

REVIEW

CURRENT THERAPEUTIC STRATEGIES IN APPROACHING PELVIC LATERAL ADENOPATHY IN RECTAL CANCER

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SUMMARY

Introduction: Rectal cancer is still an important morbidity and mortality cause in industrialized countries. The multi-disciplinary management requires continuous improvement in terms of investigative procedures and therapeutic strategies. The surgical treatment, either anterior resection or abdominal-perineal resection with total mesorectum excision (TME) represents the "gold standard" of the therapeutic algorithm as it is the main method intended to achieve oncological radicalness. Both surgical resection with TME and the neo-adjuvant and adjuvant treatment strategies crucially contribute to the decrease of local relapses and possibly to the control of systemic disseminations thus improving survival. The pelvic lateral adenopathy detected in a significant number of patients determines local relapse and the survival of the patient with rectal neoplasm. Within the surgical treatment of rectal cancer, the dissection of the lymph nodes of the lateral pelvic compartment with or without neo-adjuvant chemoradiotherapy is currently a controversial subject.

Materials and methods: In carrying out this paperwork, publications from 2010-2015 were analyzed; these publications contain significant data, well supported by specialty studies regarding the therapeutic attitude towards pelvic lateral lymphadenopathy in rectal cancer. At the same time, it was also analyzed the conformity of references related to the proposed therapeutic strategies that lead to the improvement of oncological results as well as the reproducibility of the used methods.

Results: The studies provide exact data regarding the importance of pelvic lateral adenopathy in the evolution and prognosis of the patient suffering from rectal neoplasm. It is also highlighted the favorable effect of LPLD – lateral pelvic lymph node dissection in improving the survival rate even under the conditions of a significant associated morbidity. Assessment by MRI (magnetic resonance imaging) of the lateral pelvic compartment is necessary in order to detect adenopathies at risk correlated with disseminated disease but also for setting up the therapeutic algorithm. The imagistic assessment of pelvic lateral lymph nodes is poor

RÉSUMÉ

Stratégies thérapeutiques courantes dans l'approche de l'adénopathie latérale pelvienne en cas de cancer rectal

Introduction: Le cancer du rectum reste une cause majeure de morbidité et de mortalité dans les pays industrialisés. La gestion pluridisciplinaire nécessite une amélioration constante en termes de méthodes d'investigation et de stratégies thérapeutiques. Le traitement chirurgical, la résection antérieure ou celle abdomino-périnéale avec l'excision totale du mésorectum (ETM) représente l'algorithme thérapeutique «le standard d'or», étant la principale méthode à intention radicale d'oncologie. Les deux résections chirurgicales avec ETM et les stratégies de traitement néoadjuvant et adjuvant contribuent de manière décisive à réduire la récurrence locale et au contrôle de la propagation systémique, améliorant ainsi la survie. L'adénopathie pelvienne latérale dépistée à un nombre significatif de patients, conditionne la récurrence locale et la survie du patient avec un cancer du rectum. Dans le traitement chirurgical du cancer du rectum, la dissection de compartiment ganglionnaire pelvien latéral, avec ou sans la radiochimiothérapie néoadjuvante est actuellement un sujet controversé.

Matériel et méthode: Afin de rédiger ce travail ont été évaluées les publications entre 2010-2015, présentant des données importantes appuyées par les études spécialisées, sur l'approche thérapeutique de l'adénopathie pelvienne latérale du cancer du rectum. Ont été analysés dans le même temps les rapports de conformité des stratégies thérapeutiques suggérées, qui ont conduit à l'amélioration des résultats oncologiques et à la reproductibilité des méthodes utilisées.

Résultat de la recherche: Les études fournissent des informations précises quant à l'importance de l'adénopathie pelvienne latérale dans l'évolution et le pronostic du patient atteint d'un néoplasme rectal. Il est aussi souligné l'effet favorable, de la dissection ganglionnaire pelvienne latérale (LPLD – lateral pelvic lymph node dissection) dans l'amélioration de la survie, même dans des conditions d'une importante morbidité associée. L'évaluation par IRM (imagerie par résonance magnétique) du compartiment

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following neo-adjuvant chemoradiotherapy (CRT); in these conditions, some authors recommend LPLD with a prophylactic approach.

Conclusions: After reviewing the specialized literature and the evaluation of the applicability of proposed treatments, a lack of general agreement is found, regarding the therapeutic attitude towards pelvic lateral adenopathy in rectal cancer. In Europe and the USA, the lateral pelvic neoplastic determination from the rectal neoplasm is classified as system dissemination although the associated prognosis and incidence are similar with those reported in Japan where it is considered as a regional lymph node metastasis. The post-therapeutic morbidity associated with LPLD calls for a better selection of patients as well as for the improvement of the nerve preservation techniques. In order to lay down standardized recommendations, additional studies are necessary in order to carry out a highly accurate pre-operative assessment of the disease stage and to estimate both comparatively and in an associated form the therapeutic strategies: CRT and/or LPLD.

Key words: rectal cancer, lateral pelvic adenopathy, LPLD, neo-adjuvant treatment, CRT, MRI.

INTRODUCTION

Colorectal cancer is one of the most frequent neoplasms, out of which 40% is represented by rectal cancer [1]. By implementing screening programs and by modifying the risk factors, in the past 20 years, it appears that the absolute and relative number of patients has decreased. However, the rectal neoplasm remains an important issue of public healthcare and one of the main mortality causes even with the progress recorded in the last decades in the multidisciplinary management of this neoplasm.

The treatment of rectal cancer continuously evolved in the last years and currently it is a curable, complex multimodality therapy with encouraging and functional oncological results.

The surgical treatment, defined as anterior resection or abdominal-perineal resection with TME, continues to be the main therapeutic method intended to achieve an oncological radicalness in most of the cases.

For rectal malign tumors stage II or III, the current guidelines recommend neo-adjuvant CRT treatment associated with surgical resection with TME without lymphadenectomy of the lateral pelvic compartment. Depending on the histopathological result, afterwards adjuvant chemotherapeutic treatment can be added to the therapeutic protocol [2].

According to the histopathological reports, there is a percentage of 10%-20% of patients with low rectal cancer with pelvic lateral lymphadenopathy; these patients have a 40% survival rate, after 5 years, following LPLD [3].

MATERIALS AND METHODS

In carrying out this paperwork, articles and results of

pelvien latéral est nécessaire pour dépister les adénopathies à risque, en corrélation avec la maladie disséminée, ainsi que pour déterminer l'algorithme thérapeutique. Après la radiochimiothérapie (RCT) néoadjuvante, l'évaluation de l'imagerie des ganglions lymphatiques pelviens latéraux est pauvre; dans ces conditions, certains auteurs recommandent LPLD avec une approche prophylactique.

Conclusions: Après avoir fait une revue de la littérature spécialisée et évalué l'applicabilité des traitements proposés, on trouve l'absence de consensus sur l'attitude thérapeutique vers l'adénopathie latérale pelvienne dans le cancer du rectum. En Europe et en Amérique, la détermination néoplasique du cancer du rectum pelvien latéral est qualifié comme une diffusion systémique, bien que l'incidence et le pronostic soient similaires à ceux rapportés au Japon, où elle est considérée comme une métastase ganglionnaire régionale. La morbidité post-thérapeutique associée au LPLD exige une meilleure sélection des patients, et l'amélioration des techniques de la préservation des nerfs. Pour formuler les recommandations normalisées, d'autres études sont nécessaires pour atteindre une grande précision du stade préopératoire de la maladie et pour évaluer comparativement et sous forme associée les stratégies thérapeutiques: RCT et / ou LPLD.

Mots clés: cancer du rectum, adénopathie latérale pelvienne, LPLD, traitement néoadjuvant, RCT, IRM

studies published in the last 10 years were analyzed, by accessing references of Pubmed, Cochrane, Embase databases. Scientific paperwork available between 2005 and 2015 was reviewed, particularly those relevant for the chosen topic, through a systematic research in the specialty literature.

The keywords used in order to restrain the search area were: rectal cancer, lateral pelvic adenopathy, LPLD, neo-adjuvant treatment, CRT, MRI.

Anatomic notions

The lymphatic dissemination way is the most common form of rectal cancer extension and it is carried out by permeation or embolization. The lymphatic invasion usually occurs in anatomic sequences, first the mesorectal lymph nodes are invaded and then the largest part of the lymph is drained in the upper rectal and lower mesenteric lymph nodes. In advanced forms of neoplastic diseases with lymph node tumoral invasion, the proximal lymphatic current can be blocked and thus a retrograde lymphatic dissemination is created with the invasion of the lateral and inguinal pelvic lymph nodes [4].

Low rectal cancers of less than 6 cm from the anocutaneous line can drain the lymph as well as along the lower and medium rectal vessels in the lateral pelvic lymph nodes [5]. The invasion of inguinal lymph nodes is rare and it is carried out in the low rectal cancer invading the dentate line [6].

At the level of the lateral pelvis, Canessa et al. identified by dissection an average number of 28 lymph nodes, classified in three groups, presacral, hypogastric and obturator, with sizes between 2 mm and 13 mm. Most of hypogastric lymph nodes were found above the lower hypogastric plexus; in the obturator fossa the highest number of lymph nodes was found out. Their excision during extended lymphadenectomy in surgical

treatment of rectal cancer implies the careful dissection of all the lateral-pelvic vascular-nervous elements [7].

General data

Regarding the evolution of the patient with rectal neoplasm, the regional lymphatic dissemination represents one of the most important independent prognosis factors correlated with survival. In 1958, Dukes and Bussey reported a histopathological incidence of lymph node related determinations of 51.9% of the total of 1732 patients subject to surgical resection for rectal cancer. The invasion of loco-regional lymph nodes determines survival at 5 years as it is of 32% for patients with positive lymph nodes compared with 83% in patients without lymph node infiltration according to the data of the same study [8].

The number of tumoral invaded lymph nodes is also important regarding the evolution and survival of the patient suffering from rectal cancer. The literature data are clear in this regard, the survival at 5 years in cases of more than 10 tumoral lymph nodes dramatically decreases independently of the degree of tumoral invasion at the level of the rectal wall directly proportional with the number of invaded lymph nodes: from 63% in case of a sole lymph node metastasis to 2% in case of more than 10 lymph nodes which are neoplastically invaded [8].

Regarding the imagistic assessment of loco-regional lymph nodes, in the specialty literature there is a great variety of reports irrespectively of the used imaging method and the results are disappointing compared with the accuracy of the tumoral extension determination [9].

The trans-rectal ultrasonography (ERUS) can provide accurate results in 61-83% of cases, better than clinical examination or by computerized tomography (CR) and comparable with those obtained by phased array MRI and endorectal coil MRI [10].

The false positive results may occur due to the peritumoral inflammatory reactive lymph nodes or the cross-section image of perirectal blood vessels. Underestimation of the lymph node related involvement can also occur. The probe may not detect the lymph nodes of the pelvic lateral compartment or of the proximal mesorectum and the lymph node micrometastases can be difficult to evaluate [11].

Regarding the use of MRI, the studies reported accuracy between 57-85% in detecting the lymph node tumoral invasion [12], [13]. A meta-analysis of 90 studies showed a MRI specificity and sensitivity in detecting risk adenopathy of 76%, respectively 66% [14].

The T2 sequence images, in oblique axial plane with increased resolution allow the morphological evaluation of the pelvic lymph nodes; thus the accuracy increases regarding their diagnosis as benign or malignant, mainly since the size as a diagnostic criteria proved to have a limited value. The lymph node heterogeneous signal as well as the spiculated appearance and the irregular edges are suggestive for malignancy. The inhomogeneous signal is correlated with necrosis, tumoral deposit or extra-cellular mucin. The reactive or inflammatory adenopathies instead are characterized by regular, well-defined edges with homogeneous signal [15].

However, what limits this evaluation is the significantly long learning curve, as Brown et al. mentioned [16].

By adding DW-MRI (MRI with diffusion sequence) to the standard MRI evaluation, we notice an increase of the sensitivity and specificity of the detection of lymph node metastases to 93%, respectively 81% [17].

The preliminary studies recommend the use of USPIO (ultrasmall superparamagnetic iron oxide), a contrast substance with lymph node tropism that can improve the accuracy of diagnosing lymph node metastases. The T2 sequence images are obtained after 24 hours after USPIO administration, the areas with a low signal are considered normal while a lack of signal shows a lymph node tumoral invasion. The sensitivity and specificity were reported to be 63%, respectively 93% with USPIO, however, nowadays, it is not recommended in the clinical practice as it is not yet approved by the FDA (Food and Drug Administration) [18].

In the pre-operative staging of rectal cancer, the use of MRI with FOV (field of view) of 16 cm allows the evaluation of the mesorectum and of the lateral pelvic compartment. This makes possible to identify patients with a risk of residual disease after the TME surgical resection [15]. The MRI evaluation of the lateral pelvic compartment is important in order to detect risk tumoral adenopathies correlated with disseminated diseases and decrease of survival. Their frequency is higher in case of aggressive tumors located in the lower rectum [19].

The neo-adjuvant CRT treatment frequently decreases the number and the size of loco-regional lymph nodes in rectal cancer. CRT can also determine the atrophy of the lymphatic tissues which decreases the performance of the lymph node dissection. The number of lymph nodes sampled after neo-adjuvant therapy and surgical resection is in average lower than the one obtained only after surgical treatment [20].

The N re-staging by post-treatment neo-adjuvant MRI was evaluated in a recent study and the accuracy of the imagistic method was reported to be 88% with a positive predictive value of 80% [21].

The present guidelines recommend as standardized treatment for II/III stage rectal cancer neo-adjuvant therapy and anterior resection or abdominal-perineal resection with TME without dissection of the lateral pelvic lymph nodes (LPLD – lateral pelvic lymph node dissection). Within the TNM staging (7), proposed by AJCC (American Joint Committee on Cancer) in 2010, metastization at the level of all these lymph nodes is not clearly defined and UICC (Union for International Cancer Control) considers it a distant metastasis [22].

However, despite these recommendations, in Japan, the extended lateral lymphadenectomy together with TME continues to represent the standard surgical treatment of rectal cancer and the secondary determinations at this level are considered only regional lymph node metastases [3]. The dissection of lymph nodes can be therapeutically carried out when the tumoral invasion is obvious or prophylactically although this represents a controversy [23].

According to the Japanese classification of colorectal

cancer, the lymphadenectomy of the lateral pelvic compartment added to the TME surgical treatment of rectal cancer implies the dissection of internal iliac, common iliac, external iliac and obturator lymph nodes [24].

The first one to describe lateral lymphatic dissemination in rectal cancer was Gerota in 1895 [25]. Afterwards, many studies confirmed and described the lymph nodes around the internal iliac arteries and at the level of the obturator space [26], [27]. Based on these descriptions, a bilaterally extended lateral pelvic lymphadenectomy was attempted in order to improve the local control. However, it was obtained a higher rate of complications without a real benefit regarding survival [28].

In Japan, beginning with the 1970s, the lateral pelvic lymphadenectomy became a routine practice in the surgical treatment of lower rectal cancer (located below the peritoneal reflection according to Japanese guidelines) and continued the publication of works confirming the decrease of local recurrence rate and the improvement of survival [29]. However, the procedure associates an increased morbidity by harming the autonomous nerve plexus, increases the duration of the surgical intervention and blood loss [30]. It is absolutely necessary the refinement of the surgical technique in order to get a good local control and, at the same time, a good quality of life [31].

DISCUSSIONS

The reasons for which LPLD is indicated in T3/T4 rectal cancer, located at the level of below the peritoneal reflection, are supported by many studies and meta-analyses; it is true that most of them are coming from Japanese authors as it is the current recommendation of the Japanese guidelines [32].

The percentage of metastazation at the level of lateral pelvic lymph nodes in lower rectal cancer is not negligible as it is about 10%-20% [33]. Akiyoshi et al. found out about 15% of the cases of lateral pelvic tumoral adenopathies [3] and Ueo et al. proved the variation of this percentage depending on the tumor location: for tumors located up to 2 cm compared to the anocutaneous line – 42% and for tumors located between 6 and 8 cm compared to the anocutaneous line – 10.5% [19].

The data resulted from a multi-center study that investigated 2916 patients with rectal neoplasm showed a significant increase of local recurrence associated with: T3/T4 stage, lower rectal tumors, poorly differentiated adenocarcinomas or lateral pelvic lymph node secondary determinations as the latter were identified in 20% of the cases [34].

Kusters et al. also proved that local recurrence in rectal cancer can occur because of lateral pelvic adenopathies [35].

Also, Kim et al. showed that the metastazation at the level of lateral pelvic lymph nodes represented a major cause of pelvic relapse in low rectal cancer [36].

On the other hand, survival at 5 years is around 40% in patients with lateral pelvic lymph node determinations to which LPLD is performed [3].

The possibility of tumoral involvement of the lateral pelvic lymph nodes is high in case of: poorly differentiated

tumors larger than 4 cm with present lymphovascular invasion and a high number of mesorectal adenopathies, tumors located distal to the peritoneal reflection or in female sex [37].

If there is a consensus in the therapeutic guidelines regarding the recommendation of LPLD in cases suspected of metastatic adenopathy, this is not the case regarding the possibility of prophylactic approach of the lateral pelvic lymph node compartment.

Although one study published promising data regarding CT accuracy in evaluating adenopathies in low rectal cancer (sensitivity and specificity of 95%, respectively 94%), the imagistic accuracy in detecting metastases at the level of the lateral pelvic compartment is far from being acceptable and it is the reason why some Japanese authors recommend LPLD even with a prophylactic intent [38].

The aim of the JCOGO0212 multi-center study, currently ongoing, which comparatively analyzes the effect of TME surgical resection with or without LPLD in patients with II/III stage rectal tumors, considered not to have lateral pelvic adenopathies evaluated by CR or MRI, is to clarify the indications for prophylactic lateral lymph node dissection [23].

The difference between therapeutic and prophylactic LPLD is referring not only to indications (with or without clinical suspicion of metastatic adenopathy) but also to the resection procedure: in case of therapeutic excision, the internal, external, common, obturator, presacral and sacral iliac lymph nodes are dissected (these latter groups only if they are increased in volume) but also the uni/bilateral autonomous nerve plexus, depending on the location of the metastatic area. The prophylactic LPLD does not include the presacral and sacral lymph nodes or the autonomous nerve plexus [23].

In Europe and North America, however, the general approach is to treat the lateral pelvic adenopathies by neo-adjuvant CRT due to the high morbidity associated with the LPLD intervention but also due to the fact that this type of metastazation is considered a systemic determination despite the data proving an incidence and a prognosis of the presence of lateral pelvic adenopathy similar in Japan as well as in Western countries [39].

There is controversy related to the staging of lateral pelvic adenopathy as M1 systemic disease or as loco-regional lymph node metastasis inLARC (locally advanced rectal cancer). The survival at 5 years was of 45.8% in patients on whom LPLD was performed, better than the one recorded in patients with surgically resected hepatic metastases, as Sugihara et al. proved [34]. On the other hand, the survival of patients with positive pelvic lateral lymph nodes has great variations as it is between 25% and 80%, which proves the unfavorable systemic evolutionary trend in some cases [40].

A meta-analysis of the studies published between 1965 and 2009 which included 5502 patients on whom extended lymphadenectomy or only conventional surgical resection was performed, did not find significant differences regarding the oncological advantages. However, the extended lymphadenectomy associated a higher morbidity with major urinary and sexual dysfunctions [41].

In 2015 it was published the result of a study carried out between 2005 and 2013 which included 32 patients with LARC located at the level or below the peritoneal reflection. The study comparatively analyzed the CRT treatment associated with TME and bilateral LPLD (in patients with clinically diagnosed adenopathy) versus CRT associated with TME and unilateral LPLD (carried out in the lateral pelvic compartment which is suspected of lymph node tumoral invasion) or CRT and TME (in patients without pelvic lateral lymph node metastases). No significant differences of DFS (disease free survival) or OS (overall survival) were recorded between the two groups; however, the group with bilateral LPLD recorded a high rate of post-operative complications. The imagistic determinations made before and after CRT by CT, MRI and PET offered evaluations on adenopathies in accordance with the histopathological results. The study has its limits (small number of patients, insufficient post-operative monitoring) but the results support the associated approach of CRT and limited LPLD only in cases suspected of adenopathies which were evaluated by imaging both before and after CRT treatment [42].

CONCLUSIONS

The lymph node metastasis at the level of the lateral pelvic compartment is more probable in low rectal cancer which invades the dentate line.

Currently, due to the increased morbidity of the dissection of lateral pelvic lymph nodes, the targeted pre-operative radiochemotherapeutic treatment is preferred for risk adenopathies.

In Japan, the surgical treatment of low rectal cancer, which includes a TME anterior resection associated with LPLD, is believed to improve survival and to decrease the rate of local recurrences.

The controversy persists regarding the indication of LPLD with a prophylactic approach. The results of the JCOGO0212 study will offer factual data in this regard. In the analysis published until now, the following were determined: a higher rate of post-operative complications, a longer operative time with an important blood loss in the group where TME with LPLD was performed compared with the patients belonging to the group who was surgically treated only by TME.

As surgical procedure, LPLD may associate a significant post-operative morbidity, among others by harming the autonomous nerve plexus; this is why it is necessary to have a better selection of patients, together with refinement of nerve preservation techniques.

In order to make a conclusion as recommendation, future studies will have to perform:

- A pre-operative evaluation of patients with rectal neoplasm of high accuracy in order to select the patient group for which LPLD can be taken into account;
- The precise determination of the usefulness in associating CRT and LPLD or not;
- The precise analysis and the effects of the LPLD type: therapeutic or prophylactic.

All these requirements aim for three main objectives: avoidance of overtreatment, optimal oncological outcome, quality of life.

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