Management and outcome of stage 3 neuroblastoma

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Abstract

Purpose—The management of patients with International Neuroblastoma Staging System (INSS) stage 3 neuroblastoma (NB) is not consistent worldwide. We describe a single centre approach at Memorial Sloan-Kettering Cancer Centre (MSKCC) from 1991 to 2007 that minimizes therapy except for those patients with *MYCN*-amplified NB.

Methods—In this retrospective analysis of 69 patients, tumour *MYCN* was not amplified in 53 and amplified in 16. Event-free survival (EFS) and overall survival (OS) were determined by Kaplan–Meier analysis.

Results—Fourteen patients with non-*MYCN*-amplified tumours were treated with surgery alone (group A) and the remaining 39 (group B) with surgery following chemotherapy that was initiated and administered at non-MSKCC institutions. Chemotherapy was discontinued after surgery in 38/39 of the latter. The 10-year EFS and OS for all patients with *MYCN*-non-amplified NB were 74.9 ± 16.9% and 92.6 ± 5.5%, respectively. There was no difference in OS between groups A and B ($p = 0.2$; 10-year OS for groups A and B was 84.6 ± 14% and 97.1 ± 2.9%, respectively). Patients with *MYCN*-amplified disease (group C) underwent dose-intensive induction, tumour resection and local radiotherapy: 13 achieved complete or very good partial remission, and 10 received myeloablative chemotherapy. 11/16 patients also received 3F8-based immunotherapy: 10 remain free of disease. The 10-year EFS and OS for patients with *MYCN*-amplified neuroblastoma treated with immunotherapy were both 90.9 ± 8.7%.

Conclusion—Patients with *MYCN*-non-amplified stage 3 NB can be successfully treated with surgery without the need for radiotherapy or continuation of chemotherapy. Combination of dose-intensive chemotherapy, surgery, radiotherapy and immunotherapy was associated with a favourable outcome for most patients with *MYCN*-amplified stage 3 NB.

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Conflicts of interest statement
None declared.

1. Introduction

The International Neuroblastoma Staging System (INSS),[1] established in 1993 replacing the Evans and Paediatric Oncology Group (POG) systems, defined stage 3 neuroblastoma (NB) as an unresectable tumour that extends across the midline either itself, or with associated involved lymph nodes. Approximately 15% of all NB patients have stage 3 disease at diagnosis.[2] Clinical investigators include stage 3 patients in reports on locoregional NB and on high-risk, predominantly metastatic disease, and outcomes related specifically to patients with stage 3 disease are not always specifically presented.[3–7] Biological and clinical prognostic markers help stratify risk and guide therapy.[3,8] *MYCN*-amplified stage 3 NB, which accounts for ~25% of cases, is considered high-risk and is treated with aggressive multimodality programmes which use dose-intensive or dose-dense chemotherapy, surgery, radiotherapy (RT), myeloablative chemotherapy with autologous stem cell transplant (SCT) and 13-*cis*-retinoic acid. That aggressive strategy is also widely used, including by the Children's Oncology Group (COG), for *MYCN*-non-amplified stage 3 NB with the adverse prognostic markers of unfavourable histology and age >18 months. In contrast, moderatedose chemotherapy is standard of care for stage 3 NB with favourable biology. At Memorial Sloan-Kettering Cancer Centre (MSKCC), 3F8-based immunotherapy (ClinicalTrials.gov NCT00002560 or NCT00072358) is routinely used in addition to aggressive multimodality therapy for *MYCN*-amplified stage 3 NB. However, for *MYCN*-non-amplified stage 3 NB, regardless of other standard prognostic factors, our strategy is surgical resection followed by observation without exposing patients to any cytotoxic therapy (Fig. 1).[9,10] We now report an analysis of the long-term outcome of these approaches for all INSS stage 3 NB patients treated at MSKCC.

2. Patients and methods

The subjects of this retrospective report are 69 consecutive patients with INSS stage 3 NB treated at MSKCC between 1991 and 2007; patients who came to MSKCC after relapse were not included in this analysis. Although 72 patients with stage 3 NB were seen at MSKCC from 1991 to 2007, three were excluded from the analysis: one because of lack of follow-up information and two because MSKCC strategy was not followed after tumour resection (Fig. 2). Institutional Review Board approval was obtained for review of patient records. Disease status was assessed by computed tomography or magnetic resonance imaging, meta-iodobenzylguanidine (MIBG) scan, urine catecholamines and bilateral bone marrow (BM) biopsies and aspirates. In accordance with hospital rules, informed written consents for treatments were obtained from guardians after they understood the side-effects of each agent and the possibility of unforeseen toxicities. The International NB Response Criteria[1] were used: complete response (CR), no evidence of NB; very good partial response (VGPR), volume of primary mass reduced by >90%, no evidence of distant NB (including normal MIBG) except for skeletal residua, catecholamines normal; partial response (PR), >50% decrease in measurable disease and 61 positive BM site; mixed response, >50% decrease of any lesion with <50% decrease in any other; no response, <50% decrease but <25% increase in any lesion and progressive disease (PD), new lesion or >25% increase in an existing lesion. Biological parameters evaluated included serum ferritin, serum lactate dehydrogenase, histology assessed by Shimada classification, DNA index and *MYCN* gene amplification. The latter was measured by fluorescent in situ hybridization and/or Southern blot analysis. Tumours were considered to be *MYCN*-amplified if they had 5 times the

copy number (i.e. 10 copies) of the *MYCN* gene per cell. Radiology reports were reviewed for image-defined surgical risk factors currently used by the International NB Research Group (INRG) to classify localised NB.[11,12] Tumours were accordingly classified as L1 or L2.

2.1. Treatment groups

Regardless of other standard biological markers, intended treatment for the 53 patients with *MYCN*-non-amplified NB consisted of surgery to resect the tumour and involved regional lymph nodes followed by close observation without any further therapy (Table 1). Gross total resection was attempted, though not at the expense of mutilation or sacrifice of vital organs. We adopted this approach regardless of prior chemotherapy or RT. For the purposes of analysis, the 53 patients with *MYCN*-non-amplified NB were divided into two groups (Table 1): 14 treated with surgery alone without prior chemotherapy or RT (group A); and 39 who had received chemotherapy ± RT elsewhere before referral to MSKCC (group B). The 16 patients with *MYCN*-amplified tumours (group C; Table 2) were considered to have high-risk NB. Treatment consisted of dose-intensive chemotherapy and surgery followed by local RT and consolidation of CR/VGPR with myeloablative chemotherapy + SCT, 3F8-based anti-GD2 immunotherapy (ClinicalTrials.gov NCT00002560 or NCT00072358) or both.[13,14] All CR/VGPR patients in group C also received 13-*cis*-retinoic acid.

2.2. Statistical analysis

Event-free survival (EFS) and overall survival (OS) were estimated using Kaplan–Meier analyses. The log-rank test was used to determine the prognostic significance of selected variables. Events were defined as relapse, PD, secondary malignancy or death. Cut off date for follow-up was 1st March 2008 or time to last contact with patient.

3. Results

3.1. Outcome of patients with MYCN-non-amplified NB

OS and EFS for all patients with *MYCN*-non-amplified NB were 92.6 ± 5.5% and 74.9 ± 16.9%, respectively, 10 years post-diagnosis (Figs. 3 and 4).

In group A (Table 1), 13/14 patients had L2 NB. Gross total tumour resection with the preservation of vital organs was performed in five (36%) patients: all remain event-free survivors at 52–97 (median, 92) months from surgery. The other nine group A patients had minimal ($n = 7$) or extensive ($n = 2$) visible residual post-operative disease (one had residual cervical disease involving the brachial plexus, and one had NB closely approximated to the superior mesenteric artery). No patient underwent nephrectomy; three underwent laminectomy. Six of the nine remain event-free survivors at 5–82 (median, 26) months from surgery, but three had PD. A patient with pelvic and epidural disease had local PD 2 months after initial surgery and then again 2 months after debulking of the recurrence; he is currently receiving dose-intensive chemotherapy. In the above patient with residual cervical disease, progression was detected and resected 96 months from diagnosis; she received no cytotoxic therapy and remains an event-free survivor 48+ months later. The third patient had local PD at 5, 50 and 56 months from diagnosis; despite dose-intensive chemotherapy and RT after the third local recurrence, metastatic BM disease emerged and he died of NB 90 months postdiagnosis. The 10-year OS for patients treated with surgery alone was 84.6 ± 14% (Fig. 3) at a median follow-up of 59 (range 3.8–151) months.

Among the 39 patients in group B (Table 1), 35 had L2 tumours based on pre-surgical risk criteria. Before referral to MSKCC, five received dose-intensive chemotherapy and 34 (85%) modest doses of chemotherapy, including 26 patients who were treated with 1–8

(median 4) cycles of the POG/COG intermediate-risk protocol which uses modest doses of carboplatin, etoposide, cyclophosphamide and doxorubicin. Gross total resection was achieved in 25/39 (64%); laminectomy was performed in 4 patients. Fourteen patients were left with minimal ($n = 7$) or extensive ($n = 7$) visible residual NB. All patients with incomplete resection had residual disease restricted to the epidural area. Surgical complications included two nephrectomies and one intraoperative death. After surgery, all patients were observed without cytotoxic therapy except for one patient who, at diagnosis, had massive abdominal disease, including peritoneal implants, and post-operatively received whole abdominal RT and a cycle of low-dose chemotherapy. With a follow-up of 6–145 (median, 47) months from diagnosis, there have been no further adverse events. The 10-year OS and EFS were 97.1 ± 2.9% (Fig. 3).

Although chemotherapy prior to surgery was associated with superior EFS ($p = 0.02$ for group B versus group A) it did not confer OS advantage ($p = 0.5$). Biological parameters did not predict EFS in either group and the same was true for all patients with *MYCN*-non-amplified tumours: $p = 0.59$ for favourable histology versus unfavourable histology; $p = 0.63$ for diploid tumours versus hyperdiploid tumours; $p = 0.47$ for age >18 months versus age <18 months; $p = 0.67$ for age >24 months versus age <24 months. Image-defined risk factors also did not influence OS ($p = 0.65$ for L1 disease versus L2 disease). Of note two of three patients with PD had hyperdiploid tumours with favourable histology. EFS was significantly better for patients undergoing gross total resection compared with incomplete resection ($p = 0.02$), but there was no difference in OS ($p = 0.06$).

3.2. Outcome of patients with MYCN-amplified NB

In group C (Table 2), all 16 patients (M:F = 8:8; median age = 1.9 years; range 0.8–4.3 years) received dose-intensive induction chemotherapy, 11 with either MSKCC N7[13] chemotherapy or a similar COG A3973 protocol.[15] Thirteen achieved CR with chemotherapy and surgery, two patients had PD (one local despite prior surgery, one local and distant) during induction, and one patient was in PR with residual retroperitoneal tumour post-SCT. Patients in CR were consolidated systemically with myeloablative chemotherapy/SCT+3F8-based immunotherapy ($n = 7$), [131]I-3F8+3F8 ($n = 1$), 3F8 alone ($n = 2$), or myeloablative chemotherapy/SCT alone ($n = 2$). All CR/VGPR patients were also treated with 13-*cis*-retinoic acid. RT was used for local control in all patients except in one, whose family refused any consolidative therapy (he developed osteomedullary relapse 14 months from diagnosis). The patient with PR subsequently had residual tumour resected at MSKCC, with no post-operative cytotoxic therapy, and remains an event-free survivor 89+ months from diagnosis. Both the 10-year EFS and OS were 75 ± 10.8% for all 16 group C patients at a median follow-up of 60 (range 12–128) months (Fig. 3), and 90.9 ± 8.7% for the 11 treated with 3F8. Eleven of 13 patients who achieved CR survive without the evidence of disease including 7/7 treated with myeloablative chemotherapy/SCT+3F8, 1/1 treated with [131]I-3F8+3F8, 2/2 treated with 3F8 alone and 1/2 treated with myeloablative chemotherapy/SCT alone. The four patients who relapsed did so at primary (4/4) as well as in distant sites (2 in bones, 2 in liver). They died shortly after progression, with a median time from relapse to death of 3.8 months (range 2.5–5.5 months) despite salvage chemotherapy.

The 10-year OS for all patients with *MYCN*-non-amplified NB was significantly better than that for *MYCN*-amplified NB ($p = 0.03$).

4. Discussion

To date few published reports[16] have focused exclusively on the outcome of INSS stage 3 NB. In this retrospective study, we report favourable prognoses for patients with both

MYCN-non-amplified and *MYCN*-amplified stage 3 NB, adopting two divergent therapeutic strategies: a surgical emphasis while reducing exposure to cytotoxic therapy for the former group, and multimodality therapy consisting of dose-intensive induction chemotherapy, surgery, 13-*cis*-retinoic acid, myeloablative chemotherapy and/or 3F8-based anti-GD2 immunotherapy for the latter. We have previously elaborated on our rationale to avoid chemotherapy or RT in patients with *MYCN*-non-amplified locoregional disease.[9,10] Briefly, our considerations included the limited proliferative and metastatic potential of residual post-operative disease, the severity of the long-term side-effects of cytotoxic therapy,[17] the relative lack of chemoresponsiveness of some localised NB, and the curability of recurrent low-risk localised NB.[18] In the past reports we included only 4 patients with INSS stage 3 disease[19]; the current report extends the series to 14 patients, all treated with surgery alone. The intent of surgery was to achieve a gross total resection of the tumour and associated lymph nodes, but not at the expense of vital organs: nephrectomy was not required in any of the 14 patients in group A. In fact major surgical complications: nephrectomies in two patients and one perioperative death, were encountered only in group B. Although 3/14 group A patients experienced PD, only one died of NB: chemotherapy could be avoided in 12. Relapse in one patient was an unusually late event (90 months post-diagnosis), highlighting the need for continued follow-up. OS and EFS were >80%, similar to the EFS reported in the largest group of Evans stage III patients, all of whom received cytotoxic therapy in addition to attempted surgical resection.[8] Survival probabilities for our patients were comparable to those reported in two other preliminary reports on stage 3 NB: INRG analysis of *MYCN*-non-amplified patients treated on diverse protocols worldwide,[20] and COG results of protocol A3961.[21] The number of patients undergoing surgery and chemotherapy was not defined in these reports. However, given the present management approaches for stage 3 NB at non-MSKCC institutions, it is likely that a large majority of patients were treated with both surgery and chemotherapy.

Among the 39 group B patients with *MYCN*-non-amplified tumours first seen at MSKCC for surgical resection after chemotherapy elsewhere, further cytotoxic therapy was withheld in 97% (38/39), in many cases despite initial recommendations for chemotherapy post-surgery. Most (87%) had received intermediate-dose chemotherapy, although eight had been treated with dose-intensive chemotherapy ± RT to residual disease before surgery. Variations in pre-surgical treatments prevent definitive conclusions being drawn, but the excellent outcome (10-year EFS > 97%) suggests that the intensity and duration of prior chemotherapy were not prognostic. In addition, post-surgery chemotherapy and RT were not necessary for *MYCN*-non-amplified stage 3 patients, even when resection was incomplete as in 43%.

In keeping with referral patterns to our tertiary centre, 91% of patients with *MYCN*-non-amplified NB had image-defined pre-surgical risk factors (INRG L2 disease): gross total tumour resection was feasible in 57% (30 of 53) patients. Not surprisingly, as has been reported in a prior study on localized NB,[11,12] the presence of L2 disease correlated with completeness of resection (data not shown); however, it was not prognostic for OS. The main reason for failure to achieve complete resection was the presence of residual epidural NB (92% of patients with incomplete resection had only residual epidural tumour). The OS of >90% reflects the low malignant potential of these tumours previously described in reports detailing the good prognosis for patients with incompletely resected loco-regional NB.[22] Nevertheless, it should be emphasised that the bulk of tumours were removed, and residual disease was, in almost all cases, restricted to small amounts in the epidural space. Neither histological classification nor ploidy status was prognostic in this series, partly because of the relatively few events (2 deaths and 4 relapses in 53 patients with *MYCN*-non-amplified NB) encountered. Other prognostic markers including chromosome 1p and 11q deletions[23,24] are currently being studied in a national COG study. Although our data are

encouraging, the strategy of withholding cytotoxic therapy for all newly diagnosed non-*MYCN*-amplified stage 3 patients needs to be validated by a prospective multi-institutional study.

In contrast to our approach for patients with non-*MYCN*-amplified NB, patients with *MYCN*-amplified disease were treated aggressively with dose-intensive chemotherapy[13,15] in addition to surgery and RT. CR/VGPR was achieved in 81% similar to our previously reported results in stage 4 patients.[25] Patients who achieved CR received RT to the primary site.[26] Most patients received systemic consolidation of CR/VGPR with myeloablative chemotherapy+3F8. The ability of 3F8 to eliminate microscope BM disease was previously demonstrated among patients with stage 4 NB.[27] In this study, the relative roles of myeloablative chemotherapy and 3F8 in maintaining remission in patients with *MYCN*-amplified stage 3 NB cannot be adequately assessed because the majority of patients also underwent myeloablative chemotherapy for the remission of consolidation. However, two patients who received 3F8 alone remain alive and disease-free 57+ and 48+ months from diagnosis; and group C patients treated with 3F8 appeared to have a better prognosis than those not receiving 3F8 ($p = 0.02$ by Fisher's exact test) suggesting that myeloablative chemotherapy may not be necessary for a favourable outcome in all patients with stage 3 *MYCN*-amplified NB.

Few prior studies have specifically described outcome for *MYCN*-amplified stage 3 disease. The 4-year EFS was 32% for 29 patients with *MYCN*-amplified Evans stage III disease, most of whom were also classified as INSS stage 3, treated on the Children Cancer Group Protocol CCG-3891.[8] In contrast, the 6-year OS for 10 stage 3 *MYCN*-amplified patients on the French NBL 94 study was 80%.[28] These differences may be explained by small sample sizes and possible under-staging of patients on the earlier CCG-3891 on which most patients were enrolled prior to 1990 when ^{123}I-MIBG scans were not uniformly used for staging. For our 16 patients, both the 10-year EFS and OS were $75 \pm 10.8\%$. Unfavourable outcomes were related to failure to achieve CR/VGPR (2/3 patients not achieving CR/VGPR had PD and died of disease) and less commonly to failure to maintain remission (2/13 patients who entered CR/VGPR subsequently relapsed and died of disease). These data indicate that aggressive chemotherapeutic and surgical approaches to achieve remission followed by RT to primary site are critical for cure from *MYCN*-amplified NB. Furthermore, systemic consolidation of remission appears important given the development of distant metastases in the majority of patients who relapsed. Although not included in this analysis, 12 patients with *MYCN*-amplified stage 3 NB were treated at MSKCC after relapse; median time to relapse was 5.8 months (range 0–20.4 months) from end of therapy. Sites of relapse included primary site (10/12), distant skeletal sites (3), liver (1), central nervous system (1) and distant soft tissues (1). Six patients received 3F8-based immunotherapy: 4 developed further progression and died. Two patients remain free of disease 36+ and 84+ months after relapse. Six patients did not receive immunotherapy and all died. Median OS with 3F8 was 19 ± 2.9 months compared to 8.5 ± 0.2 months for those not receiving antibody ($p = 0.007$). This experience in relapsed *MYCN*-amplified stage 3 patients also supports the hypothesis that stage 3 patients have the propensity to develop distant metastases and that 3F8 immunotherapy may be helpful in this regard.

In summary, we conclude that stage 3 NB, irrespective of risk groups, can achieve OS >80% at long follow-up. Patients with *MYCN*-non-amplified NB appeared to have a good prognosis when treated surgically without any cytotoxic therapy. In contrast to a prior report on 227 patients treated on three German cooperative trials,[29] older age did not appear to impart a poorer prognosis for our patients. The relatively small numbers of patients >2 years at diagnosis (66 on the German studies and 21 in this report) and varying treatment approaches preclude direct comparison between the two reports. Other biological markers

such as ploidy and histology also did not add to prognostication. Furthermore, this excellent prognosis makes it unlikely that other markers currently being considered for patient stratification will significantly impact prognosis for the majority of patients with INSS stage 3 NB. Indeed it can be hypothesised that young infants with *MYCN*-non-amplified locoregional NB may have tumours with 'stage 4S' biology with the potential for spontaneous involution. A recent study described an observation alone approach for such patients,[30] however, most of the small number of patients with stage 3 NB appeared to have been eventually treated with surgery and/or chemotherapy. Of note, only 4/53 patients with *MYCN*-non-amplified NB in our study were <6 months at diagnosis. Conversely, patients with *MYCN*-amplified tumours can be successfully treated with a regimen of dose-intensive chemotherapy, aggressive surgery, RT and systemic consolidation of remission. The individual roles of myeloablative chemotherapy and 3F8 immunotherapy to maintain long-term remission in patients with *MYCN*-amplified NB need to be further investigated. The use of 3F8 antibody instead of myeloablative chemotherapy offers the potential advantage of fewer treatment-related toxicities.[31,32]

Acknowledgments

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                    │     INSS Stage 3 NB      │
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                       ↙                    ↘
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      │  MYCN-nonamplified   │      │   MYCN-amplified     │
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Surgical resection alone followed by watchful observation *regardless* of standard biological prognostic markers

Aggressive multimodality therapy for local control: chemotherapy, surgery and radiotherapy +

Systemic consolidation of remission with 3F8-based immunotherapy with or without myeloablative therapy/stem cell transplant; all patients also receive 13-cis retinoic acid
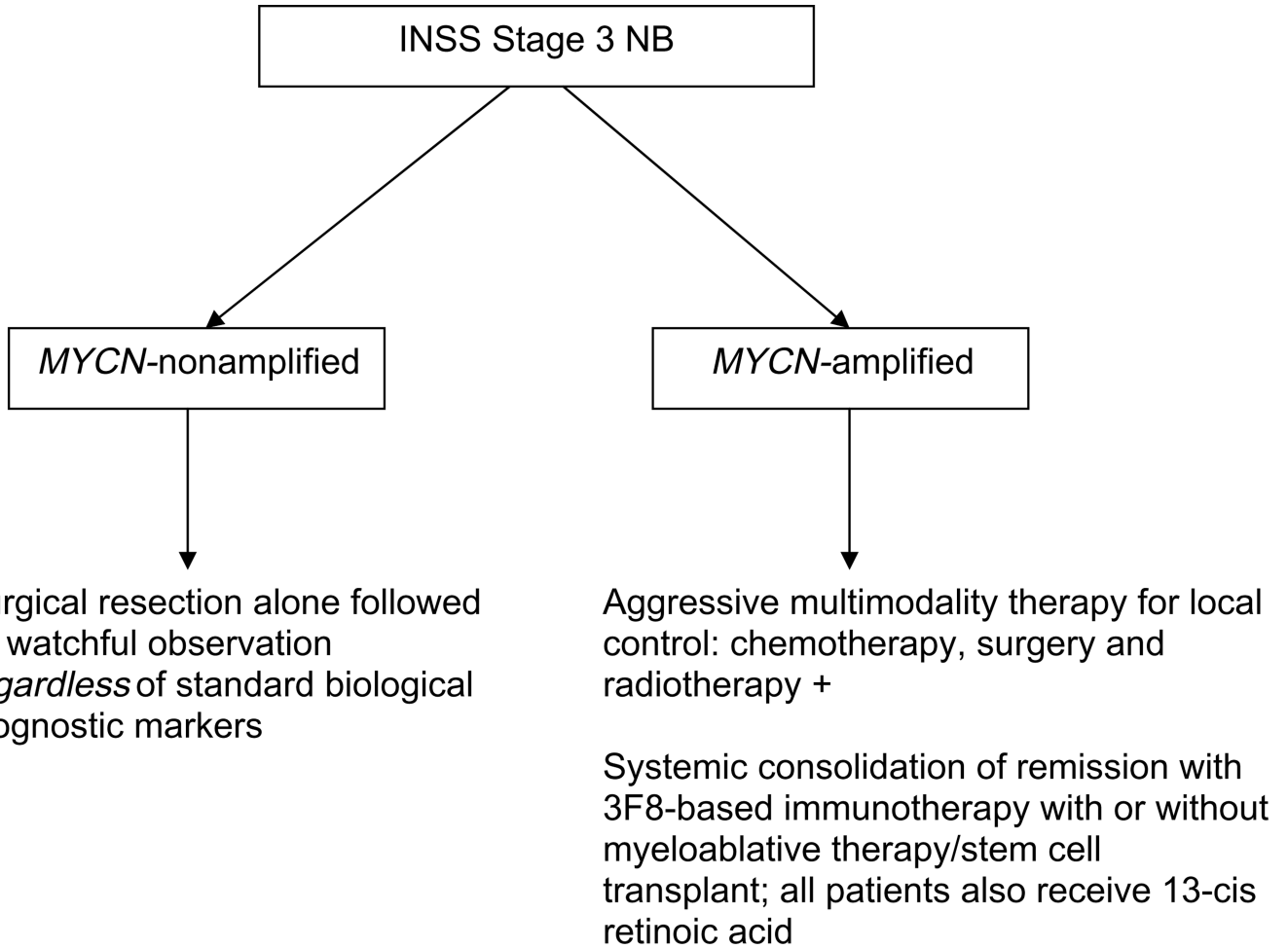
Fig. 1.
Memorial Sloan-Kettering Cancer Centre (MSKCC) algorithm for management of patients with International Neuroblastoma (NB) Staging System (INSS) stage 3 NB.
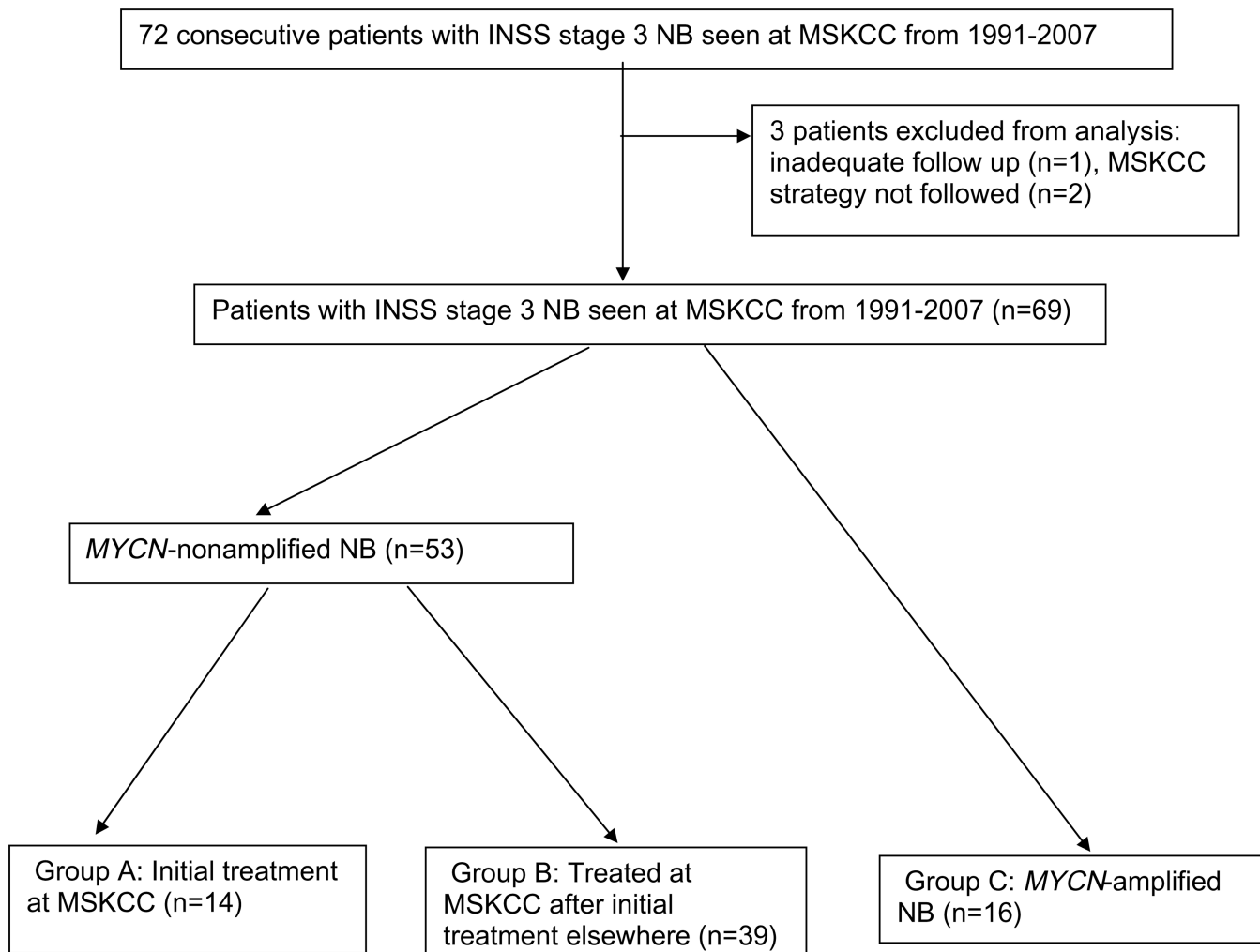
72 consecutive patients with INSS stage 3 NB seen at MSKCC from 1991-2007

3 patients excluded from analysis: inadequate follow up (n=1), MSKCC strategy not followed (n=2)

Patients with INSS stage 3 NB seen at MSKCC from 1991-2007 (n=69)

MYCN-nonamplified NB (n=53)

Group A: Initial treatment at MSKCC (n=14)

Group B: Treated at MSKCC after initial treatment elsewhere (n=39)

Group C: *MYCN*-amplified NB (n=16)

Fig. 2.
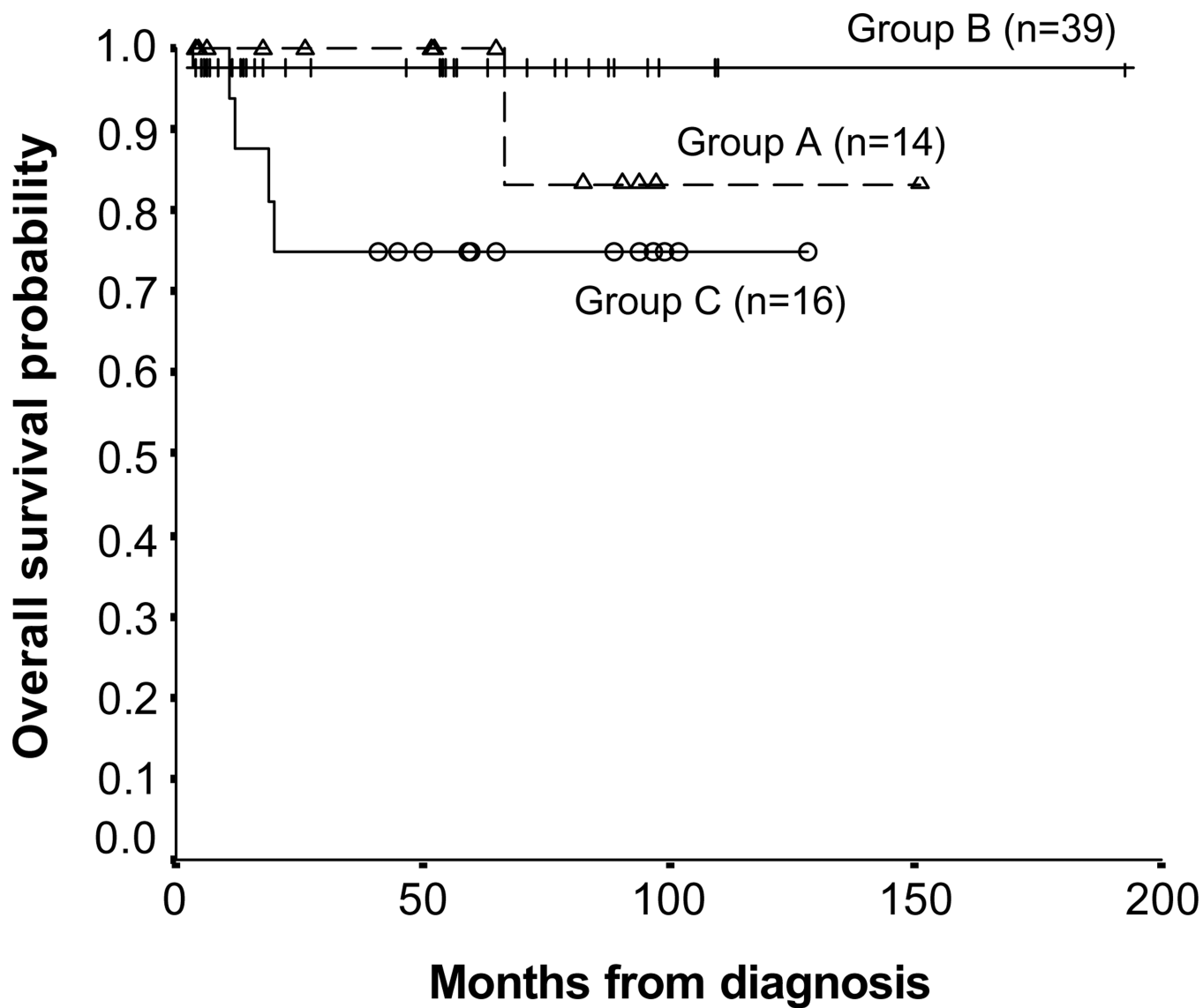Distribution of patients with stage 3 NB.

Fig. 3.
Kaplan–Meier analysis for overall survival in patients with stage 3 NB: group A: patients
with *MYCN*-non-amplified NB treated with surgical resection without chemotherapy; group
B: *MYCN*-non-amplified NB patients treated with chemotherapy at non-*MSKCC*
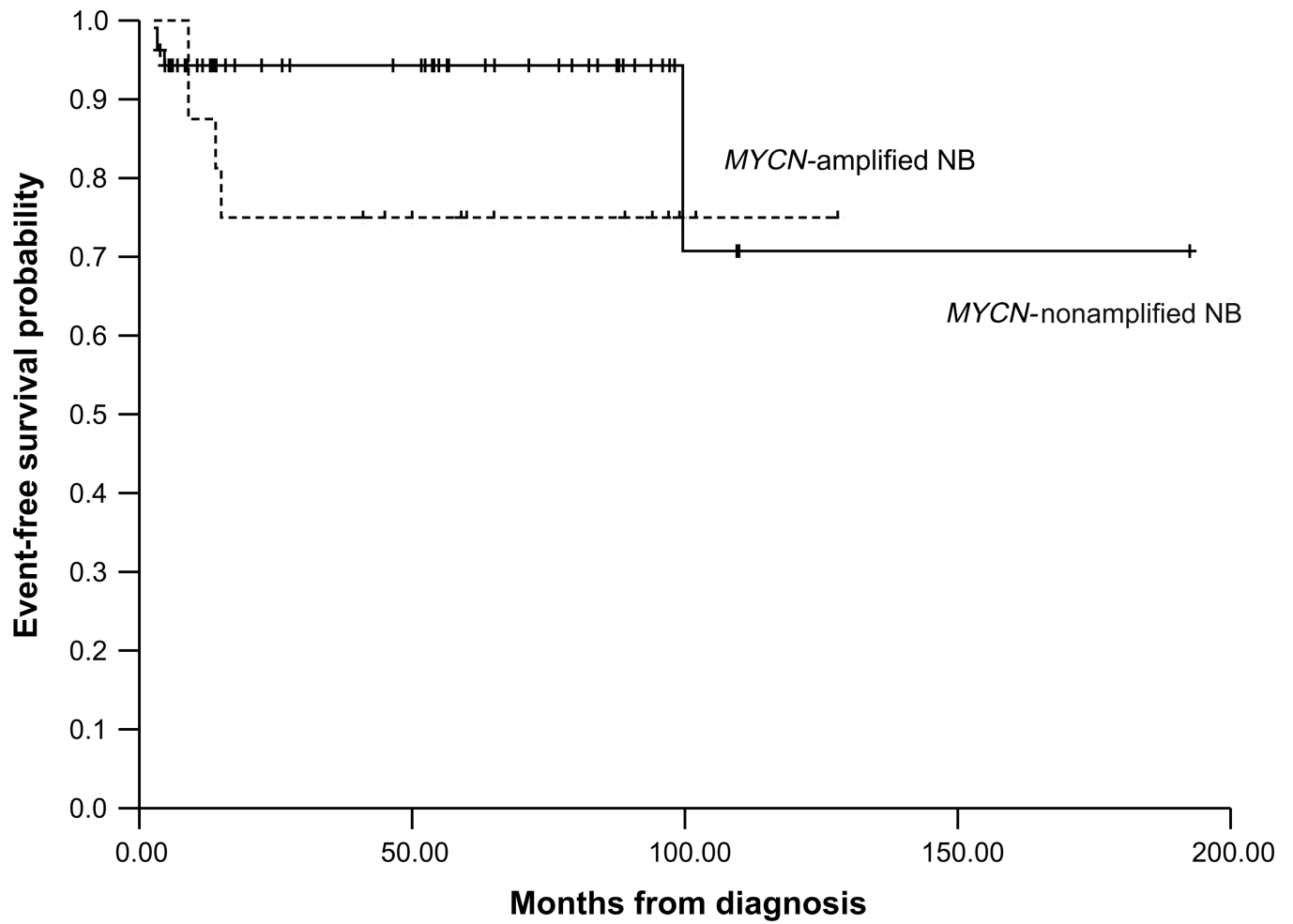institutions prior to surgical resection and group C: patients with *MYCN*-amplified NB.

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Fig. 4.
Kaplan–Meier analysis for event-free survival in patients with stage 3 NB.

Table 1

Characterisitcs and outcome of patients with MUYCN-non-amplified NB

	Group A: initial treatment at MSKCC (*n* = 14)	Group B: treated at MSKCC after initial treatment elsewhere (*n* = 39)
M:F ratio	9:5	17:22
Age:median (range) in years	1.3 (0.1–5.1)	1.6 (0.1–8.8)
Number of patients >24 months	5	16
Number of patients >12 months	10	29
Number of patients <6 months	1	3
Primary site		
Cervical	1	0
Mediastinal	3	4
Retroperitoneal	5	21
Adrenal	3	10
Pelvic	2	4
Epidural disease	7	14
L2 classification by INRG	13	35
Serum LDH (mean ± SD) U/L	354 ± 154	814 ± 687 (*n* = 20)
Serum ferritin (mean ± SD) ng/mL	64 ± 78	64 ± 52 (*n* = 17)
Hyperdiploidy	11/12	24/31
Favourable histology	12/13	28/34
Patients with diploid tumours AND unfavourable histology	0/12	0/29
Pre-surgery chemotherapy	0	39
Intermediate-dose		34
COG protocol 3961		26
Protocol 3961 – 1 cycle		1
Protocol 3961 – 2 cycles		4
Protocol 3961 – 4 cycles		11
Protocol 3961 – 8 cycles		10
Other intermediate-dose		8
High-dose	0	4
High-dose + SCT	0	1
Pre-surgery radiotherapy	0	3
Gross total resection	5	25
Relapses	3	0
Deaths	1	1
Median follow-up (months)	58.8	46.5
5 year EFS	84.6 ± 10%	97.1 ± 3%
10-year OS	84.6 ± 14%	97.1 ± 3%

Abbreviations: COG: Children's Oncology Group; EFS: event-free survival; INRG: International Neuroblastoma Research Group; MSKCC: Memorial Sloan-Kettering Cancer Centre; OS: overall survival; SCT: stem cell transplant; SD: standard deviation.

Table 2

Characterisitcs and outcome of patients with MUYCN-non-amplified NB(Group C)

No.	Age at diagnosis (years)/sex	Primary site	Post-induction status	Myeloablative chemotherapy	Current clinical status	Time since diagnosis (months)
Patients treated with 3F8						
1	0.8/F	Abdomen	CR	None	NED	57
2	1.2/M	Abdomen	PD	None	DOD; local + liver relapse	11
3	1.5/F	Abdomen	CR	Thiotepa, carboplatin, topotecan[33]	NED	92
4	1.6/F	Abdomen	CR	Carboplatin, etoposide, melphalan[8]	NED	39
5	1.6/F	Mediastinum	CR	Carboplatin, etoposide, melphalan[8]	NED	95
6	1.9/F	Abdomen	CR	Thiotepa, carboplatin, topotecan[33]	NED	97
7	1.9/M	Abdomen	CR	Carboplatin, etoposide, melphalan[8]	NED	58
8	2.6/M	Abdomen	CR	None	NED	48
9	2.9/M	Abdomen	CR	None (received ^{131}I-3F8[13])	NED	126
10	4.1/F	Abdomen	CR	Tandem regimen[5]	NED	45
11	4.3/F	Abdomen	CR	Thiotepa, carboplatin, topotecan[33]	NED	100
Patients not receiving 3F8						
12	0.7/M	Abdomen	CR	None	DOD; local + skeletal relapse	19
13	1.5/F	Abdomen	PR	None	DOD; local + skeletal relapse	12
14	2.0/M	Abdomen	CR	Carboplatin, etoposide, melphalan[8]	NED	63
15	2.5/M	Abdomen	PR	Carboplatin, etoposide, melphalan[8]	NED	89
16	4.3/M	Abdomen	CR	Carboplatin, etoposide, melphalan[8]	DOD; local + liver relapse	20

Abbreviations: CR: complete remission; DOD: died of disease; NED: no evaluable disease; PD: progressive disease; PR: partial remission.