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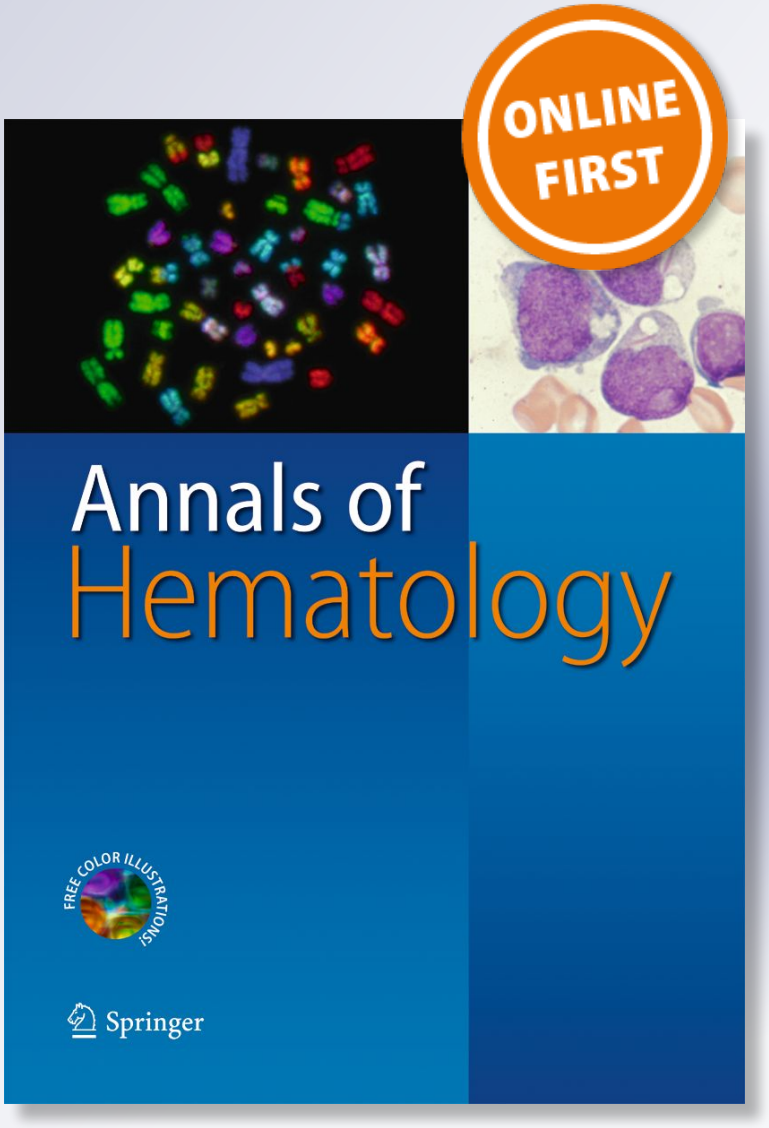

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REVIEW ARTICLE

New insights inside the interdigitating dendritic cell sarcoma—pooled analysis and review of literature

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Abstract

Interdigitating dendritic cell sarcoma is a rare haematological neoplasm with high debatable management protocols. The data extracted from 127 case reports published between 1981 and 2018 were analysed. The median age at diagnosis was 58 years with a male to female ratio of 1.65:1. The median OS and PFS of IDCS were 12 and 6 months, respectively, with a disease-specific mortality rate of 36.4%. Two-thirds of patients had a localised disease, while 30% had a disseminated form with 1-year mortality rates of 21.1% and 78.9%, respectively. Twenty per cent of cases were associated with other malignancies. Histologically, the proliferation of large spindle-shaped cells with fascicular growth was described in 84.3% of cases. Based on Cox-regression model, surgical resection was the only treatment modality linked to survival improvement with no recorded survival benefits of radiotherapy and chemotherapy. The 1-year mortality rates in resected and non-resected disease were 17.8% and 63.2%, respectively ($P < 0.0001$).

Keywords Interdigitating dendritic cell sarcoma · Dendritic cell neoplasm · Associated cancer with IDCS

Introduction

Interdigitating dendritic cell sarcoma (IDCS) is a rare malignant neoplasm that originates from antigen-presenting interdigitating dendritic cells, which is commonly present in T-cell affluent areas of the lymph nodes [1]. Clinically, it usually presents as a painless cervical, mediastinal and axillary lymphadenopathy. However, extra-nodal involvement, particularly, splenic, hepatic and testicular lesions, has been reported in nearly 30% of the cases [2]. The two major obstacles that face physicians are the disease diagnosis and disease heterogeneity. IDCS is usually recognised by being aggressive, humbly responsive to chemotherapeutic agents and having increased rates of relapse besides reduced survival. Only surgical resection has a role in the treatment of small loco-regional disease[3]. In addition to that, adjuvant chemotherapy or radiotherapy are ineffective in reducing the risk of relapse[4].

Material and methods

This research is a retrospective pooled analysis of studies and case reports concerning interdigitating dendritic cell sarcoma published in the literature between 1981 and 2018. The following terms were used for searching PubMed, ResearchGate and Google Scholar libraries: IDCS, interdigitating dendritic cell sarcoma, dendritic cell sarcoma, interdigitating neoplasm and interdigitating sarcoma. The references included in the retrieved case studies were examined carefully. Data of patients' age, gender, the year of diagnosis, geographical distribution, tumour's pathological characteristics, immunohistochemical patterns, stage, modalities of treatment, salvage interventions, relapse, progression-free survival, overall survival, use of PET CT and associated malignancies were recognised and tabulated. Cases were classified according to disease site into nodal, extra-nodal or combined and according to disease burden into limited or disseminated. The disease was considered as limited when it involved lymph nodes on

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a single side of the diaphragm with or without single extra-nodal extension and disseminated when it involves multiple lymph nodes on both sides of the diaphragm with or without extra-nodal extension.

Chi-square test was used for analysis of categorical data, while patients' survival data were evaluated by Kaplan-Meier and log-rank tests. Cox-regression model was used for validating the results of Kaplan-Meier statistics. Cases lacking survival data were excluded from survival analysis, and patients with short follow-up duration (less than 1 year) were excluded from the evaluation of 1-year mortality rates. The commercially available statistical software IBM-SPSS (version 23 for Windows; IBM Inc.) was used for data analysis. For all tests, an alpha level of 5% was used to consider the statistical significance.

Results

Patients' demographics and disease trend

A total of 127 cases were identified from 95 published studies between 1981 and 2018 [3–97]. The median age at diagnosis was 58 years (range, three months to 88 years). Males and females were involved in 62.4% and 37.6%, respectively, with a male–female ratio of 1.65:1. There was no apparent difference in median age at diagnosis between males and females, 59.5 and 56 years, respectively.

IDCS is frequently incident in North America (42.1% of reported cases) followed by South East Asia and Europe: 28.9% and 22.3%, respectively. There is an apparent rise in the disease rate over the last 20 years (Fig. 1a).

Disease diagnosis

The diagnostic workup in reported cases included CT imaging, CBC and liver and kidney function test in addition to histopathological evaluation. Only 22 authors (17.3%) used PET CT in either disease staging or detection of relapse.

The median time needed to achieve a final diagnosis of IDCS was 12.5 weeks (range, 2–52). Eighty-four per cent of the patients were diagnosed as IDCS, while the remaining cases had other diagnoses such as low-grade lymphoma (five cases) or chronic inflammatory conditions (seven cases) before establishing the final diagnosis of IDCS.

The most common histopathological picture of IDCS was a proliferation of large spindle-shaped cells with fascicular and whorled growth (84.3%). A considerable proportion of tumours (43%) showed a tumour infiltrating mature lymphocytes and histiocytes with occasional granuloma formation (three cases). Several immunohistochemical markers had been used to establish a final diagnosis of IDCS. The most frequently expressed molecules were S100, CD68, Vimentin and CD1a, in 95.8%, 58%, 38.7% and 4.5% of cases, respectively. There was a consensus that expression of CK, CD20, CD79a, CD3, CD15, CD30, CD21 and CD35 by the tumour cells should be negative.

Associated malignancies

Analysis of published studies showed an association of IDCS with other malignant neoplasms 25 (19.7%) of cases, including 16 haematological and nine non-haematological tumours (Table 1). Still, three patients had a history of immunosuppression. Surprisingly, one patient had IDCS with simultaneous haematological and non-haematological tumours (acute myelomonocytic leukaemia and breast carcinoma, respectively). The median interval between IDCS and the associated (before or after) haematological neoplasm or immunosuppression was 10 (range, 0–130) months, and for non-haematological neoplasms, the median interval was 42 (range, 4–72) months. In two-thirds of the cases, the neoplasm preceded the IDCS.

Disease burden and survival

The median overall survival of IDCS was 12 months (range, 0.7–120), while the median progression-free survival was 6 months (range, 0–120) with disease-specific mortality of 36.4% (39 cases). One-year mortality rate was 39.5% for valid cases (n = 86).

Eighty-eight (69.8%) of the patients had a localised disease, while 38 (29.9%) had disseminated disease. There was a significant survival difference between localised and disseminated disease with an estimated median survival of being (not reached) and 6±1 months, respectively (log-rank $P < 0.0001$, Fig. 1b). The 1-year mortality rates were 21.1% and 78.9% for localised and disseminated disease status, respectively, Chi-square ($P < 0.0001$, OR 11.7; 95% CI 4–34.5).

Sixty-one (48.4%) cases had nodal disease (93.4% limited and 6.6% disseminated), 40 (31.7%) had extra-nodal presentation (77.5% limited and 22.5% disseminated) and 25 (19.8%) had combined nodal and extra-nodal presentation (100% disseminated) (Table 2). The most frequently involved lymph nodes were cervical, axillary and mediastinal groups, and the most frequent extra-nodal sites of involvement were skin, liver and lung (Table 3). There was a significant survival difference among nodal, extra-nodal and combined disease; the estimated median survival was (not reached) for nodal and extra-nodal and 6±0.95 months for combined disease, ($P = 0.000$, Fig. 1c). The 1-year mortality rates were 28.9%, 20% and 78.3% for nodal, extra-nodal and combined forms of the disease, respectively.

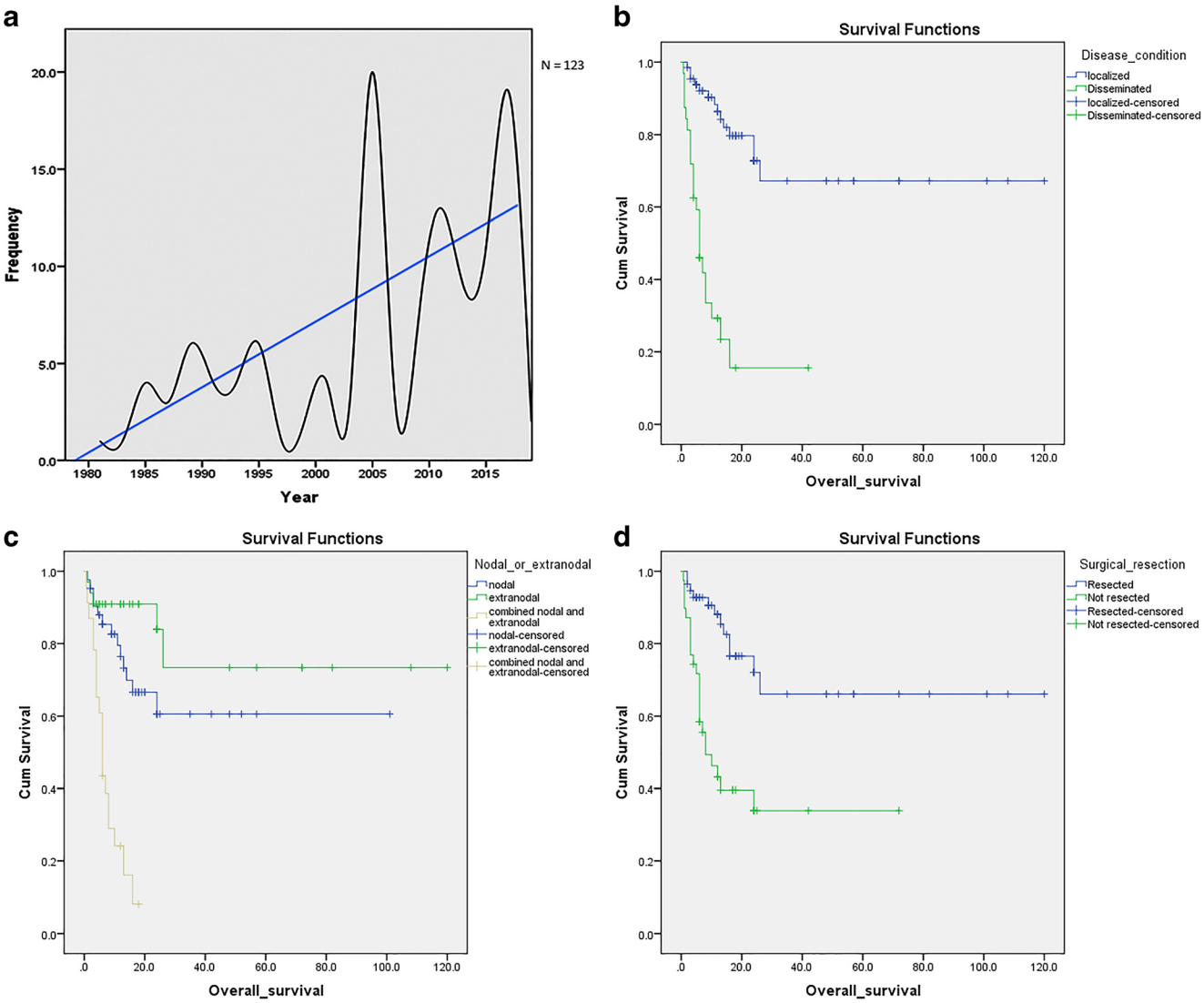

Fig. 1 **a** Linear graph showing the rising disease trend in the last decade. **b** Kaplan-Meier survival curve showing the difference between localised and disseminated disease. **c** Kaplan-Meier survival curve showing the difference among nodal, extra-nodal and combined disease. **d** Kaplan-Meier survival curve showing the difference between resected and non-resected disease

Local treatment

Data on surgical management was obtainable in 110 patients. The tumours were surgically resected in 66 (60%) patients, with a median tumour size of 4 cm (range, 1–14 cm). Patients that underwent surgical resection of IDCS had significantly improved survival compared with patients with non-resected tumours (log-rank, $P < 0.0001$, Fig. 1d), with the estimated median survival of (not reached) and 8±2.1 months, respectively. The 1-year mortality rates were 17.8% and 63.2% for patients with resected and non-resected neoplasms, respectively, chi-square $P < 0.0001$, OR 7.93 (95% CI 2.9–21.7).

Only 36 (34%) patients were treated with radiotherapy: of whom, 23 received radiotherapy as adjuvant treatment and 12 received radiotherapy as a definitive treatment. The dose of radiotherapy (mentioned in only 12 case reports) ranged between 30 and 70 Gy with a median value of 52.2 Gy. The 1-year mortality rate for patients receiving radiotherapy as a definitive treatment was 63.6% compared with 5.6% for those receiving it as an adjuvant to surgical resection, (Chi-square $P = 0.001$, OR 29.4; 95% CI 2.8–333). The use of adjuvant radiotherapy following surgical resections compared with only surgical resection failed to show any survival benefit (log-rank $P = 0.158$).

Systemic treatment

Out of the 105 reports with reliable data on chemotherapy, first-line chemotherapy was given to 52 (49.5%) patients. The most frequently used regimens were CHOP and ABVD in 24 and seven patients, respectively. Other less frequent combinations included CHOP alternating with ESHAP, CHOPE alternating with DHAP, m-BACOB,

Table 1 Shows the association between IDCS and other malignancies

IDCS associated condition	Number of cases
No associated malignancy or immunosuppression	99 (78%)
Associated immunosuppression	3 (2.4%)
Associated haematological malignancies/immunosuppression	16 (12.6%)
CLL/SLL	9
B-cell Lymphoma	3
NK/T cell Lymphoma	1
Hodgkin Lymphoma	1
Lymphoblastic lymphoma	1
Acute myelomonocytic leukaemia *	1
Associated non-haematological malignancies	9 (7%)
Colon cancer	2
HCC	1
Gastric adenocarcinoma	1
Breast cancer *	2
Leiomyosarcoma	1
Anaplastic oligodendroglioma	1
SCC of the skin and TCC of the bladder	1

*This case had suffered both acute myelomonocytic leukaemia and breast cancer

CVP, CHVP, gemcitabine/docetaxel, ICE plus intercaecal methotrexate, 'etoposide, cyclophosphamide, doxorubicin and bleomycin', ALL induction protocol, 'cyclophosphamide, methotrexate, daunorubicin, vincristine, etoposide, mechlorethamine, procarbazine', 'prednisolone/chlorambucil', 'methotrexate, vincristine, bleomycin, etoposide, mitoxantrone, ifosfamide, cytosine-arabinoside, melphalan' and 'paclitaxel, vinorelbine'.

For simplification, the regimens of used chemotherapy could be assorted, according to their intensity, into three categories: low, moderate and high intensities. Eleven patients received highly-intensive regimens such as m-BACOP, CHOP alternating with DHAP or ESHAP, ALL-based protocols, Alkylating agent/platinum/anthracycline combinations with methotrexate, etoposide, L-asparaginase or bleomycin. Moderately intensive regimens including CHOP or ABVD were given for 35 patients, and low-intensity regimens including CVP or chlorambucil/steroids were used for only three patients.

Regardless of disease burden, there was no survival gain following the use of chemotherapy in the treatment of IDCS (log-rank $P = 0.271$, Fig. 2). In addition to that, adjuvant chemotherapy (n = 15 patients) exhibited no survival advantage compared with surgical resection alone ($P = 0.376$). The use of higher intensity regimen failed to demonstrate any survival benefit with the 1-year mortality rates for the low, the moderate and the high-intensity regimen of 100%, 56% and 60% ($P = 0.466$).

Disease outcome and management of relapse

In only 102 of the patients, the authors appraised the outcome of their treatment. Seventy-one of the patients responded to first-line treatment regardless of their treatment modality, while 31 patients had no tumour regression. The sixth-month, first-year and second-year relapse rates were 36.6%, 45.8% and 68.9%, respectively. The

Table 2 Shows the disease burden categorized into limited and disseminated forms

Disease type	Limited disease	Disseminated disease	Total
Nodal	57 cases	4 cases	61 cases
	93.4%	6.6%	
Extra-nodal	31 cases	9 cases	40 cases
	77.5%	22.5%	
Combined nodal and extra-nodal	0	25 cases	25 cases
	0%	100%	
Total	88 cases	38 cases	126 cases
	69.8%	30.2%	

One case report lacks any data upon disease site and burden. It was excluded from the table

Table 3 Shows the sites of involvement of IDCS

Site	%	Site	%
Cervical LN	42.5	Lung	7.9
Mediastinal LN	12.7	Pleura	4
Axillary LN	23.8	Liver	11.1
Para-aortic	14.3	Brain	0.8
Ileo-inguinal LN	12.7	Pancreases	0.8
Spleen	7.9	Stomach	0.8
Tonsils	3.2	Ileo-jejunal	5.6
Nasopharynx	2.5	Rectum	4
Nasal cavity	1.6	Kidney	2.4
Larynx	1.6	Urinary Bladder	1.6
Parotid gland	7.1	Testis	0.8
Submandibular gland	1.6	Uterus	2.4
Bone marrow	5.6	Breast	1.6
Skin	11.1	Soft-tissue	5.5

vast majority (87%) of relapses were disseminated, while only 13% were localised.

Salvage treatment was given to 22 patients; the salvage chemotherapy was used in 15 patients, while local salvage treatment was used in seven patients. The chemotherapy regimens for salvage setting were high-dose BEAM, epirubicin/high-dose cytosine arabinoside, CHOP-methotrexate, ESHAP, ABVD, IMEP, asparaginase/methotrexate/dexamethasone, CHOP, gemcitabine/docetaxel or not reported. Twelve out of the reported 15 patients died of the disease whom median overall survival was 10 months.

Salvage local treatment was used in seven patients with localised relapse; including salvage resection in six patients and radiotherapy in one patient. Three of those patients had a progressive and fatal disease.

Autologous stem cell transplant had been reported in four patients of IDCS; three of them died following the procedures, with no available data about the outcome of the remaining patient. The only patient who was treated with allogeneic BMT developed aggressive disseminated disease 4 months after transplantation.

Model generation and prognostic factors

Cox-regression model was performed to assess the impact of the age, the gender, the associated malignancy, the disease burden, the intensity of used chemotherapy and the surgical resectability on the survival of IDCS patients. Disease burden was the only independent factor that predicted disease survival. Disseminated IDCS had a hazard ratio of 7.5 (95% CI 3.7–15.15, P = 0.000, Fig. 3).

Discussion

IDCS is a rare malignant tumour arising from dendritic cells of the lymph node. To the best of our knowledge, there are only three large pooled analyses of IDCS published by C. Saygin (2013), De Pas (2008) and Perkins (2003) and reported 100, 50 and 20 cases, respectively. These studies represent the cornerstone for the current management of IDCS. In this study, a detailed analysis of 127 cases of IDCS reported in 96 studies was performed.

The median age at diagnosis of IDCS was 58 years with a relative male predilection (M:F ratio of 1.65:1), which is compatible with the previously reported ratio of 1.38:1 [32]. Contrary to older reports, IDCS is not limited to patients older than 40 years [4, 32]. Nearly 20% (27 cases) of the cases in this study are younger than 35 years and 10% (12 cases) aged below 20 years. The increased number of IDCS cases over the last two decades, possibly due to advances in diagnostic tools, could argue against the rarity of this tumour (Fig. 1a).

Diagnosis of IDCS is challenging. The median interval to achieve the final diagnosis of IDCS was 12.5 weeks. About 15% of the cases in this study had been initially diagnosed and subsequently managed as low-grade lymphoma or chronic inflammatory conditions before being considered as IDCS, which imply diverse clinical and pathological characters of this disease. The most commonly described histological pattern of IDCS was the proliferation of spindle-shaped or histiocytic cells, which is similar to other tumour-like conditions including dendritic cell tumour, histiocytic lesions and granulomatous inflammation [67]. The reported immunohistochemistry panels of IDCS was diverse. According to this pooled study, diagnosis of IDCS should be established if the tumours cells expressed S100, CD68 and Vimentin molecules with negative expression of CK, LCA, CD15, CD30, CD21 and CD35 molecules.

The mechanism behind the development of IDCS is still obscured. In this analysis, 22% of IDCS cases had immunosuppression and other haematological or non-haematological malignancies. The frequently reported haematological malignancies were CLL/SLL (nine cases) and B-cell lymphoma (three cases). In 72% of the reports, IDCS came after other malignancies with a median interval of 12 and 42 months for haematological and non-haematological tumours, respectively. This finding implies that disturbed B-cell function secondary to haematological malignancies or immunosuppression could be involved in the progression of IDCS disease. Two pieces of evidence could support this claim: firstly, the short interval between B-cell malignancies and development of IDCS and, secondly, the robust finding of Shao et al. who pointed to the capability of malignant B-cell to transform into interdigitating dendritic cells [18]. Moreover, two of the critical mutations of B-cell lymphoma, the Ig gene and MYC gene rearrangement, were reported in some cases of IDCS [98, 99].

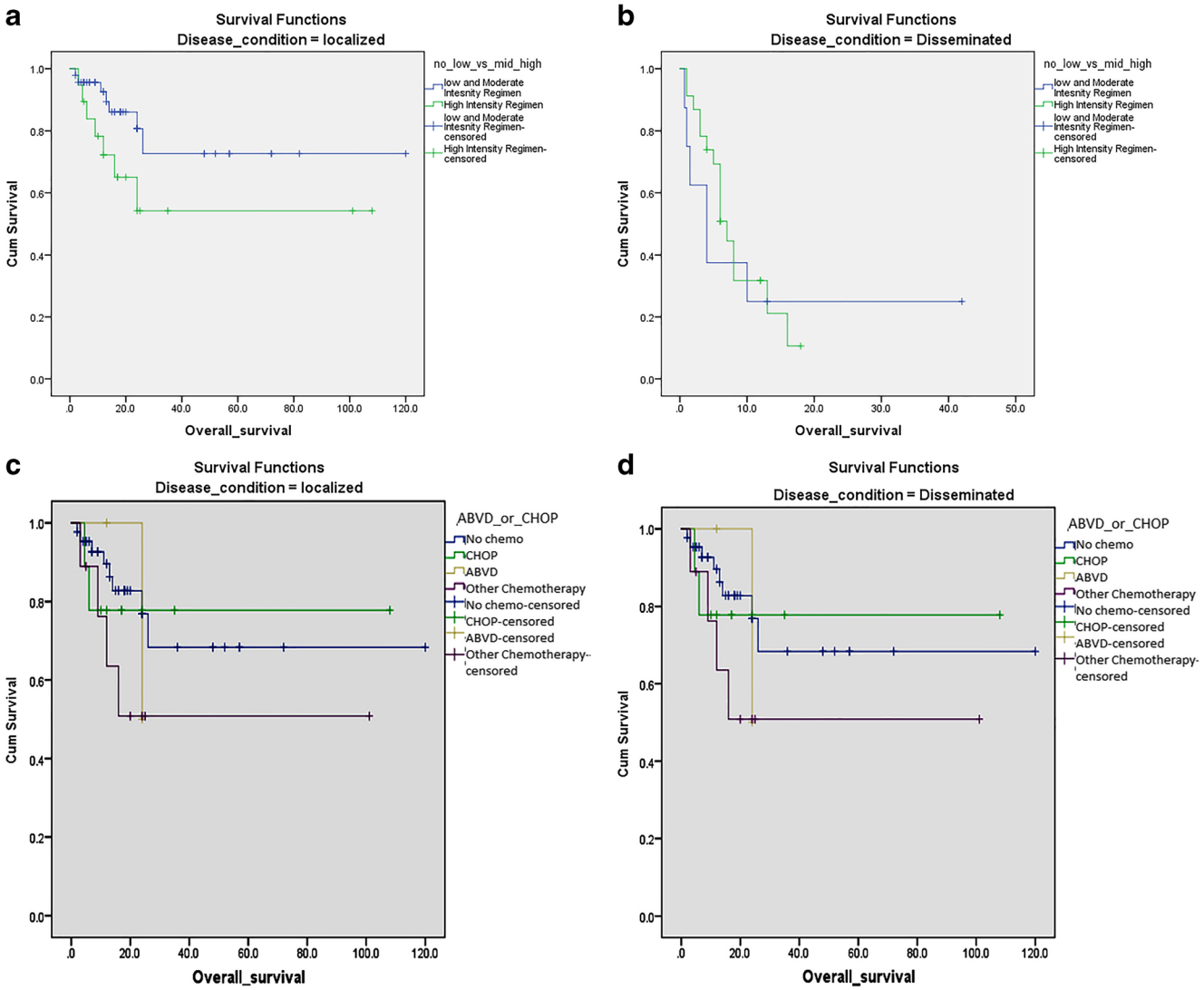

Fig. 2 **a** Kaplan-Meier survival curve showing the effect of chemotherapy intensity on localized disease. **b** Kaplan-Meier survival curve showing the effect of chemotherapy intensity on disseminated disease. **c** Kaplan-Meier survival curve showing the effect of ABVD and CHOP compared with other regimens in localized disease. **d** Kaplan-Meier survival curve showing the effect of ABVD and CHOP compared with other regimens in disseminated disease

In contrast, some findings imply different mechanisms, including the link between the use of calcineurin inhibitors, the pure T-cell suppressive drug and the subsequent IDCS development [21]. Also, some authors reported the increased membranous and cytoplasmic expression of PD-L1 and BRAF gene mutations in IDCS cells [21, 78, 100]. The pathogenesis behind IDCS is not fully understood and requires further investigations to draw solid conclusive facts.

In this study, the median overall survival of the patients was 12 months, while the median progression-free survival was 6 months with disease-specific mortality of 36.4% and the 1-year mortality rate was 40%. Two-thirds of the patients have a localised disease with 1-year mortality rates of 21% compared with 79% seen for patients with disseminated disease. Furthermore, 65% of patients with the limited disease had only lymph node involvement. On the other hand, the limited extra-nodal disease occurred in 35% of patients. The 1-year mortality rates for the isolated nodal and the isolated extra-nodal were nearly similar, 28.9% and 20%, respectively. However, disseminated with combined nodal and extra-nodal involvement had significantly reduced survival with a 1-year mortality rate of 78%. This finding is consistent with the previous report of C. Saygin et al. [32].

Surgical resection was feasible in 60% of patients in this analysis, and it was significantly associated with better disease outcome, which is similar to previous data released

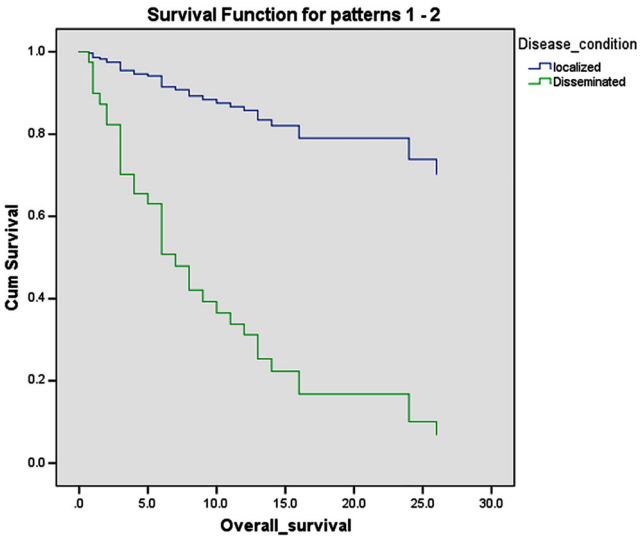

Fig. 3 Survival plot of the Cox-regression model showing the difference in disease survival between limited and advanced disease

by several authors [32, 101]. The 1-year mortality rate for the patients with resected disease was 18% compared with 63% for the patients with non-resected disease. Surgical resection based in this study was associated with better disease outcome and survival with 1-year mortality rates for the resected disease of 18% compared with 63% for the non-resected disease.

Our study found that the use of radiotherapy was controversial as it failed to show any survival benefit in the adjuvant setting (P = 0.158). However, Definitive radiotherapy was inferior in terms of survival when compared with surgical resection with a 1-year mortality rate of 64%, which was nearly the same as the 1-year mortality rate of non-resected disease.

Although the use of chemotherapy was recorded in nearly half of the case reports, no survival benefit was found in any patient's subgroups including those with advanced disease and those receiving adjuvant setting (P = 0.271 and 0.376, respectively). The most frequently used regimens were CHOP and ABVD in 46% and 14% of the patients, respectively. Regardless of the disease burden, the use of more intense regimen, even when combined with bone marrow transplantation, failed to show any survival benefit with 1-year mortality rates for low, moderate and high-intensity chemotherapeutic regimen of 100%, 56% and 60% (P = 0.466). These findings were consistent with previous reports that indicated the inadequate response of IDCS following use of chemotherapy with no superiority of one regimen over another [32].

Seventy per cent of IDCS responded initially to treatment. However, two-thirds of those patients had a relapsed disease within the following 2 years. The 1 and 2-year relapse rates were 46% and 69%; respectively. Furthermore, 87% of the relapses were disseminated and usually nonresponsive to treatment with a high risk of mortality. However, the salvage surgical resection remains a good promise for local relapse as the risk of death was much lower.

In this analysis, the median overall survival of the patients was 12 months, and the median progression-free survival was 6 months with disease-specific mortality of 36.4% and 1-year mortality rate of 40%. According to Cox-regression model, the disease burden was the only independent factor that affects disease survival with hazard ratio 7.5 (95% CI 3.7–15.15, P < 0.0001).

Conclusions

IDCS is an aggressive malignant neoplasm that is not limited to a specific age group. It has a high recurrence rate. Diagnosis of this disease is challenging, and it should be considered in the diagnostic workup of lymphoma and chronic inflammatory conditions that responded poorly to treatments. Up to date, surgical resection is the only treatment of IDCS that could guarantee longer disease-free survival, while definitive and adjuvant radiotherapy does not provide any survival benefit for the patients. Systemic chemotherapy is usually inadequate regardless of disease burden or intensity of chemotherapeutic agents. However, chemotherapy remains the only option for the advanced non-resectable disease. The single independent factor that predicts patients' survival of IDCS is the disease burden rather than disease site. Molecular studies are required for understanding the exact mechanisms behind this disease and for development of new target therapy to improve patients' survival.

Compliance with ethical standards

All procedures performed in this study were in accordance with the ethical standards of our institutional research committee and the National Standards.

Conflict of interest The authors declare that they have no conflict of interest.

Informed consent This article does not contain any studies with human participants or animals performed directly by any of the authors.

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