than 10 cm.

Unfavourable prognostic factors are the number of tumours, a size of less than 5 cm, bilaterality or involvement of more than one lobe, short period of time free of disease between surgery and metastases, and high serum level of tumour markers.

TABLE 1. **Cytoreductive surgery**

Indications	
Absolute:	
Epithelial ovarian	
Relative:	
Colorectal	
Ovarian	
Renal	
Thyroid	
Melanomas	
Used with other techniques	
Local recurrences	
Metastasectomies	
Peritonectomies	
Palliative	

Peritonectomy in combination with intraperitoneal hyperthermic chemotherapy may also be considered a cytoreductive technique. This technique is already being developped; and is only being performed by specialised surgeons and results in significant morbidity. Indications for this type of surgery are peritoneal mesotheliomas, recurrent ovarian cancer, especially if there is a long period of time free of disease, and colorectal and appendix carcinomas. Other circumstances, such as perforation of the tumour or palliation of ascites should be assessed on an individual basis.

Therefore, with the concept of cytoreduction clearly defined, it can be said that this surgical definition may also be applied to various techniques performed in oncological surgery (table 1), such as resection of metastases, local recurrences, regional disseminations, etc., provided that the tumours treated by these means are likely to be susceptible to medical oncological treatment.

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