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A Proposal for the Timing of Management of Patients with Melanoma Presenting During Pregnancy

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Abstract

The treatment of melanoma during and immediately after pregnancy poses a significant challenge to surgeons, oncologists and patients alike. With the overall increase in incidence of melanoma in the United States and worldwide, it is likely that more surgeons will be faced with management decisions regarding pregnant patients with melanoma. We report on five patients who presented to the Yale Melanoma Unit with melanoma during their pregnancy. We propose the management option of resection of the primary tumor under local anesthesia, and postponing of the sentinel lymph node biopsy until after the birth of the child. The completion lymphadenectomy can be performed if these nodes are found to be harboring metastases. We further discuss treatment options and propose an algorithm for management of patients diagnosed with melanoma while pregnant.

Introduction

The treatment of melanoma during and immediately after pregnancy poses a significant challenge to surgeons, oncologists and patients alike. Although it has been reported that the incidence of melanoma during pregnancy is increased[1], several well-designed studies refute this finding.[2] It is more likely that the incidence in pregnant and non-pregnant women is the same. Although it is known that pregnancy induces changes in melanin production manifested as melasma and linea nigra, it has never been confirmed that pregnancy-related changes in melanin production affects the risk of developing melanoma. In addition, skin evaluations by both the patient and the physician are likely to be increased at this time. This would consequently lead to an increased rate of detection, rather than a true increase in incidence in pregnant women compared to age-matched controls. Since the incidence of melanoma correlates with age[3], and women are delaying pregnancy to later in life, more pregnant women are expected to be diagnosed with melanoma than previously. However, melanoma is still the 3rd most common cancer in women who are pregnant and non-pregnant in that age group.[4]

With the overall increase in incidence of melanoma in the United States and worldwide, it is likely that more surgeons will be faced with management decisions regarding pregnant patients with melanoma. We would like to illustrate the rationale of our treatment approach to melanoma during pregnancy by presenting five representative cases. Of particular importance is the usefulness of definite resection of the primary tumor under local anesthesia and the delay of SNL biopsy until post-partum.

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Employing SLN biopsy as part of the staging for melanomas with Breslow thickness greater than 1.0 mm was first reported by Morton[5], and has become accepted as the standard of care. Nevertheless, there exist only a limited number of reports in the literature on the appropriate timing of sentinel lymph node biopsy (SLN) in pregnant patients with a new diagnosis of melanoma.[6] Most of the data concerning SLN and pregnancy is focused on patients with breast cancer. While intuitively, simply given the anatomical distance, the radioactive exposure of the fetus from the technetium should be lower in patients undergoing axillary SLN compared to groin SLN, we feel that this difference should be minimal since all radioactivity will eventually be cleared by the kidney and excreted through the bladder.

We have previously shown that patients who undergo lymphoscintigraphy before and after resection of the primary melanoma demonstrate the same or additional SLN between the first and second occasions in 89–95% of the cases.[7] This observation holds true even if the resulting defect of the resection was closed with a locoregional rotation flap. Since SLN most often requires general anesthesia, we therefore prefer to delay this part of the operation until after delivery of the baby in order to minimize the risk to the fetus. [7–9]

We report on five patients presenting with melanoma during their pregnancy, who were treated with local resection of melanoma under local anesthesia and SLN on an individual basis. The patients were referred to the Yale Melanoma Unit (YMU) by their dermatologists and were managed by one practitioner (SA).

Materials and Methods

We reviewed the records of all patients that had been referred to the Yale Melanoma Unit (YMU) from 1997–2010. During those 13 years, 3,657 patients underwent surgery for melanoma, of which eight patients had developed melanoma during their pregnancy and thus met the inclusion criterion for our review. Five out of these eight patients underwent resection during their pregnancy; the other three were so close to their delivery date that surgical resection was deferred until after delivery. Data on each of these five patients were registered at the time of their referral, and are reported in Table 1. Each biopsy specimen was reviewed by our dermatopathologists, and clinical staging was based on the 2010 TNM staging system.[10]

Treatment Options

Patient 1

A 30-year-old female who was 23 weeks pregnant was referred to YMU for management of a melanoma of the left posterior thigh. Just prior to her pregnancy, the patient noticed a lesion on the posterior aspect of her left thigh which became discolored. After her obstetrician noticed this lesion during her pregnancy, she was referred to a dermatologist who performed a shave biopsy which revealed a 1.0 mm, Clark level IV, ulcerated melanoma (T2bN0M0, stage IIB). The patient underwent a radical resection of the melanoma with 2cm margins (defect size 4cm×8cm) and closure with double advancement flaps under local anesthesia. Eight weeks post-partum, the patient underwent a left inguinal and left pelvic SLN which was negative for disease in two lymph nodes. The patient is now 20 months following her surgical resection with no evidence of disease.

Patient 2

A 31-year-old female with a history of a pigmented mole on her right back for one year was referred to a dermatologist by her obstetrician during her third trimester of pregnancy. The patient had a history of sun exposure and blistering sun burns, but no family history of

cancer. A biopsy was consistent with a 1.3 mm melanoma, superficial spreading type, Clark's level IV, without ulceration (T2aN0M0, stage IB). During her pregnancy, she underwent wide excision with two centimeter margins, followed by closure with double advancement flaps under local anesthesia. Sentinel lymph node biopsy was postponed until approximately 6 weeks after the birth of her child. Pathology showed 4 sentinel lymph nodes (two LN from the right axilla and two LN from the right groin) that were all negative for melanoma involvement. The patient has been followed for over 4 years without evidence of disease.

Patient 3

A 35-year-old female was referred to YMU at 14 weeks gestation for a 1.3 mm non-ulcerated melanoma, Clark's level IV (T2aN0M0, stage IB) on the lateral aspect of the right foot, which was noted to have changed by a family member. She had no prior history of significant sun exposure, and no family history of melanoma. The patient underwent wide excision of the lesion and closure with a plantar flap under local anesthesia during her pregnancy, and agreed to defer the sentinel lymph node biopsy until the post-partum period. Two months after the delivery of her child, the patient had two sentinel lymph nodes removed from her right inguinal chain and one sentinel lymph node removed from her right iliac-lymphatic chain. All were found to be free of tumor. She has been followed for 14 months with no evidence of recurrence.

Patient 4

A 27-year-old female was referred for a 2.9mm ulcerated melanoma of the right anterior thigh (T3b, N2a, M0, Stage IIIB). The patient stated that she discovered the lesion 9 months prior to her visit with us and that she noted how the lesion had become darker in color and increased in size during her pregnancy. At the point of consultation, the patient was 6 months pregnant with her first child.

The patient elected to undergo resection of the lesion and SNL under local anesthesia and not wait for the SLN in the post-partum period. She understood that the probability of finding micrometastasis was around 40% and would then make her a candidate for complete lymphadenectomy under general anesthesia, which would be delayed until after delivery of the child.

She was found to have 1/3 nodes positive for melanoma and underwent completion lymphadenectomy one month after the uneventful delivery of her child. The final pathology showed an additional 1/22 lymph nodes with micro-metastasis. She was started on adjuvant therapy with Interferon for one year and is now disease-free at ten years follow-up.

Patient 5

A 36-year-old female was referred by her dermatologist for a 1.1 mm non-ulcerated melanoma of the left deltoid shoulder (T2a, N0, M0, stage IB). The patient stated that she noticed a brown nodule over the left shoulder, which she had scratched off at that point. However, the lesion recurred and was noted by a dermatologist who biopsied the lesion and made the diagnosis.

The patient was approximately three weeks pregnant at the time of presentation and upon our recommendation to undergo excision under local anesthesia and delay of SLN until after delivery, went for a second opinion at another melanoma center, after which the decision was made to terminate the pregnancy. The primary tumor resection and SLN were performed under general anesthesia and showed no evidence of further lymph node involvement. The patient is now eight months post-operative without evidence of disease.

Discussion

There have been some early reports suggesting a poorer outcome for women diagnosed with melanoma during their pregnancy. However, those reports were prior to our understanding of prognostic risk factors such as tumor thickness and mitotic rates.

Since then, there have been reports to refute the concerns of worse outcomes following diagnosis of melanoma among these women. A study at Duke[11] compared 58 patients with melanoma diagnosed during pregnancy (Group 1) and 43 patients who became pregnant during 5 years of their primary melanoma (Group 2), with 585 patients who were not pregnant either at diagnosis or within 5 years of diagnosis (Group 3) as well as with a subgroup of 337 out of these 585 patients with stage I disease whose course was not confounded by pregnancy or recurrence within 2 years (Group 4). The authors observed greater tumor thickness in pregnant patients compared to the non-pregnant group (1 vs. 1.5mm), as wells as a higher frequency of ulceration (20.7 vs. 14.5%) and nodular melanomas (17.2 vs. 14.0%). Furthermore, they found that the actual disease-free interval in these patients was significantly shorter (P=0.04), which would be expected given the more advanced disease in the pregnant patient group. When comparing for the more significant prognostic factors for stage I melanoma (Clark's Level, tumor thickness, and ulceration), pregnancy had a higher negative impact regarding disease-free interval (P=0.02). However, the results indicated no difference in overall survival when comparing group 1 with group 3 (P=0.26). While, in part due to the retrospective and descriptive nature of this study, the authors were not able to exactly elucidate the responsible pathogenetic factors, they were still able to conclude that while pregnancy seems to increase the chance of recurrence of melanoma, it shows no significant effect on survival.

A WHO report[12] reviewing 92 pregnant women diagnosed with melanoma found the patients to have a worse survival curve when compared to women diagnosed with melanoma before or after their pregnancy. However, while this study showed that the pregnant group had a mean tumor thickness that was greater than the comparison group, they again found no difference in survival when comparing the groups corrected for thickness of the primary tumor. Furthermore, a review[13] of several controlled trials comparing melanoma among women showed a greater thickness in the melanoma among the pregnant women than the comparison group, but there was no significant difference in the outcome between the two groups. Finally, a recent report[14] comparing the data base containing the maternity and neonatal discharge records from 1991–1999 for the State of California to the database of the California Cancer Registry, identified 412 patients with melanoma during pregnancy or within one year of delivery, and 2,451 age-matched non-pregnant women with melanoma diagnosed during the same time period. In this large comparison study, the authors found no difference in tumor thickness, stage at diagnosis, or lymph node involvement between the two groups.

These findings refute previous concerns about the prognosis of patients with melanoma during pregnancy. Therefore, we need to be prepared to properly advise these patients with regards to the care of their melanoma. Since the large population-based study from California showed that melanoma posed no higher than normal risk to the mother nor to the child, we can focus on the proper treatment indicated for the disease. Although there was a slightly greater interval from diagnosis to treatment for the pregnant women, there was no difference in management of the malignancy and no difference in outcome.

These data support a conservative approach, and that termination of pregnancy should not be necessary. Concern has been raised in the past with regards to the potential of transplacental metastasis from the mother to the fetus. A review of the worlds literature from 1866–2002

by Alexander, et. al[15] identified only 27 cases of melanoma involving the placenta or fetus. 18 of the 27 patients (67%) resulted in healthy, unaffected infants (mean follow-up 14.2 months). How extensive the placenta was involved with disease did not correlate with the chance of transplacental spread. However, when the infant was born with evidence of disease, the prognosis was dismal. Overall, the authors came to several conclusions:

- tendency of melanoma to metastasize to the fetus relative to other tumor types is intriguing, but poorly understood. Since an intact fetal immune response should eradicate maternal cells, inadequate fetal immune response may facilitate transplacental spread and hence be responsible for what seems to be an all-or-nothing effect
- all placentas of women with suspected metastatic melanoma during pregnancy should be closely evaluated by gross and microscopic examination.
- transplacental metastasis is an overall extremely rare event, with the only risk factor seemingly to be male sex (and not like previously reported maternal age less than 30 years, primiparity, disease onset more than 3 years before current pregnancy, nodal metastasis before pregnancy, more than three sites of metastatic foci during the third trimester, primary site of the leg, and maternal death within 1 month of birth)

Neither the patient, nor the treating physician, would likely want to postpone the treatment of melanoma until after the delivery of the baby, unless the diagnosis is made very close to the anticipated delivery date. We are fortunate that most of our patients had localized disease at the time of diagnosis, and they did not need radiation therapy or chemotherapy. Therefore, the management decision was limited to the treatment of the primary melanoma and evaluation of the lymph nodes.

While most authors and melanoma centers seem to agree that resection of the primary tumor should be performed in a very timely fashion, different arguments can be made for or against immediate SNL with or without lymphadenectomy. We have previously shown that lymphatic drainage and identification of draining sentinel lymph nodes is not altered by wide local excision, even when combined with flap closure and skin rearrangement. In that study, postoperative lymphoscintigraphy after melanoma resection and flap reconstruction identified the same or additional SLNs when compared with the preoperative studies in 89–95% of the patients studied.[7] Since the delay in lymph node sampling does not affect the reliability of SLN biopsy, we advocate performing the initial lymphoscintigram and the wide local excision and flap closure under local anesthesia in all patients during their pregnancy, and delaying the SLN under general anesthesia until the post-partum period (usually 6–8 weeks after delivery).

According to the FDA, lymphoscintigraphy is safe during pregnancy, because only small doses of radioactive isotopes are used that have low penetration and a short half-life. Others have reported the safety of lymphoscintigraphy during pregnancy as well.[9,16] However, there are several disadvantages to performing a SLN biopsy during pregnancy: general anesthesia should be avoided if at all possible, to minimize potential risks to the growing brain and the development of the fetus. [8,9] Multiple studies have evaluated the risk of general anesthesia for mother and child during pregnancy. A review of the literature by Cohen-Kerem, et. al[17] included 12,452 patients and showed the complication rates following surgery with general anesthesia during pregnancy to include: a miscarriage rate of 5.8%, induction of premature labor in 3.5%, 2.5% fetal loss, a prematurity rate of 8.2% and major birth defects in 3.9%. While none of these adverse events are statistically higher than in the control population, they point out that there clearly exists a risk to the fetus. Overall, they conclude that in situations where delay of surgery would pose a high risk to mother and

child (i.e. acute appendicitis/peritonitis), then the potential risk of general anesthesia does not outweigh the risk of surgical delay.

Our recommendation is that until more accurate data becomes available regarding the risk and benefits of general anesthesia during pregnancy with respect to semi elective procedures, it is still safer to avoid this exposure for the unborn child.

Patients with metastatic melanoma identified in their SLN should undergo completion lymphadenectomy under general anesthesia. Occasionally, a SLN biopsy can be performed in selected cases under local anesthesia. However, this may be difficult in certain anatomic locations including the axilla (with deep nodes in the proximity to the thoracodorsal nerve) or the inguinal/pelvic region with deep nodes.

If the SLN is performed successfully under local anesthesia during the pregnancy and found to be positive, one alternative is to defer completion lymphadenectomy until the post-partum period (as in patient # 4). However, if the diagnosis of nodal metastasis is made by SLN biopsy under local anesthesia during pregnancy, there is the potential of psychological stress to the patient knowing that the metastatic disease would not be treated until months after completion of the pregnancy.

Furthermore, studies have also shown that the delay of SLN is unlikely to have a substantial impact on overall survival.[18] For these reasons, our recommendation for women diagnosed with melanoma during pregnancy is to perform the wide excision of the primary tumor under local anesthesia and defer lymphoscintigraphy and SLN biopsy until the post-partum period.

In our opinion, based on the previous discussion, several options can be offered to the patient according to the algorithm presented in Figure 1. For low risk (i.e. <1mm thickness with ulceration T1a) melanoma without indication for SNB, the primary lesions should be resected under local anesthesia if presenting during the first to early third semesters of the pregnancy (see first column.) On the other hand, if the patient with indications for SNB presents very late during the course of their pregnancy (late third trimester), the resection of the tumor and SLN can be deferred until after delivery of the child.

Patients presenting in between these two spectrums pose a more complex challenge and require more of an individualized approach. We believe that the patients with melanoma at low risk for nodal involvement (T1b to T2b) can undergo resection of the primary lesion under local anesthesia and delay the SLN to the post-partum period (patients #1,2, and 3.)

Those with greater risk of nodal involvement (T3 or T4) can undergo resection of the primary melanoma under local anesthesia and either delay the sentinel node biopsy until after the delivery of the child, or perform the SLN under local anesthesia. The reason to consider these patients for an immediate concurrent SLN is based on the higher risk of nodal involvement in these patients. If the SLN is positive, the completion lymphadenectomy, performed under general anesthesia, can be postponed until after delivery of the child (patient # 4). While not influencing the course of the disease or over-all survival, a positive finding may guide further treatment plans, involving all members of the multidisciplinary team in plans for completion lymphadenectomy and timely adjuvant therapy. The risks and benefits of each of these options need to be addressed individually with each patient as discussed below.

Another option would be to terminate the pregnancy when the patient presents with melanoma during the first two trimesters (patient #5). We do not recommend this approach, since the survival outcome for the patient will not be altered by this approach.

Conclusion

We report five patients treated for melanoma diagnosed during pregnancy. We propose the management option of resection of the primary tumor under local anesthesia, and postponing of the sentinel lymph node biopsy until after the birth of the child. The completion lymphadenectomy can be performed if these nodes are found to be harboring metastases. Other options in this algorithm are also discussed.

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References

1. Lens M, Bataille V. Melanoma in relation to reproductive and hormonal factors in women: current review on controversial issues. Cancer Causes Control. 2008; 19:437–442. [PubMed: 18197460]
2. O'Meara, Cress R, Xing G, Danielsen B. Malignant melanoma in pregnancy. A population-based evaluation. CA A Cancer Journal for Clinicians. Cancer. 2005 Mar 15.103:1217–1226. [PubMed: 15712209]
3. Linos E, Swetter S, Cockburn M. Increasing burden of melanoma in the United States. J Invest Dermatol. 2009; 129:1666–1674. [PubMed: 19131946]
4. Wu X, Groves F, McLaughlin C, Jemal A. Cancer incidence patterns among adolescents and young adults in the United States. Cancer Causes Control. 2005; 16:309–320. [PubMed: 15947883]
5. Morton DL, Wen DR, Wong JH, et al. Technical details of intraoperative lymphatic mapping for early stage melanoma. Arch Surg. 1992; 127:392–399. [PubMed: 1558490]
6. Mondi MM, Cuenca RE, Ollila DW. Sentinel lymph node biopsy during pregnancy: initial clinical experience. Ann Surg Oncol. 2007; 14:218–221. [PubMed: 17066225]
7. Ariyan S, Ali-Salaam P, Cheng DW, Truini C. Reliability of lymphatic mapping after wide local excision of cutaneous melanoma. Ann Surg Oncol. 2007; 14:2377–2383. [PubMed: 17541771]
8. Cohen SE. Risk of abortion following general anesthesia for surgery during pregnancy: anesthetic or surgical procedure? Anesthesiology. 1986; 65:706–707. [PubMed: 3789453]
9. Steinberg ES, Santos AC. Surgical anesthesia during pregnancy. Int Anesthesiol Clin. 1990; 28:58–66. [PubMed: 2403991]
10. Gershenwald JE, Soong SJ, Balch CM. 2010 staging system for cutaneous melanoma…and beyond. Ann Surg Oncol. 2010; 17:1475–1477. [PubMed: 20300965]
11. Reintgen DS, McCarty KS Jr, Vollmer R, Cox E, Seigler HF. Malignant melanoma and pregnancy. Cancer. 1985 Mar 15.55:1340–1344. [PubMed: 3971302]
12. MacKie RM, Bufalino R, Morabito A, Sutherland C, Cascinelli N. Lack of effect of pregnancy on outcome of melanoma. For The World Health Organisation Melanoma Program. Lancet. 1991; 337:653–655. [PubMed: 1672000]
13. Driscoll MS, Grin-Jorgensen CM, Grant-Kels JM. Does pregnancy influence the prognosis of malignant melanoma? J Am Acad Dermatol. 1993; 29:619–630. [PubMed: 8408797]
14. O'Meara AT, Cress R, Xing G, Danielsen B, Smith LH. Malignant melanoma in pregnancy. A population-based evaluation. Cancer. 2005; 103:1217–1226. [PubMed: 15712209]
15. Alexander A, Samlowski WE, Grossman D, Bruggers CS, Harris RM, Zone JJ, Noyes RD, Bowen GM, Leachman SA. Metastatic melanoma in pregnancy: risk of transplacental metastases in the infant. J Clin Oncol. 2003; 21:2179–2186. [PubMed: 12775744]
16. Pandit-Taskar N, Dauer LT, Montgomery L, St Germain J, Zanzonico PB, Divgi CR. Organ and fetal absorbed dose estimates from 99mTc-sulfur colloid lymphoscintigraphy and sentinel node localization in breast cancer patients. J Nucl Med. 2006; 47:1202–1208. [PubMed: 16818956]
17. Cohen-Kerem R, Railton C, Oren D, Lishner M. Pregnancy outcome following non-obstetric surgical intervention. Am J Surg. 2005; 190:467–473. [PubMed: 16105538]

18. Kirkwood JM, Ibrahim JG, Sondak VK, Richards J, Flaherty LE, Ernstoff MS. High- and low-dose interferon alfa-2b in high-risk melanoma: first analysis of intergroup trial E1690/S9111/C9190. J Clin Oncol. 2000:2444–2458. [PubMed: 10856105]

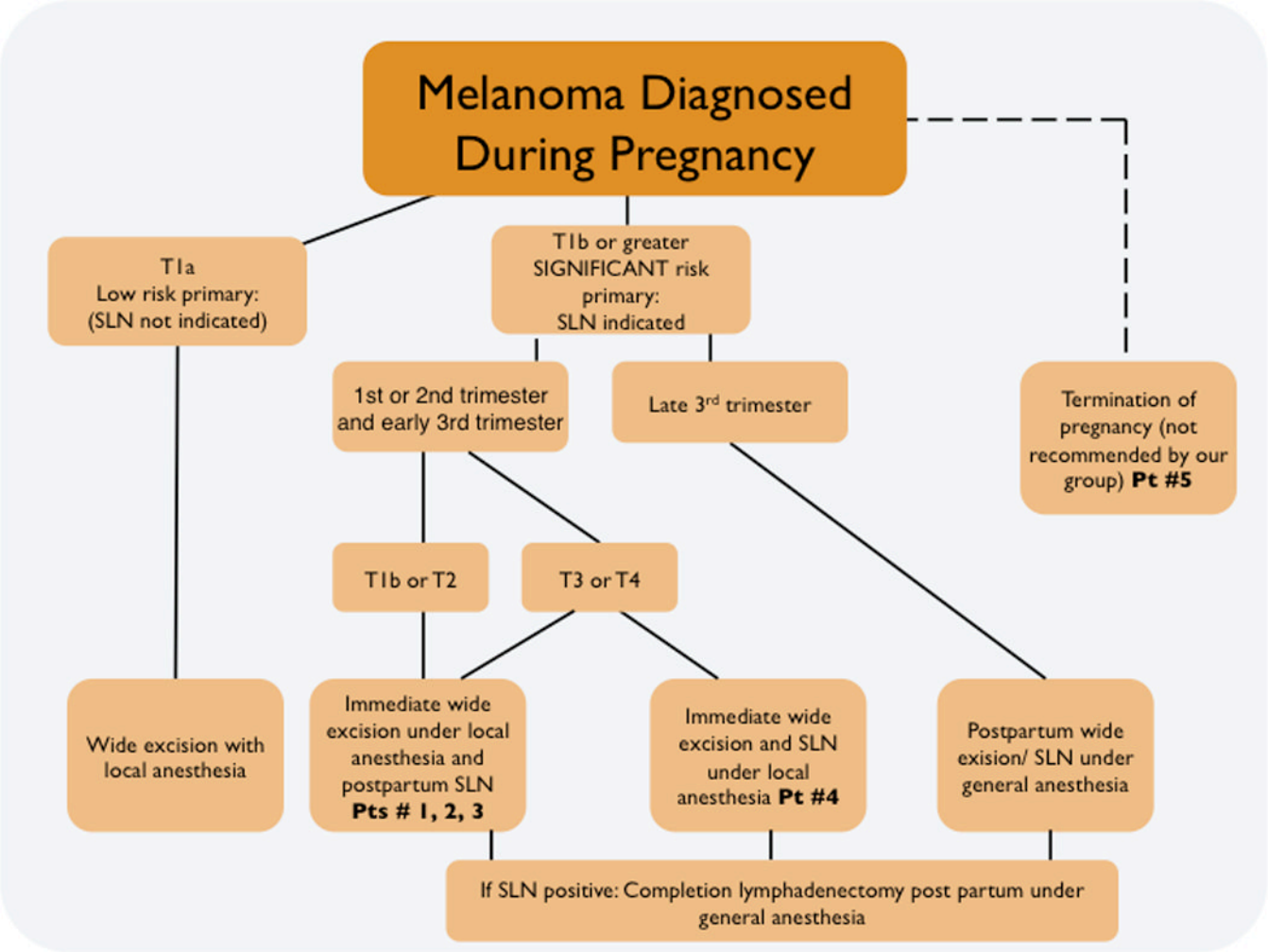

Figure 1.

Table 1

Patients presented with melanoma during pregnancy

Patient	Age	Time of Diagnosis	Lesion Location	Breslow thickness (mm)	Clark's Level	Positive Sentinel LN	TNM Staging	Outcome
1	30	2nd trimester	Left posterior thigh	1.0	IV	0/3	T2bN0M0 stage IIB	20 mos post-op, NED
2	31	3rd trimester	Right back	1.3	IV	0/2 Ax LN, 0/2 groin LN	T2aN0M0 stage IB	50 mos post-op, NED
3	35	1st trimester	Right foot	1.3	IV	0/3	T2aN0M0 stage IB	14 mos post-op, NED
4	27	2nd trimester	Right thigh	2.9	IV	1/3 (1/22 LN positive on final LAD)	T3bN2aM0 stage IIIB	10 yrs post op,NED
5	36	1st trimester	Left shoulder	1.1	IV	0/3	T2aN0M0 stage IB	8 mos post-op, NED

(LN: Lymph node, LAD: Lymphadenectomy, NED: No evidence of disease).