Surgical Oncology 25 (2016) 411–418

Contents lists available at ScienceDirect

Surgical Oncology

journal homepage: www.elsevier.com/locate/suronc

Review

Management of para-aortic lymph node metastasis in colorectal patients: A systemic review

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ARTICLE INFO

Article history:
Received 21 July 2016
Received in revised form
25 September 2016
Accepted 30 September 2016

Keywords:
Para-aortic lymph node
Colorectal cancer
Synchronous
Metachronous

ABSTRACT

Introduction: Para-aortic lymph node (PALN) involvement occurs in up to 2% of colorectal cancer (CRC) patients. While resection for isolated hepatic and pulmonary metastases in colorectal cancer is standard practice, the role of PALN dissection (PALND) in CRC has not been established and remains a controversy. We aim to perform a systematic review of the literature to determine if extensive lymphadenectomy improves survival, and is an acceptable strategy for PALN metastasis (PALNM).
Materials and methods: A systematic search of PubMed and Embase databases for studies reporting on patients with isolated PALNM in CRC was performed. Studies including patients with synchronous and metachronous PALN were included, and studies including patients with other metastases were excluded.
Results: Eighteen retrospective, single-centre studies were included in the final analysis. The reported incidence of isolated PALNM ranged from 1.3 to 1.7%. A total of 370 patients with PALNM were evaluated, of which 145 had synchronous, and 225 had metachronous PALNM. For synchronous PALNM, the 5-year overall survival (OS) after metastatectomy, ranged from 22.7% to 33.9%. For metachronous PALNM, the 5-year OS ranged from 15 to 60%; median OS was 34–40 months in the PALND versus 3–14 months for patients who did not undergo PALND. There were no reported surgery related mortalities, and overall surgical morbidity was 7.8–33%.
Conclusion: PALND for isolated PALNM from colorectal cancer can be performed with minimal morbidity and confers a survival advantage, in comparison with conventional palliative chemotherapy or chemo-radiation therapy.

Contents

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http://dx.doi.org/10.1016/j.suronc.2016.09.008
0960-7404/

1. Introduction

Para-aortic lymph node (PALN) involvement in colorectal cancer (CRC) is uncommon, with a reported incidence of less than 2% [1,2]. According to the American Joint Committee on Cancer (AJCC) [3], they represent disseminated, stage IV disease. The Japanese Society for Cancer of the Colon and Rectum (JSCCR), however, consider para-aortic lymph node metastasis (PALNM) regional, stage III disease [4,5]. With such differing views on the significance of PALNM, it is hardly surprising that management strategies have been divided [6,7].

While an aggressive surgical approach is advocated for selected patients with resectable hepatic and/or pulmonary metastasis, with reported 5-year survival rates approaching 50–70% [8–10], the optimal management for PALNM is not clearly defined. To date, several case series have reported favourable outcomes in patients who undergo PALN dissection (PALND) [1,2,11,12], however evidence is limited, and most studies are small and retrospective in nature. Furthermore, no direct comparison has been made between PALND and modern curative chemo-radiotherapy regimes.

It has been proposed that synchronous and metachronous colorectal cancer metastases have distinct tumor biologies [13]. Synchronous metastases have been associated with a more aggressive clinical picture, with patients experiencing poorer survival outcomes when compared with metachronous patients [14,15]. Most reports on PALNM however, do not differentiate between the two [1,11]. We believe that discussing their outcomes independently may shed light on their possibly distinct biologies and is crucial in the oncological management.

Given the lack of randomised trials and high quality evidence, we aim to perform a systemic review of the current literature to evaluate evidence for or against surgery in the management of PALNM in CRC. We also hope to define a management strategy for both synchronous and metachronous PALNM (s- and m-PALNM) based on the reported survival and morbidity outcomes.

2. Materials and methods

A literature search of PubMed, Ovid MEDLINE, and EMBASE databases was conducted for studies reporting on the management of PALNM in colorectal cancer, published in English from January 1958 to March 2016 (PALND for colorectal cancer was first described and published by Deddish and Stearns in 1958 [16]). The medical search headings (MeSH), 'colorectal cancer', 'para-aortic lymph nodes', 'para-aortic lymph node dissection', 'retroperitoneal lymph nodes', 'recurrence', 'synchronous' and 'metachronous metastasis' were used. Additional relevant studies were identified from the references cited in the articles identified by the database searches. This study was conducted in accordance to the PRISMA guidelines [17] (Fig. 1).

2.1. Criteria for inclusion of study

The authors identified and screened the search results for potentially eligible studies. Articles were included if they were: (1) Original articles published in English in peer-reviewed journals, (2) included CRC patients with s-PALNM identified by imaging modalities, such as computed topography (CT) or positron emission tomography (PET) scans, (3) included CRC patients with m-PALNM following primary curative surgery, and had (4) Clear documentation of patient survival and morbidity outcomes.

Articles were excluded if they: (1) were abstracts, letters, editorials, and expert opinions, (2) included CRC patients with concurrent hepatic, pulmonary, or other systemic metastasis, (3) included patients where PALND was performed prophylactically i.e. without intra-operatively detected or radiologically suspicious lymph nodes.

Studies that presented data on other distant sites of colorectal metastasis were included only if data of patients with PALNM could be isolated from other patient subgroups.

2.2. Data extraction and analysis

Data was extracted using standardised forms, which recorded patient and study characteristics, survival outcomes, post-operative morbidity and mortality when PALND was performed, and the use of neo-adjuvant and/or adjuvant chemotherapy or chemo-radiotherapy. Two distinct patient populations were identified: (1) Patients with synchronous s-PALNM) and (2) Patients with m-PALNM. Given their inherent differences, the 2 groups were analysed and outcomes determined independently.

In both 'synchronous' and 'metachronous' groups, comparison was made between patients who received curative surgery versus no surgery. In the non-surgical group, patients may have received either chemotherapy, chemo-radiotherapy or were managed conservatively. Survival and morbidity outcomes were analysed.

All studies were assessed for their level of evidence using the Oxford Centre for Evidence-Based Medicine Levels of Evidence table [18]. The authors elected to perform a descriptive review of the

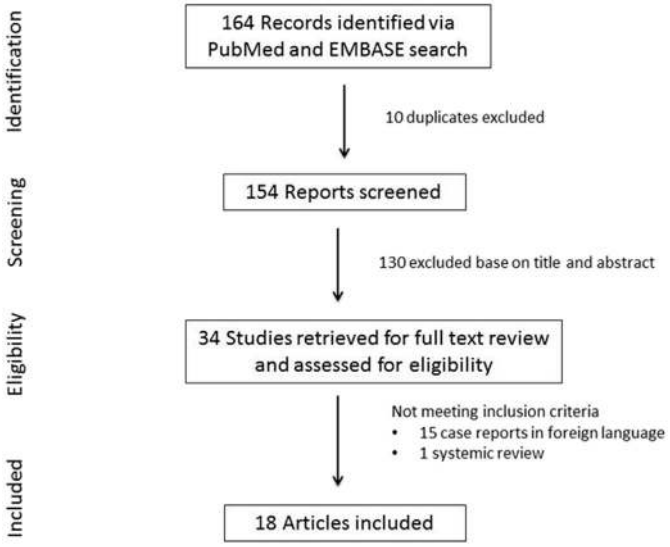

Fig. 1. Flow diagram of selection of eligible studies.

data as opposed to a meta-analysis due to the heterogeneity of the studies assessed.

3. Results

The search identified 34 relevant articles published between 1998 and 2015. All studies were retrospective cohort studies or case series. Fifteen case reports available only in Japanese as well as one systemic review were excluded. Eighteen articles were included in our final analysis.

3.1. Synchronous PALNM (s-PALNM)

Five studies addressed the management of CRC patients with s-PALNM: 4 discussed the role of surgery [19–22] while 1 evaluated non-surgical treatment [23]. All surgery was performed only after suspicious metastatic PALNs were detected either radiologically or intra-operatively, and was with curative intent.

3.2. Metachronous PALNM (m-PALNM)

Eleven studies addressed patients with m-PALNM: 6 reported on the role of surgery [2,6,24–26] while 5 described non-surgical treatment [27–31]. In the former group, 2 were cohort studies that compared the outcomes of surgical versus non-surgical management [2,12]. The remaining 4 case series reported on colorectal recurrences in both local-regional and distant sites [6,24–26]; we extracted only data pertaining to para-aortic nodal recurrences where possible. In the non-surgical group, 3 case series and 2 case reports described the outcomes of curative chemo-radiation therapy in m-PALNM patients.

Two studies reported on s- and m-PALNM collectively: Choi et al. [1] described 24 patients with isolated PALNM, of whom 19 had synchronous and 5 metachronous disease. Gagniere et al. [11] retrospectively analysed 25 patients who underwent radical retroperitoneal lymphadenectomy for 19 patients with synchronous metastasis and 6 with metachronous disease. Survival and morbidity outcomes could not be distinguished between s- and m-groups in these 2 series and as such their outcomes were reported independently.

In total, our systemic review evaluated a total of 370 patients with CRC-related PALNM, for which 145 patients had s-PALNM and 225 patients had m-PALNM.

3.3. Outcomes of patients with synchronous PALNM

PALND was performed in 264 patients with s-PALNM (Table 1). CT and PET-CT scans were the imaging modalities used in the diagnosis of PALNM. Min (2009) [19] and Bae et al. [20] considered a lymph node to be radiologically positive if it was >0.5 cm at the short-axis diameter, had spiculated or indistinct borders, or showed a mottled heterogenic pattern on CT scan. The PALN had to lie between the left renal vein and the bilateral common iliac vessels. A hot uptake on PET or PET-CT also indicated metastatic disease. Pre-operative imaging identified 264 patients with radiologically suspicious lymph nodes, however only 118 had histologically positive PALNDM; as such the positive predictive value of pre-operative imaging was 44.7% (118/264). The mean number of positive PALN retrieved intra-operatively ranged from 1.1 to 4.4.

PALND described by all authors [19–22] involved the removal of all lymphatic tissues along the aorta, bounded superiorly by the left renal vein and inferiorly by bilateral common iliac vessels. There was no operative mortality, but reported morbidity ranged from 7.8 to 15% in 2 series [20,22] and included acute urinary retention, ileus, surgical site infections (SSI), and anastomotic leak. Morbidity and mortality data from Min (2009) et al. [19] was not included as the outcomes of lateral pelvic lymph node dissection were reported together and information of PALND could not be extracted independently. Similarly, Atsushi et al. [21] included data of 6 additional patients with 'extra-regional' but non-PALN disease. Nevertheless, morbidities in the latter 2 studies were not significantly higher (ranged from 18.8 to 20.5%).

19%–25% of patients received neoadjuvant chemoradiaton therapy prior to PALND [19,21,22]. None of the studies however reported on their institution's indications for therapy, duration of treatment, or regime used.

In the 2 larger series [19,20] involving 43 and 49 patients respectively, 5-year overall survival (OS) ranged from 22.7% to 33.9% and 5-year disease free survival (DFS) from 17.6% to 26.5%. Bae et al. [20] went on to compare survival outcomes amongst 3 patient groups: those who underwent regional lymphadenectomy versus PALND versus liver resection. Significantly better OS and DFS were found in patients who received regional lymph node dissection, while patients with s-PALNM and liver metastasis shared similar survival rates. The number of positive PALNM was identified as a prognostic factor for OS in 2 studies [21,22].

In a series of patients who underwent laparoscopic PALND, Sung et al. [22] reported a mean operating time of 192.3 min and a 3-year OS and DFS of 65.7% and 40.2% respectively.

3.4. Outcomes of patients with synchronous & metachronous PALNM

There were 2 papers that evaluated patients with s- and m-PALNM collectively (Table 2).

By comparing patients who had undergone PALND versus no

Table 1
Synchronous Para-aortic lymph node Metastasis in Colorectal cancer.

Study	Year	Design	Site of primary	No. PALND*	No. (+) PALNM#	Resection margin	Morbidity (%)	Mortality	Disease free survival	Overall survival	Adjuvant therapy (%)
Surgical management											
Min BS et al. [19]	2009	Case series	Rectum	85	43	–	–	–	5-yr 17.6%	5-yr 22.7%	–
Bae SU et al. [20]	2015	Case series	Colorectal^	129	49	Not specified	7.8%	None	5-yr 26.5%	5-yr 33.9%	CT 100%
Atsushi et al. [21]	2015	Cohort study	Colon 80% Rectum 20%	10	10	R0 100%	–	None	–	–	–
Song et al. [22]	2015	Case series	Colon 67.5% Rectum 32.5%	40	16	Not specified	15%	None	3-yr 40.2%	3-yr 65.7%	CT 100%
Non-Surgical Management											
Takenoue T [23]	1999	Case study	Rectum	1	1	NA	100%	None	–	5-yr 100%	CT 100%

Table 2
Synchronous & Metachronous Para-aortic lymph node Metastasis in Colorectal cancer.

Study	Year	Design	Site of primary	No. Cases		Resection margin	Morbidity (%)	Mortality	Disease free survival	Overall survival	Adjuvant therapy (%)
Choi et al. [1]	2010	Case control	Colon 62.5% Rectum37.5%	24	s-PALNM 19 m-PALNM 5	Not specified	25%	None	5-yr 22%	5-yr 53.4%	CT 96%
Gagnière et al. [11]	2015	Case series	Colorectal^	10	s-PALNM 7 m-PALNM 3	Not specified	Not specified	None	5-yr 51%	5-yr 56%	–

- Unable to extract data.
* Number of PALND performed.
#number of histologically proven PALNM.
^ breakdown between colon and rectum not specified.
CT: Chemotherapy.

surgery for isolated PALNM, Choi et al. [1] concluded that surgery resulted in superior survival outcomes (5-year OS was 53.4% versus 12% respectively, $p = 0.045$). A 25% morbidity rate was reported, with 3 patients suffering SSIs, 2 ileus, and 1 had excessive bleeding. In the PALND group, the presence 2 or less PALNM was found to be significantly associated with a better median survival. Median OS for patients with s-PALNM was 29 months versus 61 months in patients with m-PALNM ($p = 0.227$) after PALND.

Gagniere et al. [11] reported the outcome of PALND in a series of 25 patients: 10 with isolated PALNM and 15 with concurrent extra-PALNM. 5-year OS and DFS was 56% and 51% respectively in patients with isolated PALNM, and was 51% and 13% respectively for those with extra-PALN metastasis. There was no 90-day mortality, and morbidity outcomes for PALND alone could not be extracted as it was reported collectively with patients who had underwent metastectomy for non-PALN sites.

3.5. Outcomes of patients with metachronous PALNM

3.5.1. Surgery

Metachronous PALNM was defined as recurrence occurring >6 months following curative surgery for primary CRC. Median disease free interval (DFI) ranged from 14 to 23 months [2,12,26](Table 3A). While Shibata [2] and Razik et al. [26] reported that patients' symptoms led to the diagnosis of recurrent disease in 33–56% of patients, Min et al. [12] found all patients to be asymptomatic and an elevated serum carcinoembryonic antigen (CEA) to be the first sign of recurrence in the majority (63.2%). Radiological diagnosis of PALNM was as defined previously; routine surveillance CT scans identified up to 36.5% of m-PALNM.

Four case series evaluated the outcome of surgery for 87 m-PALNM patients with concomittant resectable local and/or distant metastasis [6,24–26]. PALND was the only operative procedure in 76 patients. Median time from the diagnosis of m-PALNM to surgery was 6 (range 0.3–38) months in one series [26], the delay was attributed to the pre-operative used of chemoradiation therapy, though isolated data on patients with only PALNM could not be obtained. Razik et al. [26] reported a morbidity rate of 52%, for which a majority (45% out of 52%) were minor Clavien-Dindo grade 1 or 2 complications [32]. Median OS for patients with isolated PALNM ranged from 44 to 53 months compared with 8–34 months in those with concomitant sites of metastasis. R0 resections as well as the absence of concomitant local recurrence were predictors of superior survival outcomes.

Shibata and Min et al. only included patients with isolated m-PALNM [2,12]. A total of 26 patients who underwent curative PALND were compared with 37 who received chemotherapy or chemo-radiation therapy. Neoadjuvant chemotherapy and radiotherapy were given to 6 and 4 (out of 20) patients respectively in Shibata's series [2]. 24% (14 patients) underwent an 'extended' resection which was defined as PALND in addition to resection of an adjacent structure or organ excluding small bowel. The kidney was the most commonly involved organ ($n = 9$). There was no perioperative mortality; morbidity ranged from 28 to 33%. A significant difference in OS favouring surgical resection was found in both series, median OS was 34–40 months in the PALND group versus 3–14 months in the non-PALND group. 56%–80% of patients suffered a 2nd recurrence despite curative PALND. In Min's series [12], distant metastasis was the predominant pattern of recurrence. A longer DFI, tumor size < 5 cm, infra-renal location of PALNM, well-differentiated primary colorectal tumor, surgical resection as well as the ability to achieve R0 resection were predictors of a favourable OS.

Table 3A
Surgery in Metachronous Para-aortic lymph node Metastasis in Colorectal cancer.

Study	Year	Design	Site of primary	No. Cases	Median DFI	Resection Margin	Morbidity (%)	Mortality	DFS	OS	Adjuvant therapy (%)
Goldberg et al. [24]	1998	Cohort study	All colon	10	–	30% R0	–	–	–	–	–
Shibata et al. [2]	2002	Case series	Colon 80% Rectum 20%	20	23 mths	75% R0 25% R1/R2	28%	None	5-yr 10%	5-yr 15%	CT 70% RT 25%
Bowne et al. [6]	2005	Case series	All colon	12	–	–	–	–	–	–	–
Min BS et al. [12]	2008	Case series	Colon 50% Rectum 50%	6	14 mths	Not specified	33%	None	Not specified	Median 34 mths	CT100%
Dumont et al. [25]	2012	Case series	Colorectal^	14	–	100% R0	Not specified	Not specified	–	–	–
Razik et al. [26]	2013	Case series	Colorectal^	40	–	82.5% R0 12.5% R1 5% R2	–	None	–	5-yr 60%	–

- Unable to extract data.
^ breakdown between colon and rectum not specified.
CT: Chemotherapy.

Table 3B
Non-Surgical management of Metachronous Para-aortic lymph node Metastasis in Colorectal cancer.

Study	Year	Design	Site of primary	No. Cases	Median DFI	Morbidity	Mortality	OS	DFS	Treatment strategy	Treatment Response
Min BS et al. [12]	2008	Case series	Colon 44% Rectum 56%	32	18 mths	Not specified	None	Median 14 mths	NA	40% Chemotherapy 37.5% Concurrent Chemo-RT 22.5% Chemotherapy, sequential RT	PD 100%
Kim MS et al. [27]	2009	Case series	All Rectal	7	21 mths	43%	None	3-yr 71.4%	–	Chemotherapy then Stereotactic body radiotherapy	CR 43% PR 57%
Yeo et al. [28]	2010	Case series	Colon 40% Rectum 60%	22	15 mths	82%	None	5-yr 36.4%	5-yr 25.6%	Curative Chemo-RT	CR 60% PR 27% SD 13%
Tomonori et al. [29]	2012	Case study	Recto-sigmoid	1	24 mths	100%	None	3y5m	2y5m	Chemo-RT and Bevacizumab	CR 100%
Yasuda S et al. [30]	2012	Case study	Colon	1	30 mths	100%	None	9yr2m	6y11m	Chemo-RT	CR 100%
Lee JS et al. [31]	2015	Cohort study	Colorectal^	52	13 mths	51.9%	None	2-yr 69.6%	2-yr 37.5%	Either: (1) Chemotherapy and upfront RT or (2) Chemotherapy and deferred RT	CR 31%

PD: Progressive disease.
CR: Complete response.
PR: Partial response.
SD: Stable disease.
– Unable to extract data.
^ breakdown between colon and rectum not specified.
CT: Chemotherapy.
RT: Radiotherapy.

3.5.2. No surgery

Several RT techniques were described in the 3 larger series (Table 3B): Kim et al. [27] evaluated the use of chemotherapy followed by stereotactic body RT (SBRT), Yeo et al. [28] administered three-dimensional conformal RT or helical tomo-therapy with concurrent chemotherapy, while Lee JS et al. [31] compared upfront versus deferred RT using conventional or short course RT. Gross tumor volume (GTV) encompassed all involved LNs observed on CT and PET-CT and was used in the assessment of disease burden. Response to treatment was evaluated using the Response Evaluation Criteria in Solid Tumours (RECIST) [33], where complete response (CR) was defined as the disappearance of all treated lesions, partial response (PR) a decrease of at least 30% in the sum of the longest diameter of the treated lesions, progressive disease (PD) an increase of at least 20% in the sum of the longest diameter of the treated lesions or the appearance of new lesions, and stable disease (SD) as neither a partial response nor progressive disease. Treatment toxicity was assessed using the Common Terminology Criteria for Adverse Events version 3.0 [34].

Median DFI ranged from 13 to 30 months. Grade 1 or 2 gastrointestinal toxicities were reported in 28.5–81.8% of patients. High grade toxicity was rare, and only one patient in Kim et al.'s series suffered a grade 4 cardiac event requiring bypass surgery [27]. Rates of CR following treatment ranged from 43 to 100%, PR 27–57%, and SD 13%. Min et al. reported progressive disease in all patients receiving chemoradiation therapy. Overall survival outcomes were also significantly worse when compared to patients who underwent surgical resection [12]. Excluding Min's series [12], median OS in the 3 larger RT series ranged from 37 to 41 months [27,28,31]. Patients who experience CR post-RT had a 5-year OS of 61.5% versus 25% in patients with PR. Re-recurrence rates ranged from 60 to 68%. Indicators of a favourable prognosis were a longer DFI, good response to chemoradiation therapy, as well as a low GTV.

4. Discussion

PALND was first described in 1950 by Dr Deddish as a modification of the Miles abdominoperineal resection (APR) in the management of rectal cancer [16]. By prophylactic dissection of lymph node-bearing tissues from the para-aortic and vena caval regions between the ureters from the duodenum down to the levator ani muscles, PALND aimed to reduce local recurrence rates, which was common despite APR [35]. However, routine PALND have since been abandoned by most western institutions in view of the increased surgical morbidity without corresponding improvements in recurrence rates and overall survival [36,37]. In the last decade, PALND has been adopted mainly for curative purposes in s- and m-PALNM. Based on the results of our systemic review, the incidences of surgical complications ranged from 7.8 to 33%, and were mainly low grade in nature. While the safety of extensive lymphadenectomy is reassuring, there remains controversy regarding the indication and survival benefits of PALND in PALNM.

In CRC patients with hepatic or pulmonary metastases, complete resection of metastases has been shown to improve survival over palliative chemotherapy [8–10]. Similarly, by comparing the outcomes of PALNM patients who received surgery versus no surgery, Shibata, Choi and Min (2008) et al. concurred that a significantly better survival was seen in the patients who received an R0 resection. Predictors of improved survival outcomes in s-PALNM patients, who underwent concurrent resection of primary tumor and PALND, were well-differentiated histology, as well as low volume (i.e less than 2 PALNM) disease. In patients with metachronous metastasis, a longer DFI was found to be associated with improved OS and DFS. With this information, we can better select for patients who may benefit from PALND.

If PALNM were to behave like liver metastases, we would expect synchronous disease to exhibit a more aggressive clinical course and poorer survival compared to metachronous PALNM. However, 5-year OS and DFS seemed to be relatively similar in both groups; ranging from 22.7% to 65.7% and 17.6%–40.2% respectively in the s-PALNM group and 15%–60% and 10%–25.6% respectively in the m-PALNM group. In Choi's series, while patients with m-PALNM showed a marginally improved median OS when compared s-PALNM (61 months versus 29 months), however this was not statistically significant.

Chemotherapy with or without radiation therapy (RT) has been used as a form of salvage therapy for patients with m-PALNM. Various chemotherapy regimens including either one or a combination of fluropyrimidines (including 5-Fluorourcil plus leucovorin, capecitabine, tegafur plus uracil), oxaliplatin, irinotecan, and

bevacizumab have been described. Radiation therapies (RT) were usually in the form of concurrent chemoradiation therapy or followed sequentially after systemic chemotherapy [12,27–31]. In earlier PALNM-related series, the role of systemic chemotherapy and/or chemo-radiotherapy was mainly palliative in nature. Median OS ranged from 14 to 37 months, and a suboptimal response with progressive disease was common [12,27]. However, in recent years, improvements in chemotherapy and radiation techniques have led to its use in PALNM with curative intent [28,31]. Yeo et al. [28] reported a 5-year OS of 36.4% with concurrent chemo- RT, which was comparable to the outcomes of surgical resection. Morbidities were limited to low grade gastrointestinal toxicities, and extensive surgery was adverted. An expert review by Albandar et al. [38] further emphasized on the role of peri-operative chemotherapy in the selection of suitable candidates for PALND as tumor regression or non-progression post chemo- or targeted therapy may imply favourable biology, thereby selecting for patients more likely to benefit from surgery. While PALND will continue to play an important role in the management of PALNM, the use of chemo-RT in unsuitable surgical candidates, or as an adjunct peri-operatively should be considered.

In the context of liver metastasis in CRC, upfront metastectomy is recommended in surgically amenable metachronous metastasis (4 or fewer lesions, absence of bilobar involvement, radiologically negative portal lymph node) [39,40]. A single-staged resection may also be performed in synchronous disease if only a minor liver resection is required [41]. In m-PALNM, we believe that upfront surgery can be offered if the lesions are deemed resectable and neoadjuvant chemo-RT be reserved only for borderline resectable or unresectable disease. In resectable s-PALNM, 2 options exist: (1) upfront resection of both primary tumor and PALNM or (2) neoadjuvant chemo-RT followed by surgery. Based on our review, neoadjuvant chemotherapy was used in 25% of m-PALNM and in 19–25% of s-PALNM patients. Neoadjuvant chemo-RT was given in 16% of the patients in Shibata's series and in 50% of Min's (2008) series. None of these studies however stated the indication for neoadjuvant therapy and its effect on subsequent surgical management. While the potential benefits include reduction in cancer volume and improving R0 resection, further clarification on the selection criteria, treatment regimen used, and duration of therapy is required.

Recurrence following curative treatment was common in both s- and m-PALNM groups. In patients who had undergone PALND, adjuvant chemotherapy administered in most series included 5-flurouracil/leucovorin (5-FU), or FOLFOX (5-FU and oxaliplatin) regimens. Despite a compliance rate of 86.6–100%, 56%–80% of patients suffered either local or distant recurrences. In Min's (2008) series, distant metastasis was the predominant pattern of recurrence. Similarly, recurrence rate was 60–68% in patients who received chemo-RT alone[23,26]. With such high recurrence rates, it is evident that CRC patients with PALNM have a poor prognosis, and given the potential morbidity of PALND, it is therefore important to identify patient factors that may help with selecting patients who are likely to benefit from PALND.

Our review highlighted that all available studies on the management of PALNM were retrospective in nature, limited by small sample size. There was also heterogeneity in the patient populations included in each study, and isolated data on PALNM often could not be extracted from patients who had concomitant sites of distant metastasis. In addition, only the management of infra-renal

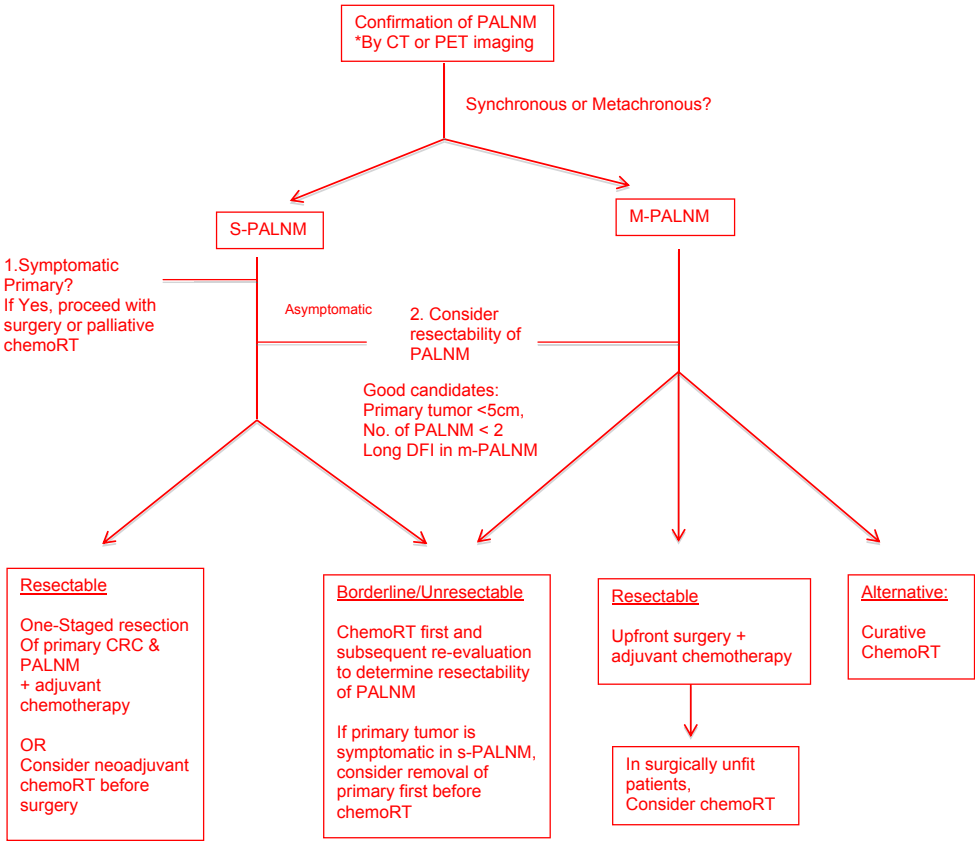

Fig. 2. Flow diagram on the strategy of management for PALNM.

PALNM has been addressed in this review, as supra-renal involvement of the aorta was often deemed unamenable to surgical resection. In light of evidence supporting the role of chemo-RT therapy, randomised control trials are required to determine the optimal course of management for both s- and m-PALNM.

5. Conclusion

PALNM in CRC is associated with poor survival outcomes and high rates of recurrent disease. While upfront surgery in resectable metastatic disease have been shown to confer acceptable survival and morbidity outcomes, its role remains debatable in the absence of multi-centre, randomised studies. Peri-operative chemotherapy should be considered. Curative chemoradiation therapy may also be an option for patients who are poor surgical candidates or who refuse PALND. A multi-disciplinary approach is definitely favoured and treatment strategies individualised. We suggest the following strategy for management of CRC associated PALNM (Fig. 2).

Authorship statement

All authors listed have contributed sufficiently to the project to be included as authors.

Conflict of interest statement

Authors declare no conflict of interests.

References

[1] P.W. Choi, H.C. Kim, A.Y. Kim, S.H. Jung, C.S. Yu, J.C. Kim, Extensive lymphadenectomy in colorectal cancer with isolated para-aortic lymph node metastasis below the level of renal vessels, J. Surg. Oncol. 101 (1) (2010 Jan 1) 66–71. PubMed ID: 19842140.

[2] D. Shibata, P.B. Paty, J.G. Guillem, W.D. Wong, A.M. Cohen, Surgical management of isolated retroperitoneal recurrences of colorectal carcinoma, Dis. Colon Rectum 45 (6) (2002 Jun) 795–801. PubMed ID: 12072633.

[3] S.B. Edge, D.R. Byrd, C.C. Compton, et al. (Eds.), AJCC (American Joint Committee on Cancer) Cancer Staging Manual, seventh ed., Springer, New York, 2010, p. 143.

[4] T. Watanabe, M. Itabashi, Y. Shimada, S. Tanaka, Y. Ito, Y. Ajioka, T. Hamaguchi, I. Hyodo, M. Igarashi, H. Ishida, M. Ishiguro, Y. Kanemitsu, N. Kokudo, K. Muro, A. Ochiai, M. Oguchi, Y. Ohkura, Y. Saito, Y. Sakai, H. Ueno, T. Yoshino, T. Fujimori, N. Koinuma, T. Morita, G. Nishimura, Y. Sakata, K. Takahashi, H. Takiuchi, O. Tsuruta, T. Yamaguchi, M. Yoshida, N. Yamaguchi, K. Kotake, K. Sugihara, Japanese society for Cancer of the colon and rectum. Japanese society for Cancer of the colon and rectum (JSCCR) guidelines 2010 for the treatment of colorectal cancer, Int. J. Clin. Oncol. 17 (1) (2012 Feb 16) 1–29. PubMed ID: 22002491.

[5] C.A. Quadros, M.F. Falco, M.E. Carvalho, P.A. Ladeia, A. Lopes, Metastases to retroperitoneal or lateral pelvic lymph nodes indicated unfavorable survival and high pelvic recurrence rates in a cohort of 102 patients with low rectal adenocarcinoma, J. Surg. Oncol. 106 (6) (2012 Nov) 653–658. PubMed ID: 22535617.

[6] W.B. Bowne, B. Lee, W.D. Wong, et al., Operative salvage for locoregional recurrent colon cancer after curative resection: an analysis of 100 cases, Dis. Colon Rectum 48 (2005) 897–909.

[7] W.E. Taylor, J.H. Donohue, L.L. Gunderson, et al., The Mayo Clinic experience with multimodality treatment of locally advanced or recurrent colon cancer, Ann. Surg. Oncol. 9 (2002) 177–185.

[8] M.A. Choti, J.V. Sitzmann, M.F. Tiburi, et al., Trends in long-term survival following liver resection for hepatic colorectal metastases, Ann. Surg. 235 (2002) 759–766.

[9] S.A. Shah, R. Haddad, W. Al-Sukhni, et al., Surgical resection of hepatic and pulmonary metastases from colorectal carcinoma, J. Am. Coll. Surg. 202 (2006) 468.

[10] T. Lehnert, H.P. Knaebel, M. Duck, et al., Sequential hepatic and pulmonary resections for metastatic colorectal cancer, Br. J. Surg. 86 (1999) 241–243.

[11] J. Gagnière, A. Dupré, S. Chabaud, P. Peyrat, P. Meeus, M. Rivoire, Retroperitoneal nodal metastases from colorectal cancer: curable metastases with radicalretroperitoneal lymphadenectomy in selected patients, Eur. J. Surg. Oncol. 41 (6) (2015 Jun) 731–737. PMID: 25899983.

[12] B.S. Min, N.K. Kim, S.K. Sohn, C.H. Cho, K.Y. Lee, S.H. Baik, Isolated paraaortic lymph-node recurrence after the curative resection of colorectal carcinoma, J. Surg. Oncol. 97 (2) (2008 Feb 1) 136–140. PubMed ID: 17963247.

[13] A.A. Slesser, P. Georgiou, G. Brown, S. Mudan, R. Goldin, P. Tekkis, The tumour biology of synchronous and metachronous colorectal liver metastases: a systematic review, Clin. Exp. Metastasis 30 (4) (2013 Apr) 457–470. PubMed ID: 23180209.

[14] R. Kumar, T.J. Price, C. Beeke, K. Jain, G. Patel, R. Padbury, G.P. Young, D. Roder, A. Townsend, S. Bishnoi, C.S. Karapetis, Colorectal cancer survival: an analysis of patients with metastatic disease synchronous and metachronous with the primary tumor, Clin. Colorectal Cancer 13 (2) (2014 Jun 18) 87–93. PubMed ID: 24373733.

[15] E.K. Tan, L.L. Ooi, Colorectal cancer liver metastases - understanding the differences in the management of synchronous and metachronous disease, Ann. Acad. Med. Singap. 39 (9) (2010 Sep) 719–733. PubMed ID: 20957308.

[16] M.W. Stearns Jr., M.R. Deddish, Five-year results of abdominopelvic lymph node dissection for carcinoma of the rectum, Dis. Colon Rectum 2 (1959) 169–172.

[17] D. Moher, A. Liberati, J. Tetzlaff, D.G. Altman, PRISMA Group Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement, BMJ 339 (2009 Mar) b2535. PubMed ID: 19622551.

[18] Howick J, Chalmers I, Glasziou P, Greenhalgh T, Heneghan C, Liberati A, Moschetti I, Phillips B, Thornton H, Goddard O, Hodgkinson M. "The Oxford 2011 Levels of Evidence". Oxford Centre for Evidence-Based Medicine. http://www.cebm.net/index.aspx?o=5653. (accessed 23 January 2012).

[19] B.S. Min, J.S. Kim, N.K. Kim, J.S. Lim, K.Y. Lee, C.H. Cho, S.K. Sohn, Extended lymph node dissection for rectal cancer with radiologically diagnosed extramesenteric lymph node metastasis, Ann. Surg. Oncol. 16 (12) (2009 Dec) 3271–3278. PubMed ID: 19763693.

[20] S.U. Bae, Y.D. Han, M.S. Cho, H. Hur, B.S. Min, S.H. Baik, K.Y. Lee, N.K. Kim, Oncologic outcomes of colon Cancer patients with extraregional lymph node metastasis: comparison of isolated paraaortic lymph node metastasis with resectable liver metastasis, Ann. Surg. Oncol. 23 (5) (2016 May) 1562–1568. PubMed ID: 26714940.

[21] Atsushi Ogura, Takashi Akiyoshi, Yukiko Takatsu, Jun Nagata, Toshiya Nagasaki, Tsuyoshi Konishi, Yoshiya Fujimoto, Satoshi Nagayama, Yosuke Fukunaga, Masashi Ueno, The significance of extended lymphadenectomy for colorectal cancer with isolated synchronous extraregional lymph node metastasis, Asian J. Surg. (2015 Nov 20). PubMed ID: 26776452 pii: S1015-9584(15)00124-4.

[22] S.H. Song, S.Y. Park, J.S. Park, H.J. Kim, C.S. Yang, G.S. Choi, Laparoscopic paraaortic lymph node dissection for patients with primary colorectal cancer and clinically suspected para-aortic lymph nodes, Ann. Surg. Treat. Res. 90 (1) (2016 Jan) 29–35. PubMed ID: 26793690.

[23] T. Takenoue, Y. Yamada, S. Miyagawa, Y. Akiyama, K. Koyama, H. Nagawa, Cisplatin-5-fluorouracil therapy with remarkable effect and 5-year survival for paraaortic lymph node metastases of rectal carcinoma in females: a case report, Jpn. J. Clin. Oncol. 29 (11) (1999 Nov) 582–586. PubMed ID: 10678563.

[24] R.M. Goldberg, T.R. Fleming, C.M. Tangen, et al., Surgery for recurrent colon cancer: strategies for identifying resectable recurrence and success rates after resection. EasternCooperative oncology group, the north central Cancer treatment group, and the southwest oncology group, Ann. Intern Med. 129 (1998) 27–35.

[25] F. Dumont, K. Kothodinis, D. Goere, et al., Central retroperitoneal recurrences from colorectal cancer: are lymph node and locore- gional recurrences the same disease? Eur. J. Surg. Oncol. 38 (2012) 611–616.

[26] R. Razik, F.S. Zih, E. Haase, A. Mathieson, L. Sandhu, B. Cummings, T. Lindsay, A.J. Smith, C.J. Swallow, Long-term outcomes following resection of retroperitoneal recurrence of colorectal cancer, Eur. J. Surg. Oncol. 40 (6) (2014 Jun) 739–746. Epub 2013 Nov 1. PMID:24246611.

[27] M.S. Kim, C.K. Cho, K.M. Yang, D.H. Lee, S.M. Moon, Y.J. Shin, Stereotactic body radiotherapy for isolated paraaortic lymph node recurrence from colorectal cancer, World J. Gastroenterol. 15 (48) (2009 Dec 28) 6091–6095.

[28] S.G. Yeo, D.Y. Kim, T.H. Kim, et al., Curative chemoradiotherapy for isolated retroperitoneal lymph node recurrence of colorectal cancer, Radiother. Oncol. 97 (2010) 307–311.

[29] T. Miyazawa, K. Ebe, N. Koide, N. Fujita, Complete response of isolated paraaortic lymph node recurrence from rectosigmoid Cancer treated byChemoradiation therapy with capecitabine/oxaliplatin plus bevacizumab: a case report, Case Rep. Oncol. 5 (2) (2012 May) 216–221, http://dx.doi.org/10.1159/000338840. Epub 2012 May 3.

[30] S. Yasuda, H. Kamata, T. Machida, K. Okada, A. Tanaka, T. Suzuki, S. Sadahiro, Y. Ohizumi, A case of isolated paraaortic lymph node recurrence from colon cancer successfully treated withchemoradiotherapy, Tokai J. Exp. Clin. Med. 37 (2) (2012 Jul 20) 47–50.

[31] Jeongshim Lee, Jee Suk Chang, Incorporation of radiotherapy in the multidisciplinary treatment of isolated retroperitoneal lymph node recurrence from colorectal cancer, Ann Surg Oncol 22 (2015) 1520–1526.

[32] D. Dindo, N. Demartines, P.A. Clavien, Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and 108 results of a survey, Ann. Surg. 240 (2004) 205e213.

[33] E.A. Eisenhauera, P. Therasseb, J. Bogaertsc et al New response evaluation criteria in solid tumours:Revised RECIST guideline (version 1.1) Eur. J. Of Cancer 45 (2009) 228–247.

[34] Cox JD, Stetz J, Pajak TF. Toxicity Criteria of the Radiation Therapy Oncology Group (RTOG) and the European, Organization for Research and Treatment of Cancer.

[35] M.R. Deddish, Discussion on the treatment ofadvanced cancer of the rectum,

Proc. Roy.Soc.Med. 43 (1950) 1075.
[36] R.E. Glass, J.K. Ritchie, H.R. Thompson, C.V. Mann, The results of surgical treatment of cancer of the rectum by radical resection and extended abdomino-iliac lymphadenectomy, Br. J. Surg. 72 (1985) 599–601.
[37] A. Leggeri, M. Roseano, A. Balani, A. Turoldo, Lumboaortic andiliac lymphadenectomy: what is the role today? Dis. Colon Rectum 37 (1994) S54–S61.
[38] M.H. Albandar, M.S. Cho, S.U. Bae, N.K. Kim, Surgical management of extraregional lymph node metastasis in colorectal cancer, Expert Rev. Anticancer Ther. 16 (5) (2016 May) 503–513.
[39] V.P. Khatri, N.J. Petrelli, J. Belghiti, Extending the frontiers of surgical therapy for hepatic colorectal metastases: is there a limit? J. Clin. Oncol. 23 (33) (2005) 8490.
[40] K.K. Tanabe, Palliative liver resections, J. Surg. Oncol. 80 (2) (2002) 69.
[41] K. Tanaka, H. Shimada, K. Matsuo, Y. Nagano, I. Endo, H. Sekido, et al., Outcome after simultaneous colorectal and hepatic resection for colorectalcancer with synchronous metastases, Surgery 136 (2004) 650–659.